CLH report

Proposal for Harmonised Classification and Labelling

**Based on Regulation (EC) No 1272/2008 (CLP Regulation),
Annex VI, Part 2**

Chemical name: Talc (Mg3H2(SiO3)4)

EC Number: **238-877-9**

CAS Number: **14807-96-6**

Index Number: **-**

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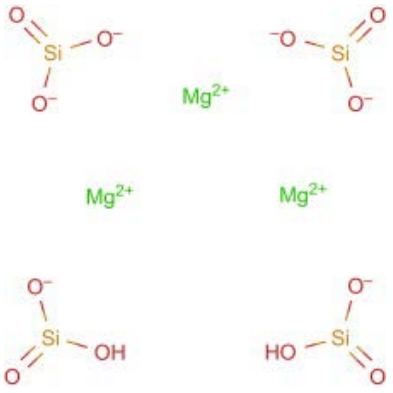
CONTENTS

1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 1: Substance identity and information related to molecular and structural formula of the substance

Name(s) in the IUPAC nomenclature or other international chemical name(s)	Talc ($Mg_3H_2(SiO_3)_4$
Other names (usual name, trade name, abbreviation)	Agalite Asbestine Dioxosilane - oxomagnesium hydrate Hydrous magnesium silicate Magnesium silicate, hydrous Soapstone Steatite Talc (non-fibrous) Talc E553b Talc: Hydrated magnesium silicate Talc powder Talc, containing no asbestos fibres Talcum Trimagnesium Trimagnesium dioxido(oxo)silane hydroxy-oxido-oxosilane Non-asbestiform talc Oxosilanediol
ISO common name (if available and appropriate)	Talc ($Mg_3H_2(SiO_3)_4$)
EC number (if available and appropriate)	238-877-9
EC name (if available and appropriate)	Talc (Mg3H2(SiO3)4)
CAS number (if available)	14807-96-6
Other identity code (if available)	-
Molecular formula	$Mg_3H_2(SiO_3)_4$
Structural formula	
SMILES notation (if available)	-
Molecular weight or molecular weight range	379.27 g/mol
Information on optical activity and typical ratio of	-

(stereo) isomers (if applicable and appropriate)	
Degree of purity (%) (if relevant for the entry in Annex VI)	-

1.2 Composition of the substance

Table 2: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	**Concentration range (% w/w minimum and maximum in multi-constituent substances)**	**Current CLH in Annex VI Table 3 (CLP)**	**Current self-classification and labelling (CLP)**
Talc ($Mg_3H_2(SiO_3)_4$; CAS 14807-96-6; EC 238-877-9) • Mineral talc • Industrial-grade talc (mix of talc and other minerals) • Cosmetic talc	See confidential annex	-	Acute Tox. 3: H331 Acute Tox. 4: H302, H332 Eye Irrit. 2: H319 Carc. 1A: H350 STOT SE 3: H335 (inhalation; other: respiratory tract), H335 (Lungs, Thorax, or Respiration: Bronchogenic carcinoma) STOT RE 1: H372 (lungs; other: respiratory system), H372 (lung, inhalation) Majority of notifiers: no self-classification

Table 3: Impurities (non-confidential information) if relevant for the classification of the substance

Impurity (Name and numerical identifier)	**Concentration range (% w/w minimum and maximum)**	**Current CLH in Annex VI Table 3 (CLP)**	**Current self-classification and labelling (CLP)**	**The impurity contributes to the classification and labelling**
Magnesium carbonate (CAS 546-93-0)	See confidential annex	-	Acute Tox. 4: H302, H312 Skin Irrit. 2: H315 Eye Irrit. 2: H319 STOT RE 2: H373	No
Chlorite (CAS 14998-27-7)	See confidential annex	-	-	No
Quartz (SiO_2; CAS 14808-60-7)	See confidential annex		Acute Tox. 4: H302, H332 Skin Irrit. 2: H315 Eye Irrit. 2: H319 Muta. 2: H341 Carc. 1A: H350 Carc. 1B: H350 Carc. 2: H351 STOT SE 1: H370 STOT SE 2: H371 STOT SE 3: H335 STOT RE 1: H372 STOT RE 2: H373	No

Impurity (Name and numerical identifier)	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3 (CLP)	Current self-classification and labelling (CLP)	The impurity contributes to the classification and labelling
Dolomite (CAS 16389-88-1)	See confidential annex	-	Eye Irrit. 2: H319	No

Table 4: Additives (non-confidential information) if relevant for the classification of the substance

Additive (Name and numerical identifier)	Function	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3 (CLP)	Current self-classification and labelling (CLP)	The additive contributes to the classification and labelling
The substance does not contain additives.					

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 5: Proposed harmonised classification and labelling

	Index No	Chemical name	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATEs	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	No current Annex VI entry										
Dossier submitter's proposal	TBD	Talc (Mg3H2(SiO3)4)	238-877-9	14807-96-6	Carc. 2 STOT RE 1	H351 H372 (lungs)(inhalation)	GHS08 Dgr	H351 H372 (lungs) (inhalation)		-	#
Resulting entry in Annex VI if adopted by RAC and agreed by Commission	TBD	Talc (Mg3H2(SiO3)4)	238-877-9	14807-96-6	Carc. 2 STOT RE 1	H351 H372 (lungs)(inhalation)	GHS08 Dgr	H351 H372 (lungs) (inhalation)		-	#

Inclusion of the following specific note is suggested for Carcinogenicity: *If the substance is to be placed on the market as fibres (with diameter < 3 μm, length > 5 μm and aspect ratio ≥ 3:1) or particles of the substance fulfilling the WHO fibre criteria or as particles with modified surface chemistry, their hazardous properties must be evaluated in accordance with Title II of this Regulation, to assess whether a higher category (Carc. 1B or 1A) and/or specification of routes of exposure should be applied.*

Table 6: Reason for not proposing harmonised classification and status under consultation

Hazard class	Reason for no classification	Within the scope of consultation
Explosives	Hazard class not assessed in this dossier	No
Flammable gases (including chemically unstable gases)	Hazard class not assessed in this dossier	No
Oxidising gases	Hazard class not assessed in this dossier	No
Gases under pressure	Hazard class not assessed in this dossier	No
Flammable liquids	Hazard class not assessed in this dossier	No
Flammable solids	Hazard class not assessed in this dossier	No
Self-reactive substances	Hazard class not assessed in this dossier	No
Pyrophoric liquids	Hazard class not assessed in this dossier	No
Pyrophoric solids	Hazard class not assessed in this dossier	No
Self-heating substances	Hazard class not assessed in this dossier	No
Substances which in contact with water emit flammable gases	Hazard class not assessed in this dossier	No
Oxidising liquids	Hazard class not assessed in this dossier	No
Oxidising solids	Hazard class not assessed in this dossier	No
Organic peroxides	Hazard class not assessed in this dossier	No
Corrosive to metals	Hazard class not assessed in this dossier	No
Acute toxicity via oral route	Hazard class not assessed in this dossier	No
Acute toxicity via dermal route	Hazard class not assessed in this dossier	No
Acute toxicity via inhalation route	Hazard class not assessed in this dossier	No
Skin corrosion/irritation	Hazard class not assessed in this dossier	No
Serious eye damage/eye irritation	Hazard class not assessed in this dossier	No
Respiratory sensitisation	Hazard class not assessed in this dossier	No
Skin sensitisation	Hazard class not assessed in this dossier	No
Germ cell mutagenicity	Hazard class not assessed in this dossier	No
Carcinogenicity	Harmonised classification proposed	Yes
Reproductive toxicity	Hazard class not assessed in this dossier	No
Specific target organ toxicity-single exposure	Hazard class not assessed in this dossier	No
Specific target organ toxicity-repeated exposure	Harmonised classification proposed	Yes
Aspiration hazard	Hazard class not assessed in this dossier	No
Hazardous to the aquatic environment	Hazard class not assessed in this dossier	No
Hazardous to the ozone layer	Hazard class not assessed in this dossier	No

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

Talc does not have a harmonised classification. A risk management option analysis (RMOA)[1] focussed on occupational industrial or professional exposure to talc not containing asbestos or asbestiform fibres, was submitted by the competent authority of the Netherlands (CA NL) in 2021. It was concluded to draft a proposal for harmonised classification for talc not containing asbestos or asbestiform fibres as Carc. 2 and STOT RE 1, and a proposal for an indicative OEL, considering fibre concentration in respirable talc. This combination of risk management options was expected to result in a decreasing incidence of lung diseases for workers in relevant fields of work.

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

There is no requirement for justification that action is needed at Community level for harmonised classification for talc not containing asbestos or asbestiform fibres as Carc. 2. The substance has (suspected) CMR properties (carcinogenicity). For harmonised classification for talc not containing asbestos or asbestiform fibres as STOT RE 1 classification is considered justified due to evaluation of existing data.

5 IDENTIFIED USES

Talc is used in a wide variety of different processes of manufacturing in different industries, as filling component (bleaching, whitening/filling agent, pharmaceuticals), carrier (coating, dye, paper industry), separator (rubber), processing aid (ceramics), non-reactive processing aid (agriculture), and anticaking agent (food). Cosmetic-grade talc is used in cosmetics, additive in personal care products and body powders.

6 DATA SOURCES

The REACH registration dossier for talc (ECHA Dissemination, 2022; last modified: 1 June 2022), has been analysed for study references, which then have been considered as data sources for this CLH report.

Further, the following reviews with toxicological risk assessments on talc were used:

- International Agency for Research on Cancer (IARC; 1987). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. VOLUME 42. Silica and Some Silicates[2]
- The Dutch Expert Committee on Occupational Safety (DECOS; 1991). Health-based recommended occupational exposure limit for talc dusts[3]
- International Agency for Research on Cancer (IARC; 2010). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. VOLUME 93. Carbon Black, Titanium Dioxide, and Talc[4]
- MAK Value Documentations, Vol. 22 (2006). Talc (without asbestos fibres) (respirable fraction)[5]
- Danish Environmental Protection Agency (2016). Talcum, cosmetic grade (non-fibrous): Evaluation of health hazards and proposal of a health-based quality criterion for ambient air[6]

[1] https://echa.europa.eu/nl/assessment-regulatory-needs/-/dislist/details/0b0236e186365261

[2] https://publications.iarc.fr/_publications/media/download/1590/d3f74eb781daf26f18ccf3a5fd7f87cd00f4ed90.pdf

[3] https://www.ser.nl/api/Mfiles/DownloadFirstDocument?Id=2115a424-3173-4c66-a6ff-feca96317672

[4] https://monographs.iarc.who.int/wp-content/uploads/2018/06/mono93.pdf

[5] https://onlinelibrary.wiley.com/doi/10.1002/3527600418.mb1480796nfae0022

[6] https://www2.mst.dk/Udgiv/publications/2016/10/978-87-93529-23-6.pdf

- Health Canada (2021). Screening Assessment Talc (Mg3H2(SiO3)4)[7]

7 PHYSICOCHEMICAL PROPERTIES

Table 7: Summary of physicochemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20°C and 101,3 kPa	Solid: talc is a white odourless powder	ECHA Dissemination (2022)	
Melting/freezing point	Above 900°C, talc progressively loses its hydroxyl groups .Above 1050°C, talc re-crystallises into different forms of enstatite (anhydrous magnesium silicate). Talc's melting point is at 1500°C.	ECHA Dissemination (2022)	Registration dossier: data from handbook or 'collection of data'.
Boiling point	-	ECHA Dissemination (2022)	Registration dossier: the study does not need to be conducted because the substance is a solid which melts above 300°C.
Relative density	2.7-2.8	ECHA Dissemination (2022)	Registration dossier: data from handbook or 'collection of data'.
Vapour pressure	A QSAR method predicts the vapour pressure of this substance to be 1.48×10^{-2} Pa at 25°C.	ECHA Dissemination (2022)	Registration dossier: calculated..
Surface tension	-	ECHA Dissemination (2022)	Registration dossier: the study does not need to be conducted because water solubility is below 1 mg/L at 20°C.
Water solubility	Insoluble in water. Talc is practically insoluble in water.< 0.1 mg/L at 25°C	ECHA Dissemination (2022)	Registration dossier: data from handbook or 'collection of data'.
Partition coefficient n-octanol/water	A reliable QSAR method predicts a value for the partition co-efficient (logKow) of -9.40 for this substance.	ECHA Dissemination (2022)	Registration dossier: calculated.
Flash point	-	ECHA Dissemination (2022)	Registration dossier: the study does not need to be conducted because the substance is inorganic.
Flammability	-	ECHA Dissemination (2022)	Registration dossier: the study does not need to be conducted

[7] https://www.canada.ca/content/dam/eccc/documents/pdf/pded/talc/screening-assessment-talc.pdf

Property	Value	Reference	Comment (e.g. measured or estimated)
			because the substance is a solid.
Explosive properties	-	ECHA Dissemination (2022)	Registration dossier: the study does not need to be conducted because there are no chemical groups present in the molecule which are associated with explosive properties.
Self-ignition temperature	-	ECHA Dissemination (2022)	Registration dossier: the study does not need to be conducted because the substance is a solid having a melting point ≤ 160°C.
Oxidising properties	-	ECHA Dissemination (2022)	Registration dossier: the study does not need to be conducted because there are no chemical groups present in the molecule which are associated with oxidising properties and hence, the classification procedure does not need to be applied.
Granulometry	D10: 1.072 µm D50: 5.58 µm D90: 19.745 µm	ECHA Dissemination (2022)	Measured
Stability in organic solvents and identity of relevant degradation products	-	ECHA Dissemination (2022)	Registration dossier: the study does not need to be conducted because the substance is inorganic.
Dissociation constant	-	ECHA Dissemination (2022)	Registration dossier: the study does not need to be conducted because the substance is insoluble.
Viscosity	-	ECHA Dissemination (2022)	Registration dossier: the study does not need to be conducted because the substance is a solid.

8 EVALUATION OF PHYSICAL HAZARDS

Not evaluated in this dossier.

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

Table 8: Summary table of toxicokinetic studies

Method	Results	Remarks	Reference
Inhalation			
Single exposure (40-75 mg/m^3), 2-h nose-only, neutron activated high-grade cosmetic talc (purity 95% w/w), MMAD 6.4-6.9 µm	6-8% of inhaled dose (20-80 µg) reached the alveoli, with a biological half-life of 7-10 days Complete clearance from the	Unusually short clearance time may be related to limitations in	Wehner et al. (1977b)

Method	Results	Remarks	Reference
Golden Syrian hamsters (n = 44, female) Four animals were sacrificed at 11 different time points (15 and 100 min; 4 and 21 h; 2, 4, 8, 19, 36, 68 and 132 days) No test guideline study GLP: no	alveoli was reached 4 months after exposure. No translocation of talc was observed into the liver, kidneys, ovaries or other organs in hamsters. Several hundred micrograms of talc were found in the faecal samples. Results of a leaching study to be described elsewhere suggest that the picogram quantities of ^{60}Co found in the urine probably represented leached ^{60}Co absorbed in the gastro-intestinal tract.	sensitivity of detection methods. The large size of particles likely hampers uptake via inhalation (adopted from IARC 2010).	
Oral			
Gastric intubation (single dose) of high-grade cosmetic (neutron-activated) talc (purity 95% w/w), MMAD 6.4-6.9 µm Golden Syrian hamsters (n = 6, female) Sacrificed 24 h after administration No test guideline study GLP: no	An average of approximately 3 mg talc was found in the tissues and excreta. Of this quantity, 74.5% was found in the faeces, 23.5% in the gut and 1.9% in the carcass. Intestinal absorption of talc is negligible.	-	Wehner et al. (1977a)
Single oral dose of ^{3}H-labelled talc (purified, British Pharmacopoeia, particle size unknown) Wistar rats (n = 3/group), male): 50 mg/kg bw LACA mice (n = 2/group, female): 40 mg/kg bw Dunkin/Hartley guinea-pigs (n = 3/group, female): 25 mg/kg bw Rat and guinea-pig: in one group urine and faeces were collected 24-h intervals for 4 days and on day 10. Animals in the other group were sacrificed on day 10. Mouse: two animals were killed at 6 h and two at 24 h. No test guideline study GLP: no	More than 95% of the dose was excreted in the faeces 3-4 days after dosing in all three species, and less than 2% of the radioactivity was recovered in the urine. This radioactivity probably reflected contamination of urine samples with faeces. No radioactivity was detected in the liver or kidneys.	-	Phillips et al. (1978)
Dermal: no studies available			
Intravaginal			
Intravaginal application of ^{3}H-labelled talc (purified, British Pharmacopoeia, particle size unknown; 50 mg/kg bw/d), single application or application for 6 days Large White rabbits (n = 3/group, female) Urine was collected at 24-h intervals for 3 days. Animals were sacrificed on day 3. Rabbits from the other group were sacrificed 72 h after the final dose of the 6-day	No translocation of talc to the ovaries.	-	Phillips et al. (1978)

Method	Results	Remarks	Reference
period. No test guideline study GLP: no			
Intravaginal or intrauterine application of 25 mg talc (purity and particle size unknown) Intrauterine application of talc was administered as single application (animals sacrificed 5 days after) or multiple applications on day6, 15, 22 and 30 (2 animals sacrificed on day 20 and 2 animals sacrificed on day 49) Intravaginal application of talc was administered as single application and animals were sacrificed 24 h, 48 h or 4 days after application (2 animals per group). Rats (n = 2 or 4/group) No test guideline study GLP: no	When instilled into the vagina, no talc particles were found in the ovaries after 24 and 48 h, but talc particles were found after 4 days. When instilled into the uterus, talc particles were noted in the ovaries from day 5 onwards.	-	Henderson et al. (1986)
Intravaginal application of neutron-activated cosmetic talc (purity and particle size unknown; 30 applications of 125 mg, within a 45-day period). Animals were sacrificed 2 days after last administration. Abdominal lavage was performed and the lavage fluid collected for gamma-ray analysis. Also collected for gamma-ray analysis were the following tissues/organs: ovaries, oviducts, uterus, and vagina with cervix. Cynomolgus female monkeys (n = 6) No test guideline study GLP: no	Only the samples containing vagina and cervix from the dosed monkeys contained varying quantities of talc. This demonstrates that no measurable quantities of talc, deposited by multiple applications in the vaginal fornix of the cynomolgus monkey, translocated to the uterus or beyond.	-	Wehner et al. (1986)
Other routes			
Intrapleural instillation of 10 or 20 mg talc (purity and particle size unspecified) Wistar rats (n = 20/group) Sacrificed 24 or 48 h after instillation No test guideline study GLP: no	Talc was rapidly absorbed upon intrapleural administration. 24 h after administration, talc was distributed systemically throughout the body and detected in the chest wall, lungs, heart, brain, spleen and kidneys. Polarised light revealed large numbers of irregular, strongly birefringence platy, acicular, and “Maltese Cross” crystals varying in length from 5.7-70 µm in the chest wall.	-	Werebe et al. (1999)
Intrapleural instillation of 40 mg talc (Steritalc, purity unknown, median particle size 31 µm)	Talc particles were observed in only a few organs (brain, spleen and liver, but not the kidneys)	-	Fraticelli et al. (2002)

Method	Results	Remarks	Reference
Wistar rats (n = 33/group) Sacrificed 24 or 72 h after instillation No test guideline study GLP: no	other than the lungs.		
Intrapleural instillation of 200 mg talc/kg bw (purity unknown, particle size: 8.4- or 12-µm talc) Sacrificed 24 h or 7 days after instillation New Zealand rabbits (n = 5/group, male) No test guideline study GLP: no	A tendency was seen for increased extrapulmonary distribution of the smaller particles, which were identified in the pericardium of 0/5 and 3/5 rabbits at 24 hours and 7 days, respectively. For the larger particles, one of five animals had talc in the pericardium at each time-point. Particles were identified in the liver of 3/5 animals exposed to the smaller particles 7 days after instillation; other groups had no particles in the liver. Small particles were found in the kidney of only 1/5 animals 24 hours after instillation. Both particle types were found in the spleen of 1/5 animals 24 hours after instillation. The results indicate that talc reached the lung parenchyma by breaking the mesothelial and elastic layer and that mobility was greater for the smaller particles.	-	Ferrer et al. (2002)
Intrapleural instillation of 50 or 200 mg talc /kg bw (purity unknown, particle size: 8.4-µm talc) Sacrificed 4 h, 1 day, 1 week or 1 month after instillation New Zealand rabbits (n = 5/group, male) No test guideline study GLP: no	The lung parenchyma of two and 14 rabbits of the low-dose and high-dose groups, respectively, contained talc. In the high-dose group, six of the animals had talc in the pericardium and five had talc in the liver; talc was not detected in these organs in the low-dose group. The results show that the systemic distribution of talc was dose-dependent.	-	Montes et al. (2003)
MMAD: median aerodynamic diameter			

9.1 Short summary and overall relevance of the provided toxicokinetic information on the proposed classification(s)

Animal studies

Inhalation is the main route of exposure to talc and the lungs the main target organ (Table 8). Upon inhalation, 6-8% of inhaled dose reached the alveoli, with a biological half-life of 7-10 days in Golden Syrian hamsters (Wehner et al. 1977b). Elimination of talc is predominately via the faeces (Wehner et al. 1977a; Phillips et al. 1978; Wehner et al. 1977b). Complete clearance from the

alveoli was reached 4 months after exposure via inhalation and no translocation of talc was observed into the liver, kidneys or ovaries (Wehner et al. 1977b). It is not believed that talc accumulates in the body. It is noted that the MMAD of talc particles used in the study of Wehner et al. (1977b) is large, possibly explaining the predominant excretion via faeces. The study is considered of limited reliability.

Oral exposure to talc is not of concern as no intestinal absorption or translocation of ingested talc to liver or kidneys was detected in rats, mice, guinea-pigs, rabbits and hamsters, using radioactive tracers (Wehner et al. 1977a; Phillips et al. 1978).

There are no toxicokinetic animal studies available for talc via the dermal route. According to the registrant in the online registration dossier, the permeability of talc to human skin is quite low as calculated by a QSAR model (DERMWIN v2.01 QSAR model); the permeability coefficient was 5.24×10^{-8} mg/cm^2, which is around 0.1% of the skin penetration rate.

No translocation of talc to the ovaries was reported upon intravaginal application in rabbits or monkeys (Phillips et al. 1978; Wehner et al. 1986). However, in rats, translocation of talc into the ovaries was noted upon instillation into the vagina after 4 days or after instillation into the uterus after 5 days (Henderson et al. 1986).

Ambiguous results are reported regarding distribution of talc upon intrapleural administration. Talc was detected in every organ of all animals in one study upon intrapleural administration through a catheter in rats (Werebe et al. 1999). However, talc particles were only observed in a few organs upon intrapleural administration in rats in another study (Fraticelli et al. 2002). In other studies a dose-dependent systemic distribution of talc and a tendency for increased extrapulmonary distribution of smaller talc particles were observed in rabbits (Ferrer et al. 2002; Montes et al. 2003).

Human studies

Talc may contain fibrous particles, according WHO definition[8], up to 30% of the total talc particulates as shown by x-ray diffraction, although minor amounts of other fibrous minerals (e.g. tremolite, anthophyllite, chrysotile and pyrophyllite) could be present (Cralley et al. 1968). Talc particles, especially fibrous talc, were found in bronchoalveolar lavage fluid upon occupational exposure to talc many years after last exposure and are thus highly biopersistent [(de Vuyst et al. 1987; Dodson et al. 1995; Gylseth et al. 1984; Johnson et al. 1986; Redondo et al. 1988; Gysbrechts et al. 1998) - adopted from MAK (2012)]. However, in some investigations no distinction between talc and anthophyllite could be made and thus co-exposure to anthophyllite should be assumed.

Talc particles were found in the uterus and the ovaries upon perineal application in multiple studies [(Wehner 2002; Whysner and Mohan 2000; Henderson et al. 1971; Chang and Risch 1997; Cramer et al. 1999; Johnson et al. 2020)]. Distribution of talc into the lung, spleen, kidney, liver, brain, retina adrenal and thyroid gland occurs after injection, as observed in drugs-addicts that use intravenous injection of drugs containing talc as filler [(AtLee 1972; Crouch and Churg 1983; Groth et al. 1972; Lamb and Roberts 1972) - adopted from NTP (1993)].

[8] WHO definition fibres: length to diameter ratio >3:1; length >5 µm; diameter <3 µm

10 EVALUATION OF HEALTH HAZARDS

10.1 Acute toxicity - oral route

Not evaluated in this dossier.

10.2 Acute toxicity - dermal route

Not evaluated in this dossier.

10.3 Acute toxicity - inhalation route

Not evaluated in this dossier.

10.4 Not evaluated in this dossier. Skin corrosion/irritation

Not evaluated in this dossier.

10.5 Serious eye damage/eye irritation

Not evaluated in this dossier.

10.6 Respiratory sensitisation

Not evaluated in this dossier.

10.7 Skin sensitisation

Not evaluated in this dossier.

10.8 Germ cell mutagenicity

Not evaluated in this dossier

10.9 Carcinogenicity

Table 9: Summary table of animal studies on carcinogenicity

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
Inhalation			
Similar to OECD TG 453 with deviations: there were difficulties maintaining control of chamber concentrations; week 11-18: too high concentrations in 18 mg/m^3 chamber (30 to 40 mg/m^3); week	MP10-52 grade talc aerosols (≥96% talc, free of asbestos, virtually free of silica, 0.2-1.2% absorbed water, 1.0% iron, 0.5-0.7% aluminium,	*Non neoplastic effects:* Survival and number of deaths of exposed male and female rats were similar to that of the controls. Body weight was reduced in female rats (6/18 mg/m^3: -3/-14%), no significant body weight changes were noted in males. Details on haematology, clinical chemistry, urinalysis and food/water consumption were not reported. Lung burden data suggest that either clearance of talc was not substantially impaired by increasing the exposure concentration, or that clearance of talc was impaired similarly at both exposure levels. Viability (0, 6, 18	NTP (1993)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
70-82: too low concentrations in all exposure chambers. F344/N rats (n = 50/group/sex, satellite group of 22/group/sex for measurements on lung) GLP RL 1	0.35-0.5% fluorine, other impurities ≤0.1%) 0, 6 or 18 mg/m^3 (MMAD 2.7 and 3.2 µm, resp.; GSD 1.9 µm) Whole body, 6 h per day, 5 days per week Lifetime study *See Annex I for more details*	mg/m^3 male: 64%, 67%, 58%; female: 83%, 75%, 61%) and phagocytic activity (male: 83%, 63%, 65%; female: 76%, 67%, 70%) of macrophages recovered from lavage fluid were not statistically significantly affected in any dose group after 24 months. Lung: incidences of granulomatous inflammation (average severity minimal to moderate; 0, 6, 18 mg/m^3 male: 2/49, 50/50**, 49/50**; female: 2/50, 47/48**, 50/50**), peribronchial hyperplasia (minimal to mild; male: 0/49, 12/50**, 8/50**; female: 0/50, 8/48**, 9/50**), alveolar epithelial hyperplasia (minimal to mild; male: 5/49, 26/50**, 38/50**; female: 2/50, 27/48**, 47/50**) and interstitial fibrosis (minimal to mild; male: 1/49, 16,50**, 33/50**; female: 1/50, 24/48**, 45/50**) were increased in all exposed rats at final sacrifice. In females, an increases in alveolar squamous metaplasia (minimal; 0/50, 0/48, 8/50**) and squamous cysts (0/50, 1/48, 7/50**) were noted at the highest dose. Adrenal Medulla: no increased incidence of hyperplasia in the adrenal medulla observed in exposed males (0, 6, 18 mg/m^3: 20/49, 8/48**, 9/47*) or females (22/48, 20/47, 16/49) compared to controls at final sacrifice. Absolute and relative lung weights were increased, at the end of the study (6/18 mg/m^3 vs. control, males: 110/220%**, females: 193*/292%**). *Neoplastic effects:* A statistically significantly increased incidence of lung cancer was observed in females; alveolar/bronchiolar adenoma (0, 6, 18 mg/m^3: 1/50, 0/48, 9/50**), alveolar/bronchiolar carcinoma (0/50, 0/48, 5/50*), alveolar/bronchiolar adenoma or carcinoma (1/50, 0/48, 13/50**). No statistically significantly increased incidence of lung cancer was noted in males; alveolar/bronchiolar adenoma (0/49, 1/50, 1/50), alveolar/bronchiolar carcinoma (0/49, 0/50, 1/50), alveolar/bronchiolar adenoma or carcinoma (0/49, 1/50, 1/50). In both males and females, a statistically significantly increased incidence of adrenal medulla pheochromocytoma was noted; benign (male: 25/49, 30/48, 36/47**; female: 13/48, 14/47, 18/49), malignant (male: 3/49, 3/48, 7/47; female: 0/48, 1/47, 10/49**), complex (male: 0/49, 2/48, 1/47; female: 0/48, 0/47, 0/49), benign, malignant or complex (male: 26/49, 32/48, 37/47**; female: 13/48, 14/47, 23/49*).	
No test guideline study. Limitations: description of materials, methods and results is	Italian talc (00000 grade, 40% as respirable (not specified) dust, 92% talc; 0.5-1% quartz, mean	*Non neoplastic effects:* Survival of exposed rats (6 and 12 months group combined: 24/48) were similar to the control group (27/48). *Neoplastic effects:* No lung neoplasms were noted in the 6-month and control group; one lung adenoma (1/24) was noted in the 12-month group.	Wagner et al. (1977)[9]

[9] Adopted from NTP (1993) and IARC (2010)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
minimal. Wistar rats (n = 12/group/sex) Predates GLP RL 3 (limited documentation, large particle size)	size 25 µm, upper particle size of 70 µm) 0 or 10.8 mg/m^3 Whole body, 7.5 h per day, 5 days per week for 6 or 12 months (cumulative exposures: 8200 and 16,400 mg/m^3 × h (resp.)) Ten days after the end of each exposure period rats were sacrificed or 1 year after the exposure had discontinued.		
Similar to OECD TG 453, with deviations: there were difficulties maintaining control of chamber concentrations in week 70-82 (below target concentrations in all exposure chambers). B6C3F$_1$ mice (n = 50/group/sex, satellite group of 40/group/sex for measurements on lung) GLP RL 1	MP10-52 grade talc aerosols (≥96% talc, free of asbestos, virtually free of silica, 0.2-1.2% absorbed water, 1.0% iron, 0.5-0.7% aluminium, 0.35-0.5% fluorine, other impurities ≤0.1%) 0, 6 or 18 mg/m^3 (MMAD 3.3 and 3.6 µm, resp.; GSD 1.9 and 2.0 µm, resp.) Whole body, 6 h per day, 5 days per week 2-year study *See Annex I for more details*	*Non neoplastic effects:* Survival and number of deaths of exposed males and females were similar to control. Details on haematology, clinical chemistry, urinalysis and food/water consumption were not reported. Lung burden data suggest that clearance of talc from the lung was impaired, or impaired to a greater extent, in mice exposed to 18 mg/m^3 than in mice exposed to 6 mg/m^3. Lung burden was disproportionately greater at 18 mg/m^3 in comparison to 6 mg/m^3 in mice, explained by the statistically significantly reduced phagocytic activity at 18 mg/m^3. *Neoplastic effects:* No statistically significant carcinogenic effects or differences were noted.	NTP (1993)
No test guideline	Talc-based baby powder	*Non neoplastic effects:* There were no significant differences among the survival times in exposed groups or compared to	Wehner et

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
study Golden Syrian hamsters (n = 25-50/group/sex) Predates GLP RL 3 (large MMAD)	(aerosols; 95% w/w, Vermont talc), whole body exposure Three groups were exposed to 37.1 mg/m^3, mean respirable fraction 9.8 mg/m^3, MMAD of 4.9 µm; 3, 30, or 150 min/day, 5 days/week, for 30 days. Two additional groups were exposed 27.4 mg/m^3, mean respirable fraction 8.1 mg/m^3, MMAD of 6.0 µm; for 30 or 150 min/day, for 300 days. The survivors in these two groups were killed at the age of 20 months. Two groups of 25 male and 25 female hamsters were exposed to air and served as controls. *See Annex I for more details*	control groups. A statistically significantly ($p < 0.05$) lower mean survival was noted in females in all groups compared to males. No clinical signs or body weight changes related to exposure were observed. *Neoplastic effects:* No primary neoplasms were found in the respiratory system of any hamster. A few neoplasms were noted at other sites (adrenal gland, uterus, thorax, bone, lymph node and liver), their incidence was not related to exposure.	al. (1977c)[10]
Oral			
No test guideline study. Limitations: description of materials, methods and results is minimal, limited exposure period and the advanced age of	Italian talc (00000 grade, 92% talc, 3% chlorite, 1% carbonate minerals, 0.5-1% quartz; mean size 25 µm), 0	*Non neoplastic effects:* The average survival in the control and exposed group was 641 and 614 days, respectively. *Neoplastic effects:* No differences in tumour incidence were noted between control and exposed group.	Wagner et al. (1977) [10]

[10] Adopted from IARC (2010)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
the animals at the start of the study. Wistar rats (n = 8-16/group/sex) Predates GLP RL 3 (limited documentation, large particle size)	or 100 mg/day in diet for 5 months (talc-containing diet was actually given for 101 days) and then basal diet for life		
No test guideline study Wistar rats (n = 25/group/sex) Predates GLP RL 4	Commercial talc (purity unknown), 0 or 50 mg/kg bw/day, in the diet for life Lifetime study	*Non neoplastic effects:* The average survival in the control and exposed group was 702 and 649 days, respectively. *Neoplastic effects:* No significant difference in tumour incidence was found in the exposed animals compared with the control animals.	Gibel et al. (1976)[10]
Dermal: no carcinogenicity (or chronic toxicity) animal studies available for dermal exposure.			
Perineal and intravaginal			
Perineal or intravaginal exposure Experimental study. Limitations: small number of animals, test period is not sufficient to study tumour development and possible infection of animals unrelated to talc exposure. Sprague-Dawley rats (n = 7/group, female) GLP not specified RL 2	Talc (purity unknown) 0 or 100 mg talc/day in saline via intravaginal (group 3) or perineal (group 4) application for 3 months Two control groups: no intervention (group 1) and intravaginal application of saline (group 2).	*Non neoplastic effects:* No body weight changes in talc-exposed animals compared to control groups. Evidence of foreign body reaction and infection (along with an increase in inflammatory cells), and genital infection (vulvovaginitis, endometritis, salpingitis and tubal occlusion ovarian and pelvic infection) were found in all rats exposed to talc (group 3 and 4). In the control groups, 1/7 had genital inflammation in group 1 and no genital inflammation was noted in group 2. *Neoplastic effects:* No neoplastic or preneoplastic changes were found in any group.	Keskin et al. (2009)
Ovary implantation Experimental study. Limitations: groups of animals implanted for 1, 3, 6 or 18 months were also included, but no results were reported for any of these	Italian talc implants (purity unknown, 00000 grade, size 0.3-14 µm) 0 or 10 mg per ovary (100 µl of 100 mg/ml solution in	*Non neoplastic effects:* Cystic appearance of the ovaries and associated tissue, 1-18 months after exposure. Small focal areas of papillary change that were considered to be preneoplastic changes were seen in the surface epithelium of 4/10 exposed animals compared to 0/6 in controls after 12 months. *Neoplastic effects:* No neoplasms were reported	Hamilton et al. (1984)[10]

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
groups. Sprague-Dawley rats (n = 3-10/group, female) GLP not specified RL 2	saline) Three sham-operated and three sham-exposed control animals were included. Animals were sacrificed 1, 3, 6, 12 and 18 months after implantation.		
Ovary implantation Experimental study. Limitations: no documentation on clinical signs, body weight, survival etc. Wistar rats (n = 7/group, female) GLP not specified RL 3	Talc (100 mg/kg bw) powder was inserted in an incision made in the right uterine horn. The substance was applied during the proliferative phase of the menstrual cycle of rats. No operation or application was performed in the control group. No sham-operated or exposed groups were included. Animals were sacrificed one month after application.	*Non neoplastic effects:* Gene expression levels of Gsr and Sod1 (markers for oxidative stress) were statistically significantly ($p < 0.05$), and gene expression levels of other antioxidant, antiapoptotic and apoptotic genes were changed, but not statistically significant. Expression levels related to antioxidant, antiapoptotic and apoptotic miRNA (miR-98, mi-R15b, miR-34b, miR-21) genes were all statistically significantly ($p < 0.05$) increased upon talc application compared to the control group. No information on body weight, survival, clinical signs or gross pathology was provided in this study.	Yumrutas et al. (2015)
Similar to OECD TG 453 Inhalation study but perineal exposure was assumed by the study authors, as talc was covering fur and the cage bars. F344/N female rats (n = 10/group) GLP	Same as NTP, 1993 MP10-52 grade talc 0, 6 or 18 mg/m^3 (inhalation) Whole body, 6 h per day, 5 days per week Lifetime study	*Non neoplastic effects:* There was no material consistent with talc found in the ovaries or ovarian bursa from any rats from any group. This would suggest that extensive lifetime exposure to talc does not results in the deposition of talc in the ovary. *Neoplastic effects:* No increased incidence of ovarian cysts, granulosa cell or theca tumours (malignant or benign) in exposed rats compared to the control group.	Boorman and Seely (1995)

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results**	**Reference**
RL 3 (original study RL 1, but in this study a different exposure is assumed and data published as conference paper)	*See Annex I for more details*		
Similar to OECD TG 453 Inhalation study but perineal exposure was assumed by the study authors, as talc was covering fur and the cage bars. B6C3F$_1$ mice (n = 10/group) GLP RL 3 (original study RL 1, but in this study a different exposure is assumed and data published as conference paper)	Same as NTP, 1993 MP10-52 grade talc 0, 6 or 18 mg/m^3 (inhalation) Whole body, 6 h per day, 5 days per week 2-year study *See Annex I for more details*	*Neoplastic effects:* No increased incidence of ovarian cysts, granulosa cell or theca tumours (malignant or benign) in exposed rats compared to the control group.	Boorman and Seely (1995)
Other exposure routes, less relevant to human, see Annex I			
GSD: geometric standard deviation; MMAD: mass median aerodynamic diameter Statistically significant vs. control, *$p \leq 0.05$, **$p \leq 0.01$			

Table 10: Summary table of human data on carcinogenicity

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td colspan="5">Occupational exposure – talc miners and millers</td></tr>
<tr><td>Retrospective cohort study

Limitations: no smoking data for exposed workers and unexposed controls. Lack of comparability between the workers and the comparison groups could influence the mortality ratio estimates of this study (IARC 2010).

1992 male talc workers (1514 miners, 478 millers) from Val Chisone (Piedmont), Italy.</td><td>Pure talc used for pharmaceutical and cosmetic industry. Also exposure to dusts containing high levels of respirable dust (respirable range 0.5 – 5 µm as defined by British Medical Research Council criteria; contained quartz[11]). Rock-type inclusions were removed before milling so that content had quartz <2%. Small amounts of tremolite detected. Respirable dust measurements, 1948–1974;</td><td>Employment ≥1 year in talc exposed job during 1921-1974; hired 1921-1950; mortality follow-up, 1921-1974
quantitative estimation of cumulative exposure for individual workers, expressed as summed product of duration (years) and exposure (mppcf);
classification of workers into 3 levels of exposure.
Vital status, 90%; cause of death: 95% of exposed workers, 95% of controls.

Risk ratios calculated using death rates from neighbouring rural population.

Adjusted for age; comparison with unexposed, age-matched controls from neighbouring rural town;
controls matched on vital status at date of entry into study;
miners and millers exposed to a very pure form of talc;
miners also exposed to
inhalable silica;
significantly elevated</td><td>No cases of lung mesothelioma and no relationship observed with increasing time between first exposure and death or with increasing cumulative exposure..

SMR of all cases combined was 0.9 (95% CI 0.8-1.0) for miners and millers.

<u>All cancers:</u>
<table>
<tr><th>Exposure category</th><th>No. of cases/deaths</th><th>SMR (95% CI)</th></tr>
<tr><td>All miners</td><td>100</td><td>0.8 (0.6–0.9)</td></tr>
<tr><td>All millers</td><td>42</td><td>0.9 (0.7–1.2)</td></tr>
<tr><td colspan="3">Miners (mppcf-years)</td></tr>
<tr><td>Level 1: 566–1699</td><td>38</td><td>1.2 (0.8–1.6
n = 405)</td></tr>
<tr><td>Level 2: 1700–5665</td><td>28</td><td>1.0 (0.7–1.4)
n = 423</td></tr>
<tr><td>Level 3: 5666–12750</td><td>34</td><td>0.9 (0.6–1.2)
n = 518</td></tr>
<tr><td colspan="3">Miners (latency, years)[a]</td></tr>
<tr><td><20</td><td>19</td><td>1.0 (0.5-1.4)</td></tr>
<tr><td>20-40</td><td>55</td><td>0.8 (0.6-0.9; $p < 0.01$)</td></tr>
<tr><td>>40</td><td>26</td><td>0.7 (0.4-1.0; $p < 0.05$)</td></tr>
<tr><td colspan="3">Millers (mppcf-years)</td></tr>
<tr><td>Level 1: 25–141</td><td>18</td><td>1.1 (0.2–3.2)
n = 163</td></tr>
</table></td><td>Rubino et al. (1976)[12]</td></tr>
</table>

[11] IARC (2010) noted that the term silica was in fact quartz

[12] Adopted from IARC (2010)

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td>SMRs for silicosis with and without tuberculosis among miners; estimates increased with increasing cumulative exposure; no observed cases of mesothelioma;
no smoking data for exposed workers or unexposed controls.</td><td>
<table>
<tr><td>Level 2: 142–424</td><td>13</td><td>1.3 (0–2.9)
n = 144</td></tr>
<tr><td>Level 3: 425–906</td><td>11</td><td>0.7 (0.4–2.7
n = 131)</td></tr>
<tr><td colspan="3">Millers (latency, years)[a]</td></tr>
<tr><td><20</td><td>8</td><td>0.9 (0.3-1.4)</td></tr>
<tr><td>20-40</td><td>24</td><td>0.9 (0.6-1.3)</td></tr>
<tr><td>>40</td><td>10</td><td>1.0 (0.4-1.6)</td></tr>
</table>
[a] 95% CI not determined in original study or IARC (2010)
<u>Malignant neoplasm lung, bronchus and trachea:</u>
<table>
<tr><td>Exposure category</td><td>No. of cases/deaths</td><td>SMR (95% CI)</td></tr>
<tr><td>All miners</td><td>9</td><td>0.5 (0.2–0.9)</td></tr>
<tr><td>All millers</td><td>4</td><td>0.6 (0.2–1.6)</td></tr>
<tr><td colspan="3">Miners (mppcf-years)</td></tr>
<tr><td>Level 1: 566–1699</td><td>3</td><td>1.1 (0.6–1.7)</td></tr>
<tr><td>Level 2: 1700–5665</td><td>1</td><td>0.5 (0.7–2.3)</td></tr>
<tr><td>Level 3: 5666–12750</td><td>5</td><td>1.1 (0.4–1.3)</td></tr>
<tr><td colspan="3">Miners (latency, years) [a]</td></tr>
<tr><td><20</td><td>1</td><td>0.7 (0-2.1)</td></tr>
<tr><td>20-40</td><td>6</td><td>0.4 (0.1-0.8; p < 0.01)</td></tr>
<tr><td>>40</td><td>2</td><td>0.5 (0-1.2)</td></tr>
<tr><td colspan="3">Millers (mppcf-years)</td></tr>
<tr><td>Level 1: 25–141</td><td>3</td><td>1.7 (0.3–4.9)</td></tr>
<tr><td>Level 2: 142–424</td><td>1</td><td>1.3 (0–7.0)</td></tr>
<tr><td>Level 3: 425–906</td><td>0</td><td>–</td></tr>
<tr><td colspan="3">Millers (latency, years) Error! Bookmark not defined.</td></tr>
<tr><td><20</td><td>-</td><td>-</td></tr>
</table>
</td><td></td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>20-40</td><td>1</td><td>0.7 (0-2.0)</td></tr>
<tr><td>>40</td><td>3</td><td>0.7 (0-1.4)</td></tr>
</table>
[a] 95% CI not determined in original study or IARC (2010)
</td><td></td></tr>
<tr><td>Retrospective cohort study

Limitations: national death rates were available from 1951 onwards.

1678 male talc workers (1260 miners, 418 millers) from Val Chisone (Piedmont), Italy.</td><td>Re-analysis, same as Rubino et al. 1976</td><td>Re-analysis, same exposure categories as Rubino et al. (1976)

SMRs recalculated using national death rates instead of comparison with neighbouring rural population; national death rates available only from 1951 onward; rates for 1951 were applied for 1946–50.</td><td>The age-standardised mortality for all causes combined was statistically significantly increased for miners (560 observed; SMR, 1.3; 95% CI, 1.2–1.4) as well as for millers (193 observed; SMR, 1.2; 95% CI, 1.0–1.4).

<u>Lung cancer:</u>
<table>
<tr><td>Exposure category</td><td>No. of cases/deaths</td><td>SMR (95% CI)</td></tr>
<tr><td>All miners</td><td>8</td><td>0.5 (0.2–0.9)</td></tr>
<tr><td>All millers</td><td>4</td><td>0.7 (0.2–1.7)</td></tr>
<tr><td colspan="3">Miners (mppcf-years)</td></tr>
<tr><td>Level 1: 566–1699</td><td>2</td><td>0.5 (0–1.9)</td></tr>
<tr><td>Level 2: 1700–5665</td><td>1</td><td>0.2 (0.5–1.2)[a]</td></tr>
<tr><td>Level 3: 5666–12750</td><td>5</td><td>0.6 (0.2–1.4)</td></tr>
<tr><td colspan="3">Millers (mppcf-years)</td></tr>
<tr><td>Level 1: 25–141</td><td>3</td><td>2.0 (0.4–5.8)</td></tr>
<tr><td>Level 2: 142–424</td><td>1</td><td>0.7 (1.7–3.7)[a]</td></tr>
<tr><td>Level 3: 425–906</td><td>0</td><td>–</td></tr>
</table>
[a] As adopted from IARC (2010), possibly a calculation error.</td><td>Rubino et al. (1979) [12]</td></tr>
<tr><td>Retrospective cohort study

Limitations: no smoking data for exposed workers. IARC noted that the results for respiratory cancer were not analysed by latency (IARC</td><td>The talc in this region is a mixture of pure talc, magnesite, chlorite and dolomite. Airborne dust samples and bulk materials were free of asbestiform and</td><td>Employed >1 year between 1940 and 1969; mortality follow-up: date of first radiogram, 12-month employment anniversary January 1940, whichever was later; follow-up through 1975; vital status: 99%; cause of</td><td>Increased risk of lung cancer in talc miners, but expected deaths were small and a possible role of co-exposure to radon for this cannot be excluded.

<u>All causes:</u>
<table>
<tr><td>Exposure category</td><td>No. of cases/deaths</td><td>SMR (95% CI)</td></tr>
<tr><td>Total cohort</td><td>90</td><td>1.2 (0.9-1.4)</td></tr>
</table></td><td>Selevan et al. (1979) [12]</td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr>
<td>2010).

392 male talc workers (163 miners, 225 millers) from Vermont, USA.</td>
<td>levels of respirable crystalline silica was <0.25% (defined as free silica)</td>
<td>death: 94%

To calculate risk ratios, mortality rates from Vermont were used for NMRDs and respiratory cancer. For other causes of death, rates for the USA were used.

Historical insufficient information to calculate cumulative exposure histories; cohort classification based on work area. According to the authors, past exposure levels were far exceeding 20 mppcf for miners and millers.

Miners were also exposed to radon daughters (0.12-1 WL).

Adjusted for age, sex, race, calendar year; US death rates: 1940–1967; linear extrapolation for all causes of death: 1967–1969. Vermont death rates for specific causes of death: 1949–1975; workers selected from annual radiographic survey of dusty trades; no data on smoking habits for millers or miners; exposure to radon daughters in mine; radiographic evidence of pneumoconiosis in most workers who died from NMRD.</td>
<td>
<table>
<tr><td>Millers</td><td>44</td><td>1.2 (0.9-1.6)</td></tr>
<tr><td>Miners</td><td>34</td><td>1.3 (0.9-1.8)</td></tr>
</table>
<u>All cancers:</u>
<table>
<tr><th>Exposure category</th><th>No. of cases/deaths</th><th>SMR (95% CI)</th></tr>
<tr><td>Total cohort</td><td>16</td><td>1.3 (0.7-2.0)</td></tr>
<tr><td>Millers</td><td>5</td><td>0.8 (0.3-1.9)</td></tr>
<tr><td>Miners</td><td>7</td><td>1.7 (0.7-3.5)</td></tr>
</table>
<u>Respiratory cancer:</u>
<table>
<tr><th>Exposure category</th><th>No. of cases/deaths</th><th>SMR (95% CI)</th></tr>
<tr><td>Total cohort</td><td>6</td><td>1.6 (0.6-3.5)</td></tr>
<tr><td>Millers</td><td>2</td><td>1.0 (0.1–3.7)</td></tr>
<tr><td>Miners</td><td>5</td><td>4.3 (1.4–10.1),</td></tr>
</table>
</td>
<td></td>
</tr>
<tr>
<td>Retrospective</td>
<td>The talc of the area was</td>
<td>Workers active in 1949-1975 and >3</td>
<td>An increased mortality risk ratio for all cancers, lung and stomach cancers were</td>
<td>Katsnelson and</td>
</tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td>cohort study

Limitations: the IARC working group (2010) noted that the deaths observed among exposed workers included current and past workers but that the denominator comprised only currently employed persons. Observed numbers of deaths were not specified.

Male and female talc workers (numbers not specified) in a talc mine and mill in the former USSR</td><td>reported to contain no tremolite or fibrous materials and levels of quartz ranged from 0.2-1.6%.</td><td>year at the plant.

Matched control group were noncancer/nonworker deaths from the same town (number not specified).</td><td>noted in male and female talc workers.

<u>All cancers:</u>
<table><tr><th>Exposure category</th><th>Risk ratio</th></tr><tr><td>Males</td><td>5.1 ($p < 0.001$)</td></tr><tr><td>Females</td><td>6.4 ($p < 0.001$)</td></tr></table><u>Lung cancers:</u>
<table><tr><th>Exposure category</th><th>Risk ratio</th></tr><tr><td>Males</td><td>4.5 ($p < 0.02$)</td></tr><tr><td>Females</td><td>9.3 ($p > 0.05$)</td></tr></table><u>Stomach cancers:</u>
<table><tr><th>Exposure category</th><th>Risk ratio</th></tr><tr><td>Males</td><td>3.7 ($p < 0.02$)</td></tr><tr><td>Females</td><td>6.3 ($p < 0.05$)</td></tr></table></td><td>Mokronosova (1979) [12]</td></tr>
<tr><td>Retrospective cohort study

Limitations: limited documentation (e.g. smoking habits, no information on years of employment) available, observed and expected numbers of cause-specific deaths and associated relative risks were not given. The IARC Working Group noted the unconventional definition of the cohort and that causes of death were obtained differently for cases (from local</td><td>Pure talc, chlorite, dolomite, quartz (0.5-3%) and does not contain asbestos.</td><td>Workers that left employment between January 1945 and December 1981 and having worked ≥1 year.

256 were living, 209 had died and 5 were lost to follow-up; 192/204 with known occupational exposure had worked only at Luzenac.</td><td>No significant excess of mortality from cancer in general or specifically from respiratory and digestive cancers was found. No cases of mesothelioma were observed.</td><td>Leophonte et al. (1983) [12] and Leophonte and Didier (1990)</td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td>doctors, hospitals or families) and controls (from regional or national records)

470 talc workers available for study from Luzenac, France</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Retrospective cohort study

Limitations: no information on smoking habits for millers; smoking habits for miners above national average.

389 male talc workers (94 miners, 295 millers) in northern Norway.

National rates were used to calculate expected numbers of cancers and deaths.</td><td>According to the authors, Norwegian talc contains mainly pure talc and magnesite, and only trace quantities of quartz, tremolite and anthophyllite (optical and electron microscopy).

Millers worked mostly with talc from this mine (90%), but also with talc from India (10%). In addition to talc, dolomite and mica were also processed at the mill.</td><td>Employed >1 year in mine (1944-1972) or >2 years in mill (1935-1972); mortality and cancer incidence follow-up 1953-1987.

Workers were classified by total duration of employment in jobs with low, medium, high and unknown exposure.

Personal air samples collected in the early 1980s showed that total dust levels varied greatly by job category and workplace (mine, 0.9–97 mg/m^3; mill, 1.4–54 mg/m^3). Peak exposures occurred during drilling in the mine (319 mg/m^3) and in the store house in the mill (109 mg/m^3).

Samples contained <1% quartz (X-ray diffractometry) and low levels of radon daughters 1.5-7.5 pCi/L (0.02-0.08 WL) radon daughters.

Smoking habits were available for 63/94 miners and rates were above the</td><td>No association between lung cancer morbidity or respiratory disease mortality and exposure to non-asbestiform talc was found.

<u>All causes:</u>
<table>
<tr><th>Exposure category</th><th>No. of cases/deaths</th><th>SMR (95% CI)</th></tr>
<tr><td>Total cohort</td><td>117</td><td>0.8 (0.6–0.9)</td></tr>
<tr><td>Miners</td><td>27</td><td>0.8 (0.5–1.2)</td></tr>
<tr><td>Millers</td><td>90</td><td>0.7 (0.6–0.9)</td></tr>
</table>
<u>All cancers:</u>
<table>
<tr><th>Exposure category</th><th>No. of cases/deaths</th><th>SMR (95% CI)</th></tr>
<tr><td>Total cohort</td><td>26</td><td>0.8 (0.5–1.1)</td></tr>
<tr><td>Miners</td><td>9</td><td>1.3 (0.6–2.5)</td></tr>
<tr><td>Millers</td><td>17</td><td>0.6 (0.4–1.0)</td></tr>
</table>
<table>
<tr><th>Exposure category</th><th>No. of cases/deaths</th><th>SIR (95% CI)</th></tr>
<tr><td>Total cohort</td><td>46</td><td>0.9 (0.7–1.2)</td></tr>
<tr><td>Miners</td><td>15</td><td>1.4 (0.8–2.3)</td></tr>
<tr><td>Millers</td><td>31</td><td>0.8 (0.5–1.1)</td></tr>
<tr><td colspan="3">Years employed</td></tr>
<tr><td>1–4</td><td>11</td><td>1.1 (0.6–2.1)</td></tr>
<tr><td>5–19</td><td>19</td><td>0.8 (0.5–1.2)</td></tr>
<tr><td>>20</td><td>16</td><td>0.9 (0.5–1.5)</td></tr>
<tr><td colspan="3">Years since first employment</td></tr>
<tr><td>1–19</td><td>6</td><td>0.4 (0.2–0.9)</td></tr>
<tr><td>20–29</td><td>18</td><td>1.1 (0.7–1.8)</td></tr>
<tr><td>>30</td><td>22</td><td>1.1 (0.7–1.6)</td></tr>
</table></td><td>Wergeland et al. (1990)[12]</td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td>national average (76% smokers, 16% former smokers, 8% non-smokers). No information available for smoking habits for millers.

Adjusted for age, smoking (miners only); national death rates: 1953–1987; main minerals in mined talc deposit were talc and magnesite.</td><td>Lung cancers:
<table><tr><th>Exposure category</th><th>No. of cases/deaths</th><th>SIR (95% CI)</th></tr><tr><td>Total cohort</td><td>6</td><td>0.9 (0.3–2.0)</td></tr><tr><td>Miners</td><td>2</td><td>1.6 (0.2–5.7)</td></tr><tr><td>Millers</td><td>4</td><td>0.8 (0.2–2.0)</td></tr><tr><td colspan="3">Years employed</td></tr><tr><td>1–4</td><td>0</td><td>-</td></tr><tr><td>5–19</td><td>3</td><td>1.0 (0.2–3.0)</td></tr><tr><td>>20</td><td>3</td><td>1.0 (0.2–3.0)</td></tr><tr><td colspan="3">Years since first employment</td></tr><tr><td>1–19</td><td>2</td><td>1.1 (0.1–4.1)]</td></tr><tr><td>20–29</td><td>1</td><td>0.5 (1.3–2.8)[a]</td></tr><tr><td>>30</td><td>3</td><td>1.1 (0.2–3.2)</td></tr></table>[a] As adopted from IARC (2010), possibly a calculation error.

There were no observed cases of mesothelioma.

Stomach cancers:
<table><tr><th>Exposure category</th><th>No. of cases/deaths</th><th>SIR (95% CI)</th></tr><tr><td>Total cohort</td><td>6</td><td>1.1 (0.4–2.2)</td></tr><tr><td>Miners</td><td>3</td><td>2.5 (0.5–7.4)</td></tr><tr><td>Millers</td><td>3</td><td>0.7 (0.1–2.1)</td></tr><tr><td colspan="3">Years employed</td></tr><tr><td>1–4</td><td>2</td><td>2.0 (0.2–7.2)</td></tr><tr><td>5–19</td><td>2</td><td>0.8 (0.1–2.6)</td></tr><tr><td>>20</td><td>2</td><td>1.2 (0.1–4.3)</td></tr><tr><td colspan="3">Years since first employment</td></tr><tr><td>1–19</td><td>1</td><td>0.6 (1.4–3.1)[a]</td></tr><tr><td>20–29</td><td>2</td><td>1.1 (0.1–4.0)</td></tr><tr><td>>30</td><td>3</td><td>1.7 (0.3–4.8)</td></tr></table>[a] As adopted from IARC (2010), possibly a calculation error.

Other cancers:</td><td></td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td></td><td>Prostate (4 cases), SIR: 2.0 (95% CI, 0.6-5.2).</td><td></td></tr>
<tr><td>Retrospective cohort study

Limitations: information on smoking habits was available for only 52% of cases and 75% of controls, and that no specific informationwas given on the proportion of subjects alive among cases and controls at the date of interview.

1160 talc workers (1070 men, 90 women) from Luzenac, France</td><td>Pure talc, chlorite, dolomite, quartz (0.5-3%) and does not contain asbestos.</td><td>Employees were active in 1945 or hired during the period 1945-1994 and having worked ≥1 year.

Exposures assessed for case–control study; semi-quantitative, site-specific job exposure matrix based on personal dust measurements (1986 onwards) and subjective assessments by experienced workers; workers assigned to four categories of exposure: no exposure, ambient (<5 mg/m^3), medium (5–30 mg/m^3) and high (>30 mg/m^3); exposure prior to hiring also coded: none, probable exposure to quartz, certain exposure to quartz, exposure to other carcinogens.

Dust levels 1960s and 1970s generally high (ranging <5 to >30 mg/m^3). In 1990s, dust levels dropped to <5 mg/m^3.

Mortality of the cohort was evaluated from 1 January 1945 to 31 December 1996. Vital status was obtained from the local population register and national mortality files which also included information on cause</td><td>Mortality from lung cancer was non-significantly increased in subgroups of employees who were under 60 years of age, had a latency period of < 20 years or had a duration of employment of < 10 years. No increasing trend of incidences of lung cancer with increasing cumulative exposure to talc observed.

<u>All causes:</u>
<table>
<tr><th>Exposure category</th><th>No. of cases/deaths</th><th>SMR (95% CI)</th></tr>
<tr><td>Pre-1968 (male - national rates)</td><td>101</td><td>0.8 (0.6–1.0)</td></tr>
<tr><td>Post-1968 (male - national rates)</td><td>294</td><td>0.8 (0.7–0.9)</td></tr>
<tr><td>Post-1968 (male - regional rates)</td><td>294</td><td>0.9 (0.8–1.0)</td></tr>
<tr><td>Post-1968 (female - regional rates)</td><td>11</td><td>0.8 (0.4-1.4)</td></tr>
</table>
<u>All cancers (males):</u>
<table>
<tr><th>Exposure category</th><th>No. of cases/deaths</th><th>SMR (95% CI)</th></tr>
<tr><td>Post-1968 (regional rates)</td><td>80</td><td>1.0 (0.8–1.3)</td></tr>
</table>
<u>Lung cancers (males):</u>
<table>
<tr><th>Exposure category</th><th>No. of cases/deaths</th><th>SMR (95% CI)</th></tr>
<tr><td>Pre-1968 (regional rates)</td><td>1</td><td>0.3 (0.7-1.5)</td></tr>
<tr><td>Post-1968 (national rates)</td><td>21</td><td>0.9 (0.6–1.4)</td></tr>
</table></td><td>Wild (2000) [12]</td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr>
<td></td>
<td></td>
<td>of death, in most cases, for individuals who died after 1968.

Vital status 97%; cause of death: 74% pre-1968 and 98% post-1968.

Adjusted for age, sex, smoking, prior exposure to quartz (case–control study only); partial overlap of study population with Leophonte et al. (1983); extent of overlap unknown; national mortality rates applied pre- and post- 1968; regional mortality rates applied post-1968.</td>
<td>
<table>
<tr><td>Post-1968 (regional rates)</td><td>21</td><td>1.2 (0.8–1.9)</td></tr>
<tr><td>Men <60 years of age</td><td>7</td><td>2.0 (0.8–4.0)</td></tr>
<tr><td>Latency period <20 years</td><td>5</td><td>2.4 (0.8–5.6)</td></tr>
<tr><td>Duration of employment <10 years</td><td>8</td><td>2.1 (0.9–4.1)</td></tr>
</table>
<u>Stomach cancers (males):</u>
<table>
<tr><td>Exposure category</td><td>No. of cases/deaths</td><td>SMR (95% CI)</td></tr>
<tr><td>Post-1968 (national rates)</td><td>5</td><td>1.2 (0.4–2.8)</td></tr>
</table>
<u>Lung cancers (cumulative exposure, nested case-control study, males):</u>

Cumulative exposure estimates (mg/m^3–years) for individual workers. The cumulative exposure to talc dust was transformed into units of 100 years.mg/m^3. One unit is for instance obtained as 40 years at 2.5 mg/m^3 (low exposure), as 10 years of medium exposure, or as 2.5 years in a highly exposed job.
<table>
<tr><td>Exposure category</td><td>No. of cases</td><td>Odds ratio (95% CI)</td></tr>
<tr><td>Unexposed</td><td>6</td><td>1.0</td></tr>
<tr><td><100 mg/m^3–years</td><td>5</td><td>1.4</td></tr>
<tr><td>100–400 mg/m^3–years</td><td>6</td><td>2.2</td></tr>
<tr><td>400–800 mg/m^3–years</td><td>3</td><td>0.7</td></tr>
<tr><td>>800 mg/m^3–years</td><td>3</td><td>0.9</td></tr>
<tr><td>Per 100 mg/m^3–years</td><td>23</td><td>1.0 (0.9–1.1)</td></tr>
</table>
</td>
<td></td>
</tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td></td><td>Unadjusted odds ratio. No increasing trend with increasing cumulative exposure observed. Assumes a linear trend.</td><td></td></tr>
<tr><td>Retrospective cohort study

Limitations: limited information available on smoking habits for French cohort, see Wild (2000).

Male talc workers from Luzenac, France (site A; see Wild, 2000) and 542 male talc workers from 3 sites (site B, C and D) in Styrian Alps, Austria and talc workers from Luzenac, France (see Wild, 2000)</td><td>Talc from site A: as described under Wild (2000); site B: talc-chlorite mixture containing quartz (0.5-4%); site C: talc-dolomite aggregation (medium talc content 25%), containing quartz in the end products (<1%), singular parts in the mine, rich in dolomite (could contain 2–3% quartz); site D: an aggregation of more or less equal proportions of mica, chlorite, and quartz.</td><td>Austrian cohort: Employed >1 year during 1972-1995; mortality follow-up, 1972-1995; vital status: 97%;

Semi-quantitative, site-specific job exposure matrix based on personal dust measurements (1988–1992) and descriptions of workplaces from management and long- term workers; workers assigned to four categories of exposure: no exposure, ambient (<5 mg/m^3), medium (5–30 mg/m^3) and high (>30 mg/m^3); other exposures coded: quartz, other carcinogens, underground work.

French cohort as described under Wild (2000).

Nested case-control study: lung cancer, non- malignant respiratory disease; three randomly selected controls per case; lung cancer: 23 cases, 67 controls (France); 7 cases, 21 controls (Austria).

Cumulative exposure estimates (mg/m^3–years) assigned to individual workers by occupational physician using work</td><td>A small excess mortality from lung cancer observed in talc workers from both cohorts. No deaths from mesothelioma noted in both cohorts.

<u>All causes:</u>
<table><tr><th>Exposure category</th><th>No. of cases/deaths</th><th>SMR (95% CI)</th></tr><tr><td>French cohort</td><td>294</td><td>0.9 (0.8–1.0)</td></tr><tr><td>Austrian cohort</td><td>67</td><td>0.8 (0.6–1.0)</td></tr></table>
<u>All cancers:</u>
<table><tr><th>Exposure category</th><th>No. of cases/deaths</th><th>SMR (95% CI)</th></tr><tr><td>French cohort</td><td>80</td><td>1.0 (0.8–1.3)</td></tr><tr><td>Austrian cohort</td><td>17</td><td>0.7 (0.4–1.2)</td></tr></table>
<u>Lung cancers:</u>
<table><tr><th>Exposure category</th><th>No. of cases/deaths</th><th>SMR (95% CI)</th></tr><tr><td>French cohort</td><td>21</td><td>1.2 (0.8–1.9)</td></tr><tr><td>Austrian cohort</td><td>7</td><td>1.1 (0.4–2.2)</td></tr></table>
<u>Stomach cancers:</u>
<table><tr><th>Exposure category</th><th>No. of cases/deaths</th><th>SMR (95% CI)</th></tr><tr><td>French cohort</td><td>5</td><td>1.2 (0.4–2.8)</td></tr><tr><td>Austrian cohort</td><td>1</td><td>0.4 (0–2.3)</td></tr></table>
<u>Lung cancers (cumulative exposure,</u></td><td>Wild et al. (2002)[12]</td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td>histories abstracted from company records.

Adjusted for age, calendar year, smoking, exposure to quartz, exposure to other carcinogens, underground work (case–control study); study population overlaps with that of Wild (2000); French SMRs calculated by comparison with regional rates, 1968–1995; Austrian SMRs calculated by comparison with regional rates, 1972–1995; Austrian smoking information obtained from unpublished mortality studies on pneumoconiosis, from colleagues, from workers' compensation records; no missing information on smoking habits in Austrian cohort.</td><td><u>nested case-control study):</u>

Cumulative exposure estimates (mg/m^3–years) for individual workers. The cumulative exposure to talc dust was transformed into units of 100 years.mg/m^3. One unit is for instance obtained as 40 years at 2.5 mg/m^3 (low exposure), as 10 years of medium exposure, or as 2.5 years in a highly exposed job.

<table><tr><th>Exposure category</th><th>No. of cases</th><th>Odds ratio (95% CI)</th></tr><tr><td>Unexposed</td><td>9</td><td>1.0</td></tr><tr><td>≤100 mg/m^3–years</td><td>6</td><td>0.9</td></tr><tr><td>101–400 mg/m^3–years</td><td>7</td><td>1.1</td></tr><tr><td>401–800 mg/m^3–years</td><td>5</td><td>0.6</td></tr><tr><td>>801 mg/m^3–years</td><td>3</td><td>0.7</td></tr><tr><td>Per 100 mg/m^3–years</td><td>30</td><td>1.0 (0.9-1.1)</td></tr></table>
Unadjusted odds ratio; no trend observed with increasing cumulative exposure; trend not affected by adjusting for smoking, quartz exposure, underground work or by lagging the exposure estimate. Assumes a linear trend.</td><td></td></tr>
<tr><td>Retrospective cohort study

Limitations: limited data on smoking and lack of information on potential confounders (e.g. alcohol consumption).

1974 male talc workers from Val Chisone (Piedmont), Italy</td><td>Follow-up of Rubino et al. 1976 and 1979</td><td>Employed >1 year in mine or mill during 1946–1995; mortality follow- up, 1946–1995; loss to follow-up, 9%; analysis based on 1244 miners and 551 millers.

Detailed job histories from plant records; workers classified on basis of job held (miner versus miller), duration of exposure</td><td>No excess was found for total cancer mortality, nor mortality for lung cancer. No case of mesothelioma was reported.

<u>All causes:</u>

<table><tr><th>Exposure category</th><th>No. of cases/deaths</th><th>SMR (95% CI)</th></tr><tr><td>Total cohort</td><td>880</td><td>1.2 (1.1–1.3)</td></tr><tr><td>Miners</td><td>590</td><td>1.3 (1.2–1.4)</td></tr><tr><td>Millers</td><td>290</td><td>1.1 (1.0–1.2)</td></tr></table>
<u>All cancers:</u></td><td>Coggiola et al. (2003)[12]</td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td>(years) and time since first exposure (years).

In later years (not further specified), exposure levels to talc dusts were monitored and the values in the mine were between 0.5 and 2.5 mg/m^3, mean 1.1 mg/m^3 for respirable fraction (not specified) and 0.3–2.0 mg/m^3, mean 1.0 mg/m^3 for talc alone.

Adjusted for age, calendar period; study population overlaps with that of Rubino et al. (1976, 1979); national death rates used for pre-1970 period; rates for early 1950s used for 1946–1949; regional rates used for 1970–1995, except for cancers of oral cavity, oesophagus and suicide (regional rates unavailable, national rates used); no information on smoking habits; no variation in lung cancer by duration of exposure.</td><td>
<table>
<tr><th>Exposure category</th><th>No. of cases/deaths</th><th>SMR (95% CI)</th></tr>
<tr><td>Total cohort</td><td>185</td><td>1.0 (0.9–1.1)</td></tr>
<tr><td>Miners</td><td>130</td><td>1.1 (1.0–1.3)</td></tr>
<tr><td>Millers</td><td>55</td><td>0.9 (0.6–1.1)</td></tr>
<tr><td colspan="3">Years since first exposure (latency) for miners and millers</td></tr>
<tr><td><20</td><td>29</td><td>1.1 (0.8-1.6)</td></tr>
<tr><td>20–30</td><td>46</td><td>1.1 (0.8-1.5)</td></tr>
<tr><td>>30</td><td>110</td><td>0.9 (0.8-1.1)</td></tr>
</table>
<u>Lung cancers:</u>
<table>
<tr><th>Exposure category</th><th>No. of cases/deaths</th><th>SMR (95% CI)</th></tr>
<tr><td>Total cohort</td><td>44</td><td>0.9 (0.7–1.3)</td></tr>
<tr><td>Miners</td><td>33</td><td>1.1 (0.7–1.5)</td></tr>
<tr><td>Millers</td><td>11</td><td>0.7 (0.3–1.2)</td></tr>
<tr><td colspan="3">Years since first exposure (latency) for miners and millers</td></tr>
<tr><td><20</td><td>6</td><td>1.1 (0.4–2.3)</td></tr>
<tr><td>20–30</td><td>10</td><td>1.0 (0.5–1.8)</td></tr>
<tr><td>>30</td><td>28</td><td>0.9 (0.6–1.3)</td></tr>
</table>
<u>Oral cavity cancers:</u>
<table>
<tr><th>Exposure category</th><th>No. of cases/deaths</th><th>SMR (95% CI)</th></tr>
<tr><td>Total cohort</td><td>31</td><td>5.1 (3.5–7.3)</td></tr>
<tr><td>Miners</td><td>24</td><td>6.2 (3.9–9.1)</td></tr>
<tr><td>Millers</td><td>7</td><td>3.3 (1.3–6.9)</td></tr>
<tr><td colspan="3">Years since first exposure (latency) for miners and millers</td></tr>
<tr><td><20</td><td>7</td><td>7.4 (3.0-15.3)</td></tr>
<tr><td>20–30</td><td>7</td><td>4.5 (1.8-9.3)</td></tr>
<tr><td>>30</td><td>17</td><td>4.8 (2.8-7.7)</td></tr>
</table>
<u>Oesophagus cancers:</u>
<table>
<tr><th>Exposure category</th><th>No. of cases/deaths</th><th>SMR (95% CI)</th></tr>
<tr><td>Total cohort</td><td>10</td><td>2.1 (1.1–3.9)</td></tr>
</table>
</td><td></td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>Miners</td><td>7</td><td>2.3 (0.9–4.8)</td></tr>
<tr><td>Millers</td><td>3</td><td>1.8 (0.4–5.2)</td></tr>
<tr><td colspan="3">Years since first exposure (latency) for miners and millers</td></tr>
<tr><td><20</td><td>2</td><td>3.0 (0.3-11.0)</td></tr>
<tr><td>20–30</td><td>6</td><td>5.2 (1.9-11.3)</td></tr>
<tr><td>>30</td><td>2</td><td>0.7 (0.1-2.5)</td></tr>
</table>
<u>Stomach cancers:</u>
<table>
<tr><td>Exposure category</td><td>No. of cases/deaths</td><td>SMR (95% CI)</td></tr>
<tr><td>Total cohort</td><td>31</td><td>1.2 (0.8–1.6)</td></tr>
<tr><td>Miners</td><td>20</td><td>1.2 (0.7–1.8)</td></tr>
<tr><td>Millers</td><td>11</td><td>1.1 (0.5–2.0)</td></tr>
<tr><td colspan="3">Years since first exposure (latency) for miners and millers</td></tr>
<tr><td><20</td><td>3</td><td>0.6 (0.1-1.8)</td></tr>
<tr><td>20–30</td><td>8</td><td>1.2 (0.5-2.3)</td></tr>
<tr><td>>30</td><td>20</td><td>1.3 (0.8-2.0)</td></tr>
</table>
</td><td></td></tr>
<tr><td>Retrospective cohort study

Limitations: limited data on smoking and lack of information on potential confounders (e.g. alcohol consumption).

1822 talc workers (1212 miners and 610 millers) from Val Chisone (Piedmont), Italy</td><td>Follow-up of Rubino et al. (1976 and 1979) and Coggiola et al. (2003)</td><td>Employed ≥1 month in mine or mill during 1946–1995; mortality follow- up, 1946–2013; loss to follow-up, 8%; analysis based on 1166 miners and 556 millers. The analyses was restricted to male workers, as only 2.0% (35/1757) of workers were female.

Exposure levels to dust and silica were higher in miners than millers. Average respirable (not specified) dust level similar in 2007-2014 per job category. Proportion silica over total dust starkly reduced in the mill plant from 1978</td><td>No association between exposure to talc, lung cancer and mesothelioma. No deaths observed from pleural cancer and no excess mortality for lung cancer.

<u>All causes:</u>
<table>
<tr><td>Exposure category</td><td>No. of cases/deaths</td><td>SMR (95% CI)</td></tr>
<tr><td>Total cohort</td><td>1084</td><td>1.2 (1.2-1.3)</td></tr>
<tr><td>Miners</td><td>731</td><td>1.3 (1.2-1.4)</td></tr>
<tr><td>Millers</td><td>353</td><td>1.1 (1.0-1.3)</td></tr>
</table>
<u>All cancers:</u>
<table>
<tr><td>Exposure category</td><td>No. of cases/deaths</td><td>SMR (95% CI)</td></tr>
<tr><td>Total cohort</td><td>277</td><td>1.0 (0.9-1.2)</td></tr>
<tr><td>Miners</td><td>193</td><td>1.1 (1.0-1.3)</td></tr>
<tr><td>Millers</td><td>84</td><td>0.9 (0.7-1.2)</td></tr>
</table>
</td><td>Pira et al. (2017)</td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td>onwards in comparison to 1974. Average silica levels were below 0.025 mg/m^3 in miners and millers in the period of 2007-2014.

Detailed job histories from plant records; workers classified on basis of job held (miner versus miller), duration of exposure (years) and time since first exposure (years).

Adjusted for age, calendar period; study population overlaps with that of Rubino et al. (1976, 1979) and Coggiola et al. (2003); national death rates used for pre-1970 period; national death rates for early 1950s used for 1946–1949; regional rates used for 1970–2013, for cancers of oral cavity, oesophagus and suicide no regional rates were available and national rates were used instead for the whole study period.

Limited data available on smoking. Smokers in survey of 1993 (total of 200 workers): 47% of miners and 44% of millers. Smoking prevalence was similar to that of men in Italy in the mid-1990s. Smokers in survey of 2010 (total of 102 workers): 51% of</td><td>
<table>
<tr><td colspan="3">Years since first exposure (latency) for miners and millers</td></tr>
<tr><td><20</td><td>23</td><td>0.9 (0.5-1.3)</td></tr>
<tr><td>20–29</td><td>48</td><td>1.1 (0.8-1.4)</td></tr>
<tr><td>30-39</td><td>79</td><td>1.2 (0.9-1.5)</td></tr>
<tr><td>≥40</td><td>127</td><td>1.0 (0.9-1.2)</td></tr>
</table>
No linear trend observed (p = 0.60).

<u>Lung cancers:</u>
<table>
<tr><td>Exposure category</td><td>No. of cases/deaths</td><td>SMR (95% CI)</td></tr>
<tr><td>Total cohort</td><td>75</td><td>1.0 (0.8-1.3)</td></tr>
<tr><td>Miners</td><td>52</td><td>1.1 (0.8-1.4)</td></tr>
<tr><td>Millers</td><td>23</td><td>1.0 (0.6-1.4)</td></tr>
<tr><td colspan="3">Years since first exposure (latency) for miners and millers</td></tr>
<tr><td><20</td><td>5</td><td>0.8 (0.3-1.9)</td></tr>
<tr><td>20–29</td><td>9</td><td>0.8 (0.3-1.4)</td></tr>
<tr><td>30-39</td><td>21</td><td>1.1 (0.7-1.7)</td></tr>
<tr><td>≥40</td><td>40</td><td>1.2 (0.8-1.6)</td></tr>
</table>
No linear trend observed (p = 0.25).

<u>Oral and pharyngeal cancers:</u>
<table>
<tr><td>Exposure category</td><td>No. of cases/deaths</td><td>SMR (95% CI)</td></tr>
<tr><td>Total cohort</td><td>32</td><td>3.8 (2.6-5.4)</td></tr>
<tr><td>Miners</td><td>25</td><td>4.5 (2.9-6.7)</td></tr>
<tr><td>Millers</td><td>7</td><td>2.5 (1.0-5.1)</td></tr>
<tr><td colspan="3">Years since first exposure (latency) for miners and millers</td></tr>
<tr><td><20</td><td>2</td><td>2.0 (0.2-7.2)</td></tr>
<tr><td>20–29</td><td>6</td><td>3.3 (1.2-7.1)</td></tr>
<tr><td>30-39</td><td>18</td><td>7.2 (4.3-11.40</td></tr>
<tr><td>≥40</td><td>6</td><td>2.0 (0.7-4.4)</td></tr>
</table>
No linear trend observed (p = 0.97).

<u>Oesophagus cancers:</u>
</td><td></td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td>total.</td><td>
<table>
<tr><td>Exposure category</td><td>No. of cases/deaths</td><td>SMR (95% CI)</td></tr>
<tr><td>Total cohort</td><td>14</td><td>2.1 (1.2-3.6)</td></tr>
<tr><td>Miners</td><td>11</td><td>2.6 (1.3-4.6)</td></tr>
<tr><td>Millers</td><td>3</td><td>1.3 (0.3-3.9)</td></tr>
<tr><td colspan="3">Years since first exposure (latency) for miners and millers</td></tr>
<tr><td><20</td><td>2</td><td>3.0 (0.4-10.8)</td></tr>
<tr><td>20–29</td><td>6</td><td>4.6 (1.7-10.0)</td></tr>
<tr><td>30-39</td><td>3</td><td>1.6 (0.3-4.6)</td></tr>
<tr><td>≥40</td><td>3</td><td>1.1 (0.2-3.3)</td></tr>
</table>
No linear trend observed (p = 0.075).
</td><td></td></tr>
<tr><td>Retrospective cohort study

Limitations: healthy worker effect and small cohort (low statistical power).

390 male talc workers (94 miners, 296 millers) in northern Norway

National rates were used to calculate expected numbers of cancers and deaths.</td><td>Follow-up of Wergeland et al. 1990</td><td>Employed >1 year in mine (1944-1972) or >2 years in mill (1944-1972); mortality and cancer incidence follow-up 1953-2011. None were lost to follow-up.

Workers were classified by total duration of employment in jobs with low, medium, high and not exposed. Smoking data: see Wergeland et al. 1990

Dust measurements in the mill from 1965 varied between 1.3 and 393.9 mppcf (<5 µm); bagging room: 28.2 mppcf; sieving: 150-200 mppcf. Exposure levels 10-20 times the current TLV (20 mppcf[13] or 6 mg/m^3 for talc dust <5 µm with <1% quartz) were</td><td>A slight increased SIR was observed for all cancers. The slightly elevated risk for lung cancer was not statistically significant. No case of mesothelioma or cancer of the pleura or the peritoneum was recorded.

<u>All causes:</u>
<table>
<tr><td>Exposure category</td><td>No. of cases/deaths</td><td>SMR (95% CI)</td></tr>
<tr><td>Total cohort</td><td>271</td><td>0.9 (0.8-1.0)</td></tr>
<tr><td>Miners</td><td>55</td><td>0.8 (0.6-1.1)</td></tr>
<tr><td>Millers</td><td>216</td><td>0.9 (0.8-1.0)</td></tr>
</table>
<u>All cancers:</u>
<table>
<tr><td>Exposure category</td><td>No. of cases/deaths</td><td>SMR (95% CI)</td></tr>
<tr><td>Total cohort</td><td>71</td><td>0.9 (0.7-1.2)</td></tr>
<tr><td>Miners</td><td>17</td><td>1.0 (0.6-1.7)</td></tr>
<tr><td>Millers</td><td>54</td><td>0.9 (0.7-1.2)</td></tr>
<tr><td colspan="3">Years employed and years since first employment <20</td></tr>
<tr><td><10</td><td>3</td><td>1.0 (0.2-2.9)</td></tr>
<tr><td>≥10</td><td>2</td><td>0.3 (0.0-1.2)</td></tr>
</table>
</td><td>Wergeland et al. (2017)</td></tr>
</table>

[13] See US OSHA https://www.osha.gov/chemicaldata/277

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td>described. A few samples contained more quartz (3-6%).

Personal air samples were collected in the early 1980s, as described by Wergeland et al. (1990).

Rate ratios were adjusted for age according to 10-year age bands.</td><td>
<table>
<tr><td colspan="3">Years employed and years since first employment >20</td></tr>
<tr><td><10</td><td>27</td><td>1.3 (0.8-1.9)</td></tr>
<tr><td>≥10</td><td>38</td><td>0.9 (0.6-1.2)</td></tr>
</table>
<table>
<tr><td>Exposure category</td><td>No. of cases/deaths</td><td>SIR (95% CI)</td></tr>
<tr><td>Total cohort</td><td>149</td><td>1.1 (0.9-1.3)</td></tr>
<tr><td>Miners</td><td>32</td><td>1.1 (0.7-1.5)</td></tr>
<tr><td>Millers</td><td>117</td><td>1.1 (0.9-1.3)</td></tr>
</table>
<u>Lung cancer:</u>
<table>
<tr><td>Exposure category</td><td>No. of cases/deaths</td><td>SMR (95% CI)</td></tr>
<tr><td colspan="3">Years employed and years since first employment <20</td></tr>
<tr><td><10</td><td>1</td><td>2.0 (0.0-11.4)</td></tr>
<tr><td>≥10</td><td>1</td><td>1.0 (0.0-5.3)</td></tr>
<tr><td colspan="3">Years employed and years since first employment >20</td></tr>
<tr><td><10</td><td>6</td><td>1.4 (0.5-2.9)</td></tr>
<tr><td>≥10</td><td>7</td><td>0.9 (0.4-1.8)</td></tr>
</table>
<table>
<tr><td>Exposure category</td><td>No. of cases/deaths</td><td>SIR (95% CI)</td></tr>
<tr><td>Total cohort</td><td>21</td><td>1.2 (0.7-1.8)</td></tr>
<tr><td>Miners</td><td>4</td><td>1.0 (0.3-2.7)</td></tr>
<tr><td>Millers</td><td>17</td><td>1.2 (0.7-1.9)</td></tr>
</table>
<u>Stomach cancer:</u>
<table>
<tr><td>Exposure category</td><td>No. of cases/deaths</td><td>SIR (95% CI)</td></tr>
<tr><td>Total cohort</td><td>10</td><td>1.2 (0.6-2.3)</td></tr>
<tr><td>Miners</td><td>3</td><td>1.7 (0.4-4.9)</td></tr>
<tr><td>Millers</td><td>7</td><td>1.1 (0.4-2.3)</td></tr>
</table>
<u>Colo-rectal cancer:</u>
<table>
<tr><td>Exposure category</td><td>No. of cases/deaths</td><td>SIR (95% CI)</td></tr>
</table>
</td><td></td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>Total cohort</td><td>30</td><td>1.6 (1.1-2.3)</td></tr>
<tr><td>Miners</td><td>6</td><td>1.5 (0.5-3.2)</td></tr>
<tr><td>Millers</td><td>24</td><td>1.6 (1.0-2.4)</td></tr>
</table>
<u>Bladder cancer:</u>
<table>
<tr><td>Exposure category</td><td>No. of cases/deaths</td><td>SIR (95% CI)</td></tr>
<tr><td>Total cohort</td><td>13</td><td>1.4 (0.7-2.3)</td></tr>
<tr><td>Miners</td><td>1</td><td>0.5 (0.0-2.7)</td></tr>
<tr><td>Millers</td><td>12</td><td>1.6 (0.8-2.8)</td></tr>
</table>
</td><td></td></tr>
<tr><td>Retrospective cohort study

Limitations: small cohort, lack of quantitative exposure data, lack of information on other employment and other potential occupational exposures, and the lack of information on other potential confounding or interactive factors, such as tobacco smoking

427 male talc workers (200 miners, 196 millers, 30 worked in mine and mill, and occupation for 1 unknown) from Vermont, USA.</td><td>Follow-up of Selevan et al. (1979)</td><td>Employed >1 year from 1930-1940 and from 1970-1983; mortality follow-up: through 2012; 80% of cohort was deceased; loss to follow-up, 5%; analysis based employees who worked exclusively as miners or millers.

In the publication of this study, US population mortality rates were used as reference.</td><td>No evidence of increased risk of respiratory cancer; a border-line nonsignificant excess of lung cancer was reported.

One case of mesothelioma noted in talc worker who also had been exposed to asbestos, following employment of 30 years or more.

<u>All causes:</u>
<table>
<tr><td>Exposure category</td><td>No. of cases/deaths</td><td>SMR (95% CI)</td></tr>
<tr><td>Total cohort</td><td>343</td><td>1.3 (1.2-1.5)**</td></tr>
<tr><td>Millers</td><td>162</td><td>1.4 (1.2-1.7)**</td></tr>
<tr><td>Miners</td><td>154</td><td>1.2 (1.0-1.4)*</td></tr>
</table>
<u>All cancers:</u>
<table>
<tr><td>Exposure category</td><td>No. of cases/deaths</td><td>SMR (95% CI)</td></tr>
<tr><td>Total cohort</td><td>70</td><td>1.0 (0.8-1.3)</td></tr>
<tr><td>Millers</td><td>34</td><td>1.1 (0.8-1.6)</td></tr>
<tr><td>Miners</td><td>28</td><td>0.8 (0.6-1.2)</td></tr>
</table>
*$p < 0.05$, **$p < 0.01$

<u>Lung, bronchus, trachea cancers:</u>
<table>
<tr><td>Exposure category</td><td>No. of cases/deaths</td><td>SMR (95% CI)</td></tr>
</table></td><td>Fordyce et al. (2019)</td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>Total cohort</td><td>32</td><td>1.4 (1.0-2.0)</td></tr>
<tr><td>Millers</td><td>14</td><td>1.4 (0.8-2.4)</td></tr>
<tr><td>Miners</td><td>14</td><td>1.3 (0.7–2.1)</td></tr>
<tr><td colspan="3">Latency period (years)</td></tr>
<tr><td>0-14</td><td>1</td><td>0.9 (0.0-4.9)</td></tr>
<tr><td>15-29</td><td>7</td><td>1.7 (0.7-3.5)</td></tr>
<tr><td>>30</td><td>24</td><td>1.4 (0.9-2.1)</td></tr>
</table>
</td><td></td></tr>
<tr><td>Retrospective cohort study

Limitations: limited data on smoking and lack of information on potential confounders (e.g. alcohol consumption).

1822 talc workers from Val Chisone (Piedmont), Italy</td><td>Follow-up of Rubino et al. (1976 and 1979), Coggiola et al. (2003) and Pira et al. (2017).

Talc was directly sampled from the mine before any cleaning and processing in the period 2017-2020. No detectable level of asbestos was measured using electron microscopy.</td><td>Employed ≥1 month in mine or mill during 1946–1995; mortality follow- up, 1946–2020; loss to follow-up, 5%; analysis based on 1184 miners and 565 millers. The analyses was restricted to male workers. Number of subjects included in this analysis was higher compared to previous analysis (n = 1722) as missing information on a few subjects were retrieved.

Detailed job histories from plant records; workers classified on basis of job held (miner versus miller), duration of exposure (years) and time since first exposure (years).

Adjusted for age, calendar period; study population overlaps with that of Rubino et al. (1976, 1979), Coggiola et al. (2003) and Pira et al. (2017); national death rates used for pre-1970 period;</td><td>No association was found between exposure to talc and lung cancer and mesothelioma. No deaths from pleural cancer observed. Excess mortality was also noted for liver cirrhosis in miners and millers (SMR 1.9; 95% CI 1.4-2.6 and SMR 1.8; 95% CI 1.1-2.7, respectively).

Oesophageal cancer was negatively associated with duration of employment.

<u>All causes:</u>
<table>
<tr><th>Exposure category</th><th>No. of cases/deaths</th><th>SMR (95% CI)</th></tr>
<tr><td>Total cohort</td><td>1174</td><td>1.2 (1.1-1.3)</td></tr>
<tr><td>Miners</td><td>789</td><td>1.3 (1.2-1.3)</td></tr>
<tr><td>Millers</td><td>385</td><td>1.3 (1.0-1.3)</td></tr>
</table>
<u>All cancers:</u>
<table>
<tr><th>Exposure category</th><th>No. of cases/deaths</th><th>SMR (95% CI)</th></tr>
<tr><td>Total cohort</td><td>304</td><td>1.0 (0.9-1.1)</td></tr>
<tr><td>Miners</td><td>205</td><td>1.0 (0.9-1.2)</td></tr>
<tr><td>Millers</td><td>99</td><td>1.0 (0.8-1.2)</td></tr>
<tr><td colspan="3">Duration of employment (years)</td></tr>
<tr><td><15</td><td>116</td><td>1.1 (0.9-1.3)</td></tr>
<tr><td>15-24</td><td>72</td><td>0.9 (0.7-1.2)</td></tr>
<tr><td>≥25</td><td>116</td><td>1.0 (0.8-1.2)</td></tr>
</table>
<u>Lung cancers:</u></td><td>Ciocan et al. (2022)</td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td>national death rates for early 1950s used for 1946–1949; regional rates used for 1970–2020; for the period 2015-2020 regional rates for 2015-2017 were used; for cancers of oral cavity, oesophagus and suicide no regional rates were available and national rates were used instead for the whole study period.

Limited data available on smoking, see Pira et al. (2017).</td><td>
<table>
<tr><th>Exposure category</th><th>No. of cases/deaths</th><th>SMR (95% CI)</th></tr>
<tr><td>Total cohort</td><td>85</td><td>1.0 (0.8-1.3)</td></tr>
<tr><td>Miners</td><td>56</td><td>1.0 (0.8-1.3)</td></tr>
<tr><td>Millers</td><td>29</td><td>1.1 (0.7-1.5)</td></tr>
<tr><td colspan="3">Duration of employment (years)</td></tr>
<tr><td><15</td><td>31</td><td>1.0 (0.7-1.5)</td></tr>
<tr><td>15-24</td><td>18</td><td>0.9 (0.5-1.4)</td></tr>
<tr><td>≥25</td><td>36</td><td>1.1 (0.8-1.6)</td></tr>
</table>
<u>Oral and pharyngeal cancers:</u>
<table>
<tr><th>Exposure category</th><th>No. of cases/deaths</th><th>SMR (95% CI)</th></tr>
<tr><td>Total cohort</td><td>34</td><td>3.7 (2.5-5.1)</td></tr>
<tr><td>Miners</td><td>25</td><td>4.1 (2.6-6.0)</td></tr>
<tr><td>Millers</td><td>9</td><td>2.9 (1.3-5.4)</td></tr>
<tr><td colspan="3">Duration of employment (years)</td></tr>
<tr><td><15</td><td>15</td><td>4.4 (2.5-7.3)</td></tr>
<tr><td>15-24</td><td>6</td><td>2.4 (0.9-5.3)</td></tr>
<tr><td>≥25</td><td>13</td><td>3.8 (2.0-6.4)</td></tr>
</table>
<u>Oesophagus cancers:</u>
<table>
<tr><th>Exposure category</th><th>No. of cases/deaths</th><th>SMR (95% CI)</th></tr>
<tr><td>Total cohort</td><td>14</td><td>1.9 (1.1-3.2)</td></tr>
<tr><td>Miners</td><td>11</td><td>2.3 (1.1-4.1)</td></tr>
<tr><td>Millers</td><td>3</td><td>1.2 (0.3-3.5)</td></tr>
<tr><td colspan="3">Duration of employment (years)</td></tr>
<tr><td><15</td><td>8</td><td>3.1 (1.4-6.2)</td></tr>
<tr><td>15-24</td><td>4</td><td>2.0 (0.6-5.2)</td></tr>
<tr><td>≥25</td><td>2</td><td>0.7 (0.1-2.6)</td></tr>
</table>
</td><td></td></tr>
<tr><td colspan="5">Occupational exposure – user industries</td></tr>
<tr><td>Nested case-control study

Limitations: no information on composition (e.g.</td><td>No information on composition or purity of talc.

Exposure to polycyclic</td><td>100 cases of stomach cancer, 4 controls per case; matched on age, race, sex, company; in period</td><td>A significant association between stomach cancer and exposure to talc materials. The incidence of stomach cancer was related to duration of exposure, and cases commonly were exposed 10 years earlier than the</td><td>Blum et al. (1979)[12]</td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td>asbestos) or purity of talc.

Cohort of 17000 workers in 2 rubber companies in the USA</td><td>hydrocarbons, nitrosamines, carbon black, talc (high, moderate, low, none) from job histories.</td><td>of 1964-1973</td><td>comparisons.

Increased risk was observed in one site only (company A). No clear elevation of odds ratio reported for other site (company B).

<u>Stomach cancer:</u>
<table><tr><td>Exposure category</td><td>No. of cases/deaths</td><td>Odds ratio (90% CI)</td></tr><tr><td>High + moderate talc</td><td>27</td><td>2.4 (1.4–4.1)</td></tr><tr><td>High talc</td><td>13</td><td>1.3 (0.9–2.5)</td></tr></table></td><td></td></tr>
<tr><td>Nested case-control study in cohort study of Langseth et al. (1999)

Limitations: recall bias (much more information about the cases was collected

from relatives than for the controls)</td><td>Exposure to asbestos, talc and total dust from work histories, questionnaires by industrial hygienists/ senior employees and international database; personal use of talc: 76% of cases, 57% of controls; personal interviews.</td><td>46 cases of ovarian cancer, 179 matched controls; 100% histologically confirmed.

Parity, breastfeeding, tobacco smoking habits, family history of breast or ovarian cancer; conditional logistic regression; odds ratios unchanged after adjustment for confounders.</td><td>Occupational exposure to talc or dust did not increase incidence of ovarian cancer, while asbestos did (not significant).

<u>Ovarian cancer:</u>
<table><tr><td>Exposure category</td><td>Odds ratio (95% CI)</td></tr><tr><td>Total dusts</td><td>0.8 (0.4-1.7)</td></tr><tr><td>Ever talc</td><td>1.1 (0.6-2.2)</td></tr><tr><td>Ever asbestos</td><td>2.0 (0.7-5.7)</td></tr><tr><td>Asbestos according to interview</td><td>2.2 (0.5-9.1)</td></tr></table></td><td>Langseth and Kjaerheim (2004)[12]</td></tr>
<tr><td>Retrospective cohort study

Limitations: no information available on smoking patterns in the cohort of pottery workers

2055 male workers in 5 ceramic plumbing fixture plants from 1 company in the USA</td><td>Talc (type not specified) but crystalline silica was the major exposure; also exposure to non-fibrous and fibrous talc</td><td>Workers employed >1 year in period 1936-1966; mortality follow-up 1936-1981; vital status 96%.

Exposure to silica and talc assessed qualitatively by job title–department by industrial hygienist</td><td>Significantly elevated frequency of lung cancer occurred among male workers in the manufacture of ceramic plumbing fixtures in a preliminary investigation.

Exposure to nonfibrous talc is related to excess lung cancer; however, the role of silica as cofactor or a promoting agent cannot be ruled out.

<u>All causes:</u>
<table><tr><td>Exposure category</td><td>No. of cases/deaths</td><td>SMR (95% CI)</td></tr><tr><td>Total cohort</td><td>587</td><td>0.9 (0.8-1.0)*</td></tr></table>*$p < 0.05$

<u>Lung cancer:</u></td><td>Thomas and Stewart (1987); Thomas (1982) [12]</td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>Exposure category</td><td>No. of cases/deaths</td><td>SMR (95% CI)</td></tr>
<tr><td>Total cohort</td><td>52</td><td>1.4 (1.1-1.9)*</td></tr>
<tr><td colspan="3">Duration (years) of exposure to nonfibrous talc in pottery workers 1940-1980</td></tr>
<tr><td><5</td><td>2</td><td>1.0</td></tr>
<tr><td>5-14</td><td>11</td><td>2.8*</td></tr>
<tr><td>>15</td><td>8</td><td>3.6*</td></tr>
<tr><td colspan="3">Years since first exposure (latency) to nonfibrous talc in pottery workers 1940-1980</td></tr>
<tr><td><5</td><td>0</td><td>-</td></tr>
<tr><td>5-14</td><td>8</td><td>2.8*</td></tr>
<tr><td>>15</td><td>13</td><td>2.8*</td></tr>
</table>
*$p < 0.05$
<table>
<tr><td>Exposure category</td><td>No. of cases/deaths</td><td>SMR (95% CI)</td></tr>
<tr><td>High silica</td><td>44</td><td>1.8 (1.3-2.4)*</td></tr>
<tr><td>High silica+non-fibrous talc</td><td>21</td><td>2.5 (1.6-3.9)*</td></tr>
<tr><td>High silica+non-fibrous talc+fibrous talc</td><td>5</td><td>1.7 (0.6-4.0)</td></tr>
<tr><td>High silica+no talc</td><td>18</td><td>1.4 (0.8-2.2)</td></tr>
</table>
*$p < 0.05$
</td><td></td></tr>
<tr><td>Retrospective cohort study

Limitations: no information on composition (e.g. asbestos) or purity of talc.

11633 male workers in 5 rubber plants in Germany</td><td>No information on composition or purity of talc.

Exposure to dusts, carbon black and asbestos.</td><td>Workers employed >1 year; analyses performed in 8933 male blue-collar workers hired after 1950 and alive 1981; follow-up, 1981-1991; cause of death known for 97% of 1521 deceased.

Work histories</td><td>Excess mortality for stomach and lung cancer and employment in early production stages of rubber manufacturing.

<u>All causes:</u>
<table>
<tr><td>Exposure category</td><td>No. of cases/deaths</td><td>SMR (95% CI)</td></tr>
<tr><td>Total cohort</td><td>1520</td><td>1.0 (1.0-1.1)</td></tr>
</table>
<u>Lung cancer:</u></td><td>Straif et al. (1999)[12]</td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td>reconstructed from cost centre codes, and classified into six work areas.

SMRs calculated from national death rates.</td><td>
<table>
<tr><th>Exposure category</th><th>No. of cases/deaths</th><th>SMR (95% CI)</th></tr>
<tr><td>Total cohort</td><td>154</td><td>1.2 (1.0-1.4)</td></tr>
<tr><td>Work area: preparation of materials <1 year</td><td>105</td><td>1.1 (0.9-1.3)</td></tr>
<tr><td>Work area: preparation of materials ≥1 year</td><td>48</td><td>1.7 (1.2-2.2)</td></tr>
</table>
<u>Stomach cancer:</u>
<table>
<tr><th>Exposure category</th><th>No. of cases/deaths</th><th>SMR (95% CI)</th></tr>
<tr><td>Total cohort</td><td>44</td><td>1.2 (0.8-1.6)</td></tr>
<tr><td>Work area: preparation of materials <1 year</td><td>27</td><td>0.9 (0.6-1.4)</td></tr>
<tr><td>Work area: preparation of materials ≥1 year</td><td>17</td><td>1.9 (1.1-3.1)</td></tr>
</table>
</td><td></td></tr>
<tr><td>Retrospective cohort study

Limitations: no information on composition (e.g. asbestos) or purity of talc.

4247 female workers in 10 pulp and paper plants in Norway</td><td>Talc (used as filler) but the study authors noted that exposure to other substances (microbes, formaldehyde, asbestos and paper dust) may have contributed to increased risks observed.</td><td>Workers employed >1 year, 1920–1993; follow-up of cancer incidence, 1953–1993.

Comparison with 5-year age-specific rates in Norwegian women; cancer incidence from National Cancer Registry.</td><td>Increased risk of ovarian cancer was noted in women in Norway who worked in paper mills.

Short-term workers (employed <3 years) showed excess risk of lung and bladder cancer (SIR 3.0, 95% CI 1.3-5.9 and SIR 3.7, 95% CI 1.0-9.4, respectively).

<u>All cancers:</u>
<table>
<tr><th>Exposure category</th><th>No. of cases/deaths</th><th>SIR (95% CI)</th></tr>
<tr><td>Total cohort</td><td>380</td><td>1.2 (1.1-1.3)</td></tr>
</table>
<u>Ovarian cancer:</u>
<table>
<tr><th>Exposure category</th><th>No. of cases/deaths</th><th>SIR (95% CI)</th></tr>
<tr><td>Total cohort</td><td>37</td><td>1.5 (1.1-1.2)</td></tr>
<tr><td>Exposure ≥3 years</td><td>31</td><td>1.6 (1.1-2.3)</td></tr>
<tr><td>Age 25-35 years</td><td>6</td><td>8.0 (2.9-17.4)</td></tr>
</table>
</td><td>Langseth and Andersen (1999)[12]</td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>Paper mill workers</td><td>18</td><td>2.1 (1.3-3.4)</td></tr>
</table>
</td><td></td></tr>
<tr><td>Retrospective cohort study

Limitations: risk analyses that adjusted for estimates of exposure to asbestos were not presented.

Same as Straif et al. (1999)</td><td>Same as Straif et al. (1999)</td><td>Same as Straif et al. (1999) plus semi-quantitative cumulative exposure (low, medium, high) to asbestos, talc, nitrosamines, carbon black for 95% of cohort. Exposure levels were estimated by industrial hygienists. Asbestos was used in all five plants at least until the early 1980s

Exposure to talc classified in 3 categories: high (talc used as filler material and heavy used as antitacking material), moderate (moderate use of talc as antitacking material), and low (wet application of talc or no use of talc). Exposure was lagged 10 years to account for latency.</td><td>Increased lung, stomach and larynx cancer risks among rubber workers may be associated with exposure to talc. Workers were also exposed to asbestos and/or carbon black.

<u>All causes:</u>
<table>
<tr><th>Exposure category</th><th>No. of cases/deaths</th><th>SMR (95% CI)</th></tr>
<tr><td>Total cohort</td><td>1521</td><td>1.0 (1.0-1.1)</td></tr>
</table>
<u>All cancers:</u>
<table>
<tr><th>Exposure category</th><th>No. of cases/deaths</th><th>SMR (95% CI)</th></tr>
<tr><td>Total cohort</td><td>455</td><td>1.1 (1.0-1.2)</td></tr>
</table>
<u>Lung cancer:</u>
<table>
<tr><th>Exposure category</th><th>No. of cases/deaths</th><th>SMR (95% CI)</th></tr>
<tr><td>Total cohort</td><td>154</td><td>1.2 (1.0-1.4)</td></tr>
<tr><td></td><td></td><td>HRR (95% CI)</td></tr>
<tr><td>Talc low</td><td>87</td><td>1.0</td></tr>
<tr><td>Talc medium</td><td>41</td><td>1.1 (0.8-1.6)</td></tr>
<tr><td>Talc high</td><td>21</td><td>1.9 (1.1-3.1)</td></tr>
</table>
Low exposure group used as reference group. High: at least 10 years at the high exposure level; low: less than 0.5 year at the medium and high exposure levels (combined).

<u>Stomach cancer:</u>
<table>
<tr><th>Exposure category</th><th>No. of cases/deaths</th><th>SMR (95% CI)</th></tr>
<tr><td>Total cohort</td><td>44</td><td>1.2 (0.9-1.6)</td></tr>
<tr><td></td><td></td><td>HRR (95% CI)</td></tr>
<tr><td>Talc low</td><td>21</td><td>1.0</td></tr>
<tr><td>Talc medium</td><td>12</td><td>1.2 (0.6-2.4)</td></tr>
</table>
</td><td>Straif et al. (2000)[12]</td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>Talc high</td><td>11</td><td>4.3 (2.1-9.0)</td></tr>
</table>
Low exposure group used as reference group. High: at least 10 years at the high exposure level; low: less than 0.5 year at the medium and high exposure levels (combined).

<u>Larynx cancer:</u>
<table>
<tr><td>Exposure category</td><td>No. of cases/deaths</td><td>SMR (95% CI)</td></tr>
<tr><td>Total cohort</td><td>8</td><td>1.2 (0.5-2.3)</td></tr>
<tr><td></td><td></td><td>HRR (95% CI)</td></tr>
<tr><td>Talc low</td><td>3</td><td>1.0</td></tr>
<tr><td>Talc medium</td><td>2</td><td>2.8 (0.5-16.7)</td></tr>
<tr><td>Talc high</td><td>3</td><td>5.4 (1.1-27.0)</td></tr>
</table>
Low exposure group used as reference group. High: at least 10 years at the high exposure level; low: less than 0.5 year at the medium and high exposure levels (combined).

Adjusted risk ratios for estimates of exposure to asbestos were not presented.
</td><td></td></tr>
<tr><td colspan="5">Cosmetic use – case-control studies</td></tr>
<tr><td>Case-control study

Limitations: lack of information on duration and frequency of talc use. Participation rates among the controls were quite low (50%), although the authors noted in a secondary analysis that, when cases were matched to the first control selected (i.e. 100% participation), a positive association was</td><td>Talc powder use (purity unknown)</td><td>215 English-speaking Caucasian women aged 18-80 years; identified through pathology logs or tumour boards of 12 Boston hospitals; histological confirmation of diagnosis;

215 population-based controls identified through annual listings of names, ages and addresses of all Massachusetts residents; matched by age (±2 years), race, residence.

<u>Exposure assessment:</u> In-person interviews;</td><td>A statistically significant association between ovarian cancer and hygienic practices involving the use of talc on the perineum was reported.

<u>Epithelial ovarian cancer:</u>
<table>
<tr><td>Exposure category</td><td>No. of cases/deaths</td><td>Odds ratio (95% CI)</td></tr>
<tr><td>No perineal exposure</td><td>123</td><td>1.0</td></tr>
<tr><td>Any perineal exposure to talc (as dusting powder or on napkins)</td><td>92</td><td>1.6 (1.0–2.5)</td></tr>
<tr><td>As dusting powder on</td><td>32</td><td>3.3 (1.7–6.4)</td></tr>
</table>
</td><td>Cramer et al. (1982)[12]</td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td>also found (odds ratio, 2.44; P < 0.05).

215 women in Boston, MA, USA between 1978-1981;</td><td></td><td>information collected on medical history, menstrual and reproductive history, potential or definite exposure to talc.

<u>Adjustment for:</u>

Parity, menopausal status, religion, marital status, educational level, weight, age at menarche, exact parity, oral contraceptive use, postmenopausal use of hormones, tobacco smoking.</td><td><table><tr><td>perineum and sanitary napkins</td><td></td><td></td></tr></table>
Comments by IARC (2010): distribution of tumour histologies similar for exposed and unexposed cases; potential for talc exposure by way of contraceptives, pelvic surgery or perineal hygiene considered; no information on duration or frequency of talc use; low participation rates among controls (56% of cases matched with no refusals; 27% matched after 1 refusal; 17% matched after 2 or more refusals).</td><td></td></tr>
<tr><td>Case-control study

Limitations: small size and the low prevalence of genital use of talc, the lack of information on its duration and frequency and age at first use, the lack of control for other potential confounders and the increased potential for selection bias due to different interviewing protocols for cases and controls. No information was given in this brief report on the methods used in the analysis to control for confounding.

197 women in Washington, DC, USA between</td><td>Talc powder use (purity unknown)</td><td>135 incident cases treated at participating hospitals; 171 population-based controls; frequency-matched by age, race, hospital.

<u>Exposure assessment:</u>

Interviews to collect information on reproductive and sexual history, medical history, drug use and other exposures, exposure to talc categorised as ‘any’ or ‘genital’.

<u>Adjustment for:</u>

Age, race, pregnancy.</td><td>Data indicate no overall association between ‘any’ talc use and risk of ovarian cancer. However, a small group of women who specifically reported genital use of talc powders showed a non-significant excess relative risk for ovarian cancer.

<u>Epithelial ovarian cancer:</u>
<table><tr><th>Exposure category</th><th>No. of cases/deaths</th><th>Odds ratio (95% CI)</th></tr><tr><td>Any use of talc</td><td>67</td><td>0.7 (0.4-1.1)</td></tr><tr><td>Genital exposure to talc</td><td>7</td><td>2.5 (0.7-10.0)</td></tr></table>
Comments by IARC (2010): Questions on talc added after study began; no information on duration or frequency of exposure; no controlling for other potential confounders; potential for selection bias.</td><td>Hartge et al. (1983)[12]</td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td>1974-1977</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Case-control study

Limitations: lack of information on talc use

188 women in northern California, USA between 1983-1985</td><td>Talc powder (purity unknown)</td><td>188 incident cases diagnosed at 8 hospitals, aged 18–74 years; histological verification of diagnosis;

539 controls selected from women hospitalised for non-cancerous conditions (n = 280) or from the population using random digit-dialling (n = 259); matched by age (±5 years), race, hospital/date of admission (hospital controls) or telephone area code/prefix (population controls).

<u>Exposure assessment:</u>

Structured in-person interviews; information collected on medical history, menstrual and reproductive history, family history, environmental exposures (talc, coffee, alcohol, tobacco); talc exposure categorised by type of application, duration of use prior to tubal ligation or hysterectomy, frequency of use.</td><td>A non-statistically significant trend of increasing risk of epithelial ovarian cancer with increasing frequency of exposure, as measured in number of applications of talc to the perineum per month.

<u>Epithelial ovarian cancer:</u>
<table><tr><th>Type of application</th><th>No. of exposed cases</th><th>Odds ratio (95% CI)</th></tr><tr><td>Perineum only</td><td>22</td><td>1.5 (0.8–2.6)</td></tr><tr><td>Sanitary pads only</td><td>5</td><td>0.6 (0.2–1.8)</td></tr><tr><td>Diaphragm only</td><td>9</td><td>1.5 (0.6–3.6)</td></tr><tr><td>Any two</td><td>67</td><td>1.4 (0.9–2.0)</td></tr><tr><td>All three</td><td>1</td><td>0.4 (0.0–2.9)</td></tr></table>Adjustment for parity, oral contraceptive use

<table><tr><th>Duration of use (years)</th><th>No. of exposed cases</th><th>Odds ratio (95% CI)</th></tr><tr><td>None</td><td>103</td><td>1.0</td></tr><tr><td>1-9</td><td>34</td><td>1.6 (1.0–2.6)</td></tr><tr><td>≥10</td><td>50</td><td>1.1 (0.7–1.7)</td></tr></table>Adjustment for parity

<table><tr><th>Frequency of use</th><th>No. of exposed cases</th><th>Odds ratio (95% CI)</th></tr><tr><td>Never</td><td>97</td><td>1.0</td></tr><tr><td>1-20 times/month</td><td>41</td><td>1.3 (0.8–2.0)</td></tr><tr><td>≥20 times/month</td><td>44</td><td>1.5 (0.9–2.2)</td></tr><tr><td>30 times/month</td><td>-</td><td>1.3 (0.9–1.9)</td></tr></table>Adjustment for parity; p for trend: 0.19

Comments by IARC (2010): No trend of increasing risk with increasing duration of</td><td>Whittemore et al. (1988)[12]</td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td></td><td>exposure, as measured in years of talcum powder use on the perineum prior to tubal ligation or hysterectomy.</td><td></td></tr>
<tr><td>Case-control study

Limitations: limited information on talc use. As participation rates were not provided, the possibility of selection bias is difficult to evaluate. Although covariates such as oral contraceptive use or parity were available, it was not explicitly stated if they were evaluated.

235 women in London and Oxford, UK between 1978-1983</td><td>Talc powder (purity unknown)</td><td>235 incident cases from 15 hospitals, aged 65 years or under at diagnosis; diagnosed within 2 years of interview; histological confirmation of diagnosis;

451 hospital-based controls selected from same 15 hospitals; same age distribution as the cases.

<u>Exposure assessment:</u>

Interviewer-administered standard questionnaire; information obtained on reproductive and menstrual history, on exposure to exogenous oestrogens, cigarettes, talc; talc exposure categorised by frequency of use on perineum and whether it was used to store a diaphragm.

<u>Adjustment for:</u>

Age, socioeconomic status.</td><td>Women who reported talc use in the genital area more than once a week or daily had higher risks of ovarian cancer than women who used talc less frequently. The women were not asked how long they had been using talc. There was a borderline statistically significant trend of increasing risk with increasing frequency of talc use.

<u>Ovarian cancer:</u>
<table><tr><th>Frequency of use</th><th>No. of exposed cases</th><th>Odds ratio (95% CI)</th></tr><tr><td>Never</td><td>76</td><td>1.0</td></tr><tr><td>Rarely</td><td>6</td><td>0.9 (0.3–2.4)</td></tr><tr><td>Monthly</td><td>7</td><td>0.7 (0.3–1.8)</td></tr><tr><td>Weekly</td><td>57</td><td>2.0 (1.3–3.4)</td></tr><tr><td>Daily</td><td>71</td><td>1.3 (0.8-1.9)</td></tr></table>p for trend 0.05

There was no significant difference between the percentages of cases (86%) and controls (81 %) who had used and kept their diaphragm in talc.

Comments by IARC (2010): Participation rates not provided; questions on talc use added 3 months after start of study; data on talc exposure missing for 18 cases and 17 controls.</td><td>Booth et al. (1989)[12]</td></tr>
<tr><td>Case-control study

Limitations: incomplete information on powder use and its small size.

116 women in western Washington state,</td><td>Talc powder (purity unknown)</td><td>116 Caucasian women from 3 urban counties captured in Seattle- Puget Sound Cancer Surveillance System, aged 20–79 years; independent pathological review: 73% of total; histological agreement: 94% of</td><td>Perineal application of baby powder was not associated with altered risk of borderline ovarian tumours. However, perineal application of deodorizing powders alone or in combination with other talc-containing powders was associated with increased risk of ovarian tumours.

The authors reported no increase in risk with increasing number of days of powder</td><td>Harlow and Weiss (1989)[12]</td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td>USA between 1980-1985</td><td></td><td>reviewed cases; 158 white population-based controls selected by random-digit dialling; matched by age, county of residence.

<u>Exposure assessment:</u>

In-person interviews; information obtained on reproductive, sexual and medical histories, as well as perineal exposure to talc; talc exposure categorised as ‘any’ perineal use, by method of use, and by type of powder used.

<u>Adjustment for:</u>

Age, parity, use of oral contraceptives</td><td>use, although the data were not provided in the paper.

<u>Ovarian cancer:</u>

<table>
<tr><th>Exposure category</th><th>No. of exposed cases</th><th>Odds ratio (95% CI)</th></tr>
<tr><td>Any perineal exposure to powder</td><td>49</td><td>1.1 (0.7-2.1)</td></tr>
</table>

<table>
<tr><th>Type of powder</th><th>No. of exposed cases</th><th>Odds ratio (95% CI)</th></tr>
<tr><td>Corn-starch only</td><td>4</td><td>0.8 (0.2–3.8)</td></tr>
<tr><td>Baby powder only</td><td>18</td><td>0.8 (0.4–1.9)</td></tr>
<tr><td>Baby powder or combined use</td><td>22</td><td>0.9 (0.5–2.0)</td></tr>
<tr><td>Talc, unspecified (no combined use)</td><td>13</td><td>1.0 (0.4–2.4)</td></tr>
<tr><td>Deodorizing powder only</td><td>10</td><td>3.5 (1.2-28.7)</td></tr>
<tr><td>Deodorizing powder only or combined use</td><td>14</td><td>2.8 (1.1–11.7)</td></tr>
</table>

Comments by IARC (2010): Cases diagnosed with borderline (serous or mucinous) tumours; study limited by incomplete information on powder use and small size; no significant association between method of powder use and risk for borderline tumours.</td><td></td></tr>
<tr><td>Case-control study

Limitations: limited</td><td>Talc powder (purity unknown)</td><td>112 women from Beijing Cancer Registry, with a mean
age of 48.5 years;</td><td>An elevated risk was found in women with a history of long-term (>3 months) application of talc-containing dusting powder to the lower abdomen and perineum.</td><td>Chen et al. (1992)[12]</td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td>information on perineal use of talc, the lack of adjustment for other potential confounding variables, the small number of cases and the low prevalence of talc use.

112 women from Beijing, China between 1984-1986</td><td></td><td>confirmation of diagnosis by laparotomy and pathological examination in all cases; 224 population-based controls selected first on basis of area of residence of cases and then randomly from census lists of all women within 1 year of age of identified case; matched by age; mean age, 49.0 years

<u>Exposure assessment:</u>

Interviewer-administered questionnaire; information obtained on menstrual, obstetric, marital, medical, family and dietary histories as well as exposure to talc (perineally and occupationally); perineal exposure reported as yes/no

<u>Adjustment for:</u>

Education, parity</td><td><u>Epithelial ovarian cancer:</u>
<table><tr><th>Exposure category</th><th>No. of exposed cases</th><th>Odds ratio (95% CI)</th></tr><tr><td>Use on perineum or lower abdomen</td><td>7</td><td>3.9 (0.9–10.6)</td></tr></table>
Comments by IARC (2010): The Working Group noted the incomplete ascertainment of cases of ovarian cancer due to the nature of the cancer-reporting system in China, the large number of cases that were excluded due to death and the exclusion of controls who had a history of serious health problems (which may have resulted in selection bias) and the study limitations.</td><td></td></tr>
<tr><td>Case-control study

Limitations: purity and composition of talc unknown; often reported as baby powder

235 women in Boston, USA between 1984-1987</td><td>Talc powder (purity unknown)</td><td>235 white women from 10 hospitals in metropolitan Boston area, aged 18–76 years; independent pathological confirmation of diagnosis;
239 population-based controls randomly selected from town registers; matched by age (±2 years), race, precinct of residence; no history of bilateral oophorectomy
<u>Exposure</u></td><td>A life-time pattern of perineal talc use may increase the risk for epithelial ovarian cancer but is unlikely to be the aetiology for the majority of epithelial ovarian cancers.

<u>Ovarian cancer:</u>
<table><tr><th>Exposure category</th><th>No. of exposed cases</th><th>Odds ratio (95% CI)</th></tr><tr><td>Any perineal exposure to powder</td><td>114</td><td>1.5 (1.0–2.1)</td></tr><tr><td colspan="3">Method of application</td></tr><tr><td>Sanitary napkins or</td><td>9</td><td>1.1 (0.4–2.8)</td></tr></table></td><td>Harlow et al. (1992) [12]</td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td><u>assessment:</u>

In-person interviews; information collected on occupational history, medical and reproductive history, dietary history, tobacco smoking, hygienic practices including perineal exposure to talc; exposure to talc categorised by type of application, brand of powders, duration and frequency of use.
<u>Adjustment for:</u>
Parity, education, marital status, religion, use of sanitary napkins, douching, age, weight.</td><td>
<table>
<tr><td>underwear only</td><td></td><td></td></tr>
<tr><td>Partner or applications to diaphragm</td><td>20</td><td>1.2 (0.6–2.4)</td></tr>
<tr><td>Dusting on perineum</td><td>85</td><td>1.7 (1.1–2.7)</td></tr>
<tr><td colspan="3">Frequency (no. per month)</td></tr>
<tr><td>None</td><td>121</td><td>1.0</td></tr>
<tr><td><5</td><td>32</td><td>1.5 (0.8–2.7)</td></tr>
<tr><td>5–29</td><td>24</td><td>1.2 (0.6–2.2)</td></tr>
<tr><td>≥30</td><td>58</td><td>1.8 (1.1–3.0)</td></tr>
<tr><td>p for trend</td><td colspan="2">0.046</td></tr>
<tr><td colspan="3">Years of use</td></tr>
<tr><td>None</td><td>121</td><td>1.0</td></tr>
<tr><td><10</td><td>14</td><td>1.2 (0.5–2.6)</td></tr>
<tr><td>10-29</td><td>49</td><td>1.6 (1.0–2.7)</td></tr>
<tr><td>≥30</td><td>51</td><td>1.6 (1.0–2.7)</td></tr>
<tr><td>p for trend</td><td colspan="2">0.07</td></tr>
<tr><td>None</td><td>121</td><td>1.0</td></tr>
<tr><td><1000</td><td>18</td><td>1.3 (0.7–2.7)</td></tr>
<tr><td>1000-10,000</td><td>54</td><td>1.5 (0.9–2.4)</td></tr>
<tr><td>>10,000</td><td>42</td><td>1.8 (1.0–3.0)</td></tr>
<tr><td>p for trend</td><td colspan="2">0.09</td></tr>
</table>

<u>Per histologic subtype ovarian cancer[a]:</u>
<table>
<tr><th>Histology</th><th>No. of cases</th><th>Relative risk (95% CI)</th></tr>
<tr><td>Serous (borderline and invasive tumours)</td><td>60</td><td>1.4 (0.9–2.2)</td></tr>
<tr><td>Mucinous</td><td>17</td><td>1.2 (0.6–2.5)</td></tr>
<tr><td>Endometrioid</td><td>18</td><td>2.8 (1.2–6.4)</td></tr>
</table>
[a] Any or ever use of talc

Comments by IARC (2010): Odds ratio for women with >10,000 lifetime applications unchanged after excluding</td><td></td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td></td><td>applications that occurred after tubal ligation or hysterectomy (odds ratio, 1.7; 95% CI, 1.0–3.0); significant increase in odds ratio for women with >10,000 lifetime applications observed after excluding use of talc during non-ovulatory periods and after surgical sterilization (odds ratio, 2.8; 95% CI, 1.4–5.4).</td><td></td></tr>
<tr><td>Case-control study

Limitations: very small number of cases and controls, the broad definition of fibre exposure used in certain exposure variables and the limited information on perineal exposure to talc.

77 women in Baltimore, USA between 1981-1985</td><td>Talc powder (purity unknown)</td><td>77 women admitted to Johns Hopkins Hospital as in-patients for treatment or diagnosis; diagnosed within 6 months of admission; residents of the USA; pathological confirmation of diagnosis; 46 hospital-based controls selected from female in-patients with no gynaecological or malignant conditions; matched a posteriori by age (±5 years), race, closest date of diagnostic admission.

<u>Exposure assessment:</u>

Questionnaire administered by telephone and in the hospital; information collected on genital and respiratory exposure to fibre containing substances, such as talc; sources of genital exposure included contraceptive methods (diaphragm, condoms), dusting of perineum and sanitary products; sources of respiratory exposure included: use of face and/or</td><td>A long duration of genital fibre use (median duration, ≥ 37.4 years) was associated with a borderline significant increase in the risk for ovarian cancer (odds ratio, 2.4; 95% CI, 1.0–5.8) after adjustment for religion.

<u>Ovarian cancer:</u>
<table><tr><th>Exposure category</th><th>No. of exposed cases</th><th>Odds ratio (95% CI)</th></tr><tr><td>Genital fibre use</td><td>67</td><td>1.0 (0.2–4.0)</td></tr></table>Adjustment for parity.

<table><tr><th>Method of application</th><th>No. of exposed cases</th><th>Odds ratio (95% CI)</th></tr><tr><td>Diaphragm use with powder</td><td>14</td><td>3.0 (0.8–10.8)</td></tr><tr><td>Genital bath talc</td><td>22</td><td>1.7 (0.7–3.9)</td></tr><tr><td>Sanitary napkin with talc exposure</td><td>21</td><td>4.8 (1.3–17.8)</td></tr></table>Adjustment for parity and education.. No adjustment for highest weight, 1 year prior to diagnosis.

Comments by IARC (2010): Investigators encountered difficulty finding controls who met all of the matching criteria. For analysis, 46 matched sets, of which 31 sets had 2 cases and 1 control.</td><td>Rosenblatt et al. (1992)[12]</td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td>body powders; residential or occupational exposure to fibre-containing substances, such as talc, asbestos, fibreglass; estimation of ‘dose’ by adding number of years of exposure from all sources.</td><td></td><td></td></tr>
<tr><td>Case-control study

Limitations: low prevalence of perineal talc use.

189 women in Athens, Greece between 1989-1991</td><td>Talc powder (purity unknown)</td><td>189 women hospitalised for ovarian cancer surgery in 2 major cancer hospitals in Greater Athens, aged 75 years or under; histological confirmation of diagnosis; 200 hospital visitor controls (selected from visitors to patients hospitalised in the same wards as cases); not matched to cases by age.

<u>Exposure assessment:</u>

Questionnaire administered in hospital by medical residents; information collected on medical and reproductive histories, as well as personal, demographic and socioeconomic variables; qualitative assessment of talc exposure (yes/no use in the perineal region).

<u>Adjustment for:</u>

Age, education, weight, age at menarche, menopausal status,</td><td>There was no evidence that perineal application of talc was associated with increased risk. However, the frequency of reporting talc use was low in this study population.

<u>Epithelial ovarian cancer:</u>
<table><tr><th>Exposure category</th><th>No. of exposed cases</th><th>Odds ratio (95% CI)</th></tr><tr><td>No talc application in perineum</td><td>183</td><td>1.0</td></tr><tr><td>Talc application in perineum</td><td>6</td><td>1.1 (0.3-4.0)</td></tr></table>
Comments by IARC (2010): study is limited by very low prevalence of perineal talc use.</td><td>Tzonou et al. (1993)[12]</td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td>age at menopause, parity, age at first birth, smoking status, alcohol use, coffee consumption, use of analgesics, use of tranquilizers or hypnotics, use of hair dyes.</td><td></td><td></td></tr>
<tr><td>Case-control study

Limitations: restricted information on perineal use of talc Green et al. (1997).

824 incident cases in Queensland, New South Wales and Victoria in Australia between 1990-1993</td><td>Talc powder (purity unknown)</td><td>824 incident cases diagnosed and registered in all major gynaecological-oncology treatment centres in 3 states, aged 18–79 years; independent pathological confirmation of diagnosis;

860 population-based controls selected randomly from electoral rolls, stratified by age and geographical region.

Green et al. (1997) used the same number of cases but five fewer controls.

<u>Exposure assessment:</u>

Interviewer-administered standardised questionnaire in clinic (cases) or home (some cases, all controls); information collected on medical, reproductive, family and occupational histories, as well as dietary factors and history of talc use.

<u>Adjustment for:</u>

Parity; other potential</td><td>Use of talc was positively associated with occurrence of ovarian cancer according to Purdie et al. (1995).

Green et al. (1997) found an increased risk of ovarian cancer with peritoneal use of talc. However, neither duration of talc use nor age at first use were associated with risk for ovarian cancer (relative risks not provided).

<u>Epithelial ovarian cancer:</u>

<table><tr><th>Exposure category</th><th>No. of exposed cases</th><th>Odds ratio (95% CI)</th></tr><tr><td>Use of talc around the abdomen or perineum (Purdie et al. 1995)</td><td>467 (56.7%)</td><td>1.3 (1.0-1.5)</td></tr><tr><td>Peritoneal use of talc (Green et al. 1997)</td><td>467</td><td>1.3 (1.1-1.6)</td></tr></table>
Comments by IARC (2010): no comments</td><td>Purdie et al. (1995); Green et al. (1997) [12]</td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td>confounders, e.g. contraceptive use, also considered</td><td></td><td></td></tr>
<tr><td>Case-control study

Limitations: very sparse information on talc use and the unavailability of adjusted results for the association between use of talc and the risk for ovarian cancer.

200 incident cases in Israel between 1990-1993</td><td>Talc powder (purity unknown)</td><td>200 incident cases (164 invasive, 36 borderline) diagnosed and reported to Israel Cancer Registry, aged 36–64 years; histological confirmation of diagnosis;

408 population-based controls selected by random-digit dialling; matched by geographical area

<u>Exposure assessment:</u>

Interviewer-administered standard questionnaire; information collected on reproductive history, use of oral contraceptives and fertility drugs, exposure to talc; exposure to talc stratified into ‘never/seldom’, ‘moderate/a lot.’

<u>Adjustment for:</u>

No control for confounding.</td><td>The exposure of fertility drugs and risk of epithelial ovarian cancer was studied. Frequent use of talc was also examined. Risk of epithelial ovarian cancer was increased upon moderate or a lot of use of talc.

<u>Epithelial ovarian cancer:</u>
<table><tr><th>Exposure category</th><th>No. of exposed cases</th><th>Odds ratio (95% CI)</th></tr><tr><td>Use of talc moderate/a lot</td><td>21</td><td>[1.97] (p = 0.04)</td></tr></table>
Comments by IARC (2010): Study limited by the very sparse information and the unavailability of adjusted results.</td><td>Shushan et al. (1996)[12]</td></tr>
<tr><td>Case-control study

Limitations: lack of information on use of talc.

450 incident cases in metropolitan Toronto and southern Ontario, Canada between 1989-1992</td><td>Talc powder (purity unknown)</td><td>450 incident cases (primary, invasive and borderline); aged 35–79 years; histological confirmation of diagnosis; 564 population-based controls identified through provincial records of all homeowners, tenants and family members;</td><td>This investigation supports previous contentions that exposure to talc may increase risk of ovarian carcinoma.

<u>Ovarian carcinoma:</u>
<table><tr><th>Exposure category</th><th>No. of exposed cases</th><th>Odds ratio (95% CI)</th></tr><tr><td>Any exposure to talc</td><td>198</td><td>1.4 (1.1-1.9)</td></tr></table></td><td>Chang and Risch (1997)[12]</td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr>
<td></td>
<td></td>
<td>randomly selected from same residential area; matched by age within 15-year age groups.

<u>Exposure assessment:</u>

Interviewer-administered questionnaire; information collected on menstrual and reproductive history, use of hormones and oral contraceptives, and use of talc; exposure to talc categorised on basis of ‘any’ exposure, type of exposure, frequency and duration of perineal application.

<u>Adjustment for:</u>

Age at interview, duration of oral contraceptive use, parity (number of full-term pregnancies), duration of lactation per pregnancy, history of tubal ligation or hysterectomy, family history of breast or ovarian cancer.</td>
<td>
<table>
<tr><td colspan="3">Type of exposure</td></tr>
<tr><td>Sanitary napkins</td><td>51</td><td>1.3 (0.9-2.0)</td></tr>
<tr><td>After bathing</td><td>172</td><td>1.3 (1.0-1.7)</td></tr>
<tr><td colspan="3">Frequency of after-bath use (time/month)</td></tr>
<tr><td>None</td><td>-</td><td>1.0</td></tr>
<tr><td><10</td><td>76</td><td>1.8 (1.2-2.7)</td></tr>
<tr><td>10-25</td><td>54</td><td>1.1 (0.7-1.7)</td></tr>
<tr><td>>25</td><td>41</td><td>1.0 (0.6-1.5)</td></tr>
<tr><td>Per 10 applications per month</td><td>-</td><td>0.9 (.7-1.1)</td></tr>
<tr><td colspan="3">Duration of after-bath use (years)</td></tr>
<tr><td>None</td><td></td><td>1.0</td></tr>
<tr><td><30</td><td>60</td><td>1.7 (1.1–2.6)</td></tr>
<tr><td>30–40</td><td>71</td><td>1.4 (1.0–2.2)</td></tr>
<tr><td>>40</td><td>41</td><td>0.9 (0.5–1.4)</td></tr>
<tr><td>Per 10 years of use</td><td></td><td>1.1 (1.0–1.2)</td></tr>
</table>

<u>Per histologic subtype ovarian cancer[a]:</u>
<table>
<tr><th>Histology</th><th>No. of cases</th><th>Relative risk (95% CI)</th></tr>
<tr><td>Serous (borderline and invasive serous tumours)</td><td>254</td><td>1.3 (1.0–1.9)</td></tr>
<tr><td>Mucinous</td><td>80</td><td>1.6 (1.0–2.6)</td></tr>
<tr><td>Endometrioid</td><td>74</td><td>1.7 (1.0–2.8)</td></tr>
</table>
[a] Any or ever use of talc

Comments by IARC (2010): Authors do not specify whether cases were identified through a cancer registry or some other reporting mechanism. Borderline significant trend observed with increasing duration of exposure to talc, but not with increasing frequency of exposure.
</td>
<td></td>
</tr>
<tr>
<td>Case-control study</td>
<td>Talc powder (purity</td>
<td>313 incident cases (234 invasive, 79</td>
<td>There was a suggestion of an elevated risk associated with any use of talcum powder</td>
<td>Cook et al. (1997)[12]</td>
</tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr>
<td>Limitations: relatively low participation rates among the cases and controls.

313 incident cases in Western Washington State, USA between 1986-1988</td>
<td>unknown)</td>
<td>borderline) identified from records of Cancer Surveillance System of western Washington; white residents of three counties (King, Pierce, Snohomish), aged 20–79 years; no information on whether diagnosis was histologically confirmed; 422 white population-based controls selected by random digit-dialling (part of a larger control pool for several studies of cancer in women); matched by age.

<u>Exposure assessment:</u>

Structured in-person interviews; information collected on medical and reproductive histories, smoking habits, birth control methods and use of genital powders and deodorant sprays (corn-starch, talcum powder, baby powder, deodorant powder and scented body/bath powder); exposure to genital powders assessed on the basis of ‘any’ lifetime exposure, method of use and cumulative lifetime exposure (days, months or lifetime applications).

<u>Adjustment for:</u>

Age</td>
<td>and bath/body powders.

<u>Ovarian cancer:</u>
<table>
<tr><th>Exposure category</th><th>No. of exposed cases</th><th>Odds ratio (95% CI)</th></tr>
<tr><td colspan="3">Lifetime perineal application</td></tr>
<tr><td>None</td><td>154</td><td>1.0</td></tr>
<tr><td>Any</td><td>159</td><td>1.5 (1.1–2.0)</td></tr>
<tr><td colspan="3">Exclusive use of</td></tr>
<tr><td>Talcum powder only</td><td>16</td><td>1.2 (0.6-2.5)</td></tr>
<tr><td>Baby powder only</td><td>31</td><td>1.4 (0.8-2.4)</td></tr>
<tr><td colspan="3">Use of[a]</td></tr>
<tr><td>Any talcum powder</td><td>33</td><td>1.6 (0.9-2.8)</td></tr>
<tr><td>Any baby powder</td><td>52</td><td>1.1 (0.7-1.8)</td></tr>
<tr><td colspan="3">Exclusive use of powder for</td></tr>
<tr><td>Perineal dusting</td><td>55</td><td>1.8 (1.2–2.9)</td></tr>
<tr><td>Diaphragm storage</td><td>22</td><td>0.8 (0.4–1.4)</td></tr>
<tr><td>Dusting sanitary napkins</td><td>12</td><td>1.5 (0.6–3.6)</td></tr>
<tr><td>Deodorant spray</td><td>18</td><td>1.5 (0.8–3.0)</td></tr>
<tr><td colspan="3">Any use of powder for[b]</td></tr>
<tr><td>Perineal dusting</td><td>95</td><td>1.6 (1.1–2.3)</td></tr>
<tr><td>Diaphragm storage</td><td>46</td><td>1.0 (0.6–1.6)</td></tr>
<tr><td>Dusting sanitary napkins</td><td>38</td><td>0.9 (0.5–1.5)</td></tr>
<tr><td>Deodorant spray</td><td>40</td><td>1.9 (1.1–3.1)</td></tr>
<tr><td colspan="3">Cumulative lifetime perineal dusting (days)[b]</td></tr>
<tr><td>None</td><td>154</td><td>1.0</td></tr>
<tr><td>≤2000</td><td>20</td><td>1.8 (0.9–3.5)</td></tr>
<tr><td>2001–5000</td><td>24</td><td>1.6 (0.9–2.9)</td></tr>
<tr><td>5001–10 000</td><td>21</td><td>1.2 (0.6–2.4)</td></tr>
</table>
</td>
<td></td>
</tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>>10 000</td><td>28</td><td>1.8 (0.9–3.4)</td></tr>
</table>
[a]Also adjusted for the other types of powders used (yes, no)
[b]Also adjusted for methods of genital powder application

<u>Per histologic subtype ovarian cancer[a]:</u>
<table>
<tr><th>Histology</th><th>No. of cases</th><th>Relative risk (95% CI)</th></tr>
<tr><td>Serous</td><td>131</td><td>1.7 (1.1–2.5)</td></tr>
<tr><td>Mucinous</td><td>43</td><td>0.7 (0.4–1.4)</td></tr>
<tr><td>Endometrioid</td><td>36</td><td>1.2 (0.6–2.3)</td></tr>
</table>
[a] Any or ever use of talc
A significant positive trend was noted for both duration (odds ratio, 2.7; 95% CI, 1.1–6.6 for > 12 cumulative lifetime months; p for trend < 0.05) and number of lifetime applications (odds ratio, 2.6; 95% CI, 0.9–7.6 for > 500 lifetime applications; p for trend < 0.05) of genital deodorant spray.
Comments by IARC (2010): none</td><td></td></tr>
<tr><td>Case-control study
Limitations: minimal information on talc use, the low questionnaire response rate among study participants, particularly among the patients with more advanced disease, the use of a self-administered questionnaire completed during the admissions process, which may have limited</td><td>Talc powder (purity unknown)</td><td>‘Study’ group: 50 women admitted for treatment of primary extra-ovarian peritoneal cancer to Roswell Park Cancer Institute; histological confirmation of diagnosis; ‘control’ group: 466 women treated for primary ovarian cancer at same centre; pathological review of diagnosis.
<u>Exposure assessment:</u>
Self-administered, 44-item questionnaire completed at hospital</td><td>Women who had primary ovarian cancer were significantly more likely to report a history of perineal use of talc compared with women who had primary peritoneal cancer (48.1% versus 26.0%; [crude odds ratio = 2.6] p = 0.003).
<u>Primary ovarian cancer:</u>
<table>
<tr><th>Exposure category</th><th>No. of exposed cases</th><th>Odds ratio (95% CI)</th></tr>
<tr><td>Perineal use of talc</td><td>224</td><td>2.6 [crude odds ratio]</td></tr>
</table>
Comments by IARC (2010): ‘cases’ for this study were women diagnosed with primary peritoneal cancers. Case definition excluded patients with diagnoses of peritoneal mesothelioma, borderline tumours of peritoneum or invasive ovarian cancer; no healthy controls enrolled in this</td><td>Eltabbakh et al. (1998)[12]</td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td>the quality of the responses, and the lack of a ‘healthy’ comparison group.

50 cases of primary extra-ovarian peritoneal carcinoma (the ‘study’ group) and 503 cases of primary epithelial ovarian cancer (the ‘control’ group) in Buffalo, NY, USA between 1982-1986</td><td></td><td>admission.

<u>Adjustment for:</u>

No control for confounding.</td><td>study. ‘Controls’ were women diagnosed with primary epithelial ovarian cancer. Control definition excluded patients with diagnoses of non-epithelial ovarian cancer and ovarian cancer secondary to metastases from other sites.</td><td></td></tr>
<tr><td>Case-control study

Limitations: small size and the lack of any detailed information on perineal use of talc. The control participation rates may have been low (although this is not clear) and it is not certain how representative the controls were.

170 incident cases from Montreal, Canada between 1995-1996</td><td>Talc powder (purity unknown)</td><td>170 incident cases with primary invasive or borderline epithelial tumours, identified at two gynaecological clinics, aged 20–84 years; histological confirmation of diagnosis; 170 population-based controls selected by a modified random-digit dialling method; frequency-matched by age (±1 year), French Canadian ethnicity.

<u>Exposure assessment:</u>

Standardised 57-item questionnaire; telephone or in-person interviews conducted with cases, no information on how controls were interviewed; qualitative assessment of perineal talc exposure (ever/never).</td><td>Perineal talc use was a nonsignificant risk factor in this study (relative risk 2.49, p = .064).

<u>Ovarian cancer:</u>
<table><tr><th>Exposure category</th><th>No. of exposed cases</th><th>Odds ratio (95% CI)</th></tr><tr><td>‘Ever’ use of talc on perineum</td><td>[18] (10.6%)</td><td>2.5 (0.9-6.6)</td></tr></table>
Comments by IARC (2010): none</td><td>Godard et al. (1998)[12]</td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td><u>Adjustment for:</u>
Age at menarche, age at menopause, parity, age at first and last childbirth, duration of oral contraceptive use, age at last oral contraceptive use, tubal ligation, alcohol use, previous breast or abdominal surgery.</td><td></td><td></td></tr>
<tr><td>Case-control study
Limitations: recall bias and bias from confounding
563 incident cases in eastern Massachusetts and New Hampshire, USA between 1992-1997</td><td>Talc powder (purity unknown)</td><td>563 incident cases (including borderline tumours) identified through hospital tumour boards or state-wide cancer registries; age range not provided; histological confirmation of diagnosis for all cases; 523 population-based controls selected by random-digit dialling and through annual listings of names, ages and addresses of all Massachusetts residents (women over the age of 60 years); frequency-matched by age (±4 years), location of residence.
<u>Exposure assessment:</u>
In-person interviews using standardised questionnaire; information collected on medical and reproductive histories, family history and personal habits; multiple questions on potential routes of talc exposure (non-genital, genital,</td><td>There is a significant association between the use of talc in genital hygiene and risk of epithelial ovarian cancer.
<u>Primary epithelial ovarian cancer:</u>
<table>
<tr><th>Exposure category</th><th>No. of exposed cases</th><th>Odds ratio (95% CI)</th></tr>
<tr><td>No genital exposure</td><td>411</td><td>1.0</td></tr>
<tr><td>Any genital exposure</td><td>152</td><td>1.6 (1.2–2.1)</td></tr>
<tr><td colspan="3">Method of use</td></tr>
<tr><td>No use</td><td>312</td><td>1.0</td></tr>
<tr><td>Non-genital areas</td><td>99</td><td>1.1 (0.8–1.5)</td></tr>
<tr><td>Dusting perineum</td><td>71</td><td>1.5 (1.0–2.2)</td></tr>
<tr><td>Dusting sanitary napkins</td><td>20</td><td>1.5 (0.7–3.1)</td></tr>
<tr><td>Dusting underwear</td><td>8</td><td>1.2 (0.4–3.6)</td></tr>
<tr><td>More than one method</td><td>53</td><td>2.2 (1.3–3.6)</td></tr>
<tr><td colspan="3">Frequency (uses/month)</td></tr>
<tr><td>None</td><td>312</td><td>1.0</td></tr>
<tr><td><30</td><td>64</td><td>2.2 (1.4–3.6)</td></tr>
<tr><td>30-39</td><td>59</td><td>1.7 (0.8–1.8)</td></tr>
<tr><td>≥40</td><td>23</td><td>1.7 (0.8–3.1)</td></tr>
<tr><td colspan="3">Duration of use (years)</td></tr>
<tr><td>None</td><td>312</td><td>1.0</td></tr>
<tr><td><20</td><td>55</td><td>1.9 (1.2–3.0)</td></tr>
</table></td><td>Cramer et al. (1999)[12]</td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr>
<td></td>
<td></td>
<td>husband's use), brands used, age at first use, duration and frequency of use.

<u>Adjustment for:</u>

Age, study site, parity, oral contraceptive use, body mass index, family history of breast or ovarian cancer, history of tubal ligation.</td>
<td>
<table>
<tr><td>20–30</td><td>32</td><td>1.3 (0.8–2.3)</td></tr>
<tr><td>>30</td><td>59</td><td>1.4 (0.9–2.3)</td></tr>
<tr><td colspan="3">Total no. of applications</td></tr>
<tr><td>None</td><td>312</td><td>1.0</td></tr>
<tr><td><3000</td><td>51</td><td>1.8 (1.1–3.0)</td></tr>
<tr><td>3000–10 000</td><td>36</td><td>1.4 (0.8–2.4)</td></tr>
<tr><td>>10 000</td><td>59</td><td>1.4 (0.9–2.2)</td></tr>
<tr><td>p for trend</td><td colspan="2">0.16</td></tr>
<tr><td colspan="3">Total no. of applications (censored analysis)[a]</td></tr>
<tr><td>None</td><td>312</td><td>1.0</td></tr>
<tr><td><3000</td><td>59</td><td>1.5 (1.0–2.4)</td></tr>
<tr><td>3000–10 000</td><td>51</td><td>1.7 (1.1–2.8)</td></tr>
<tr><td>>10 000</td><td>36</td><td>1.8 (1.0–3.2)</td></tr>
<tr><td>p for trend</td><td></td><td>0.02</td></tr>
</table>
[a] Excludes applications following hysterectomy or tubal ligation and applications during pregnancy and periods of oral contraceptives use. Includes non-genitally exposed.

<u>Per histologic subtype ovarian cancer[a]:</u>
<table>
<tr><th>Histology</th><th>No. of cases</th><th>Relative risk (95% CI)</th></tr>
<tr><td>Serous invasive</td><td>229</td><td>1.7 (1.2–2.4)</td></tr>
<tr><td>Mucinous</td><td>83</td><td>0.8 (0.4–1.4)</td></tr>
<tr><td>Endometrioid/clear cell</td><td>130</td><td>1.0 (0.7–1.6)</td></tr>
</table>
[a] Any perineal use of talc

Comments by IARC (2010): none
</td>
<td></td>
</tr>
<tr>
<td>Case-control study

Limitations: sparse information on talc use. In addition, the use of hospital controls with non-gynaecological malignancies may</td>
<td>Talc powder (purity unknown)</td>
<td>462 incident cases admitted for treatment of primary extra-ovarian peritoneal cancer to Roswell Park Cancer Institute, mean age, 54.9 years; histological confirmation of diagnosis; 693 hospital-based</td>
<td>A significant association between the use of talcum powder and the risk of developing epithelial ovarian cancer is not demonstrable, even with prolonged exposure.

<u>Epithelial ovarian cancer:</u>
<table>
<tr><th>Exposure category</th><th>No. of exposed cases</th><th>Odds ratio (95% CI)</th></tr>
<tr><td colspan="3">Method of use</td></tr>
</table>
</td>
<td>Wong et al. (1999)[12]</td>
</tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr>
<td>have caused selection bias. Response rate to the questionnaire was low in this study population, particularly among the patients with more advanced disease.

462 incident cases in Buffalo, NY, USA between 1982-1992</td>
<td></td>
<td>controls treated for non-gynaecological malignancies at same cancer centre; mean age, 54.9 years; frequency-matched to cases by age at diagnosis (±5 years).

<u>Exposure assessment:</u>

Self-administered, 44-item questionnaire completed at hospital admission; information collected on medical, social, family, dietary and occupational histories; method of talc use (never, sanitary napkin, genital/thigh area, both) assessed and duration of use.

<u>Adjustment for:</u>

Age, parity, oral contraceptive use, smoking, family history of ovarian cancer, age at menarche, menopausal status, income, education, geographical location, history of tubal ligation or hysterectomy.</td>
<td>
<table>
<tr><td>Never</td><td>241</td><td>1.0</td></tr>
<tr><td>Sanitary napkin</td><td>13</td><td>0.9 (0.4–2.0)</td></tr>
<tr><td>Genital or thigh area</td><td>157</td><td>1.0 (0.8–1.3)</td></tr>
<tr><td>Both</td><td>51</td><td>1.1 (0.7–1.7)</td></tr>
<tr><td colspan="3">Duration of use (years)</td></tr>
<tr><td>None</td><td>241</td><td>1.0</td></tr>
<tr><td>1–9</td><td>39</td><td>0.9 (0.6–1.5)</td></tr>
<tr><td>10–19</td><td>49</td><td>1.4 (0.9–2.2)</td></tr>
<tr><td>≥20</td><td>101</td><td>0.9 (0.6–1.2)</td></tr>
</table>

<u>Per histologic subtype ovarian cancer[a]:</u>
<table>
<tr><th>Histology</th><th>No. of cases</th><th>Relative risk (95% CI)</th></tr>
<tr><td>Serous</td><td>136</td><td>1.2 (0.7–2.1)</td></tr>
<tr><td>Mucinous</td><td>11</td><td>1.5 (0.6–4.0)</td></tr>
<tr><td>Endometrioid</td><td>21</td><td>1.4 (0.7–2.7)</td></tr>
</table>
[a] Any or ever use of talc

Comments by IARC (2010): Case population largely that reported by Eltabbakh et al. (1998); 32 cases, 39 controls did not recall duration of use. The study included the sparse information on talc use. In addition, the use of hospital controls with non-gynaecological malignancies may have caused selection bias. As noted in the earlier report by Eltabbakh et al. (1998), the response rate to the questionnaire was low in this study population, particularly among the patients with more advanced disease.
</td>
<td></td>
</tr>
<tr>
<td>Case-control study

Limitations: sparse information on talc use. In analyses of duration, the use of talc on the feet was also included</td>
<td>Talc powder (purity unknown)</td>
<td>767 incident cases identified at 39 hospitals in the Delaware Valley region; aged 20–69; diagnosis within 6 months prior to interview; pathological review of a random subset of</td>
<td>Talc use applied to any part of the body or to sanitary napkins or underwear was related to ovarian cancer risk.

<u>Ovarian cancer:</u>
<table>
<tr><th>Exposure category</th><th>No. of exposed cases</th><th>Odds ratio (95% CI)</th></tr>
<tr><td colspan="3">Method of use</td></tr>
</table>
</td>
<td>Ness et al. (2000)[12]</td>
</tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr>
<td>as an exposure. The relatively low participation rates among cases was also a limitation of the study.

767 incident cases in eastern Pennsylvania, southern New Jersey and Delaware, USA between 1944-1998</td>
<td></td>
<td>cases (n = 120) 1367 population-based controls identified through random digit dialling (≤65 years of age) and Health Care Financing Administration lists (65–69 years of age); frequency matched by age and location of residence.

<u>Exposure assessment:</u>

Standardised in-person interviews; information collected on sexual activity, use of contraceptives, menstrual and reproductive history, and history and duration of talc use (genital, non-genital applications, exposure via male sexual partners).

<u>Adjustment for:</u>

Age, parity, race, family history of ovarian cancers, oral contraceptive use, tubal ligation, hysterectomy, lactation.</td>
<td>
<table>
<tr><td>Never</td><td>349</td><td>1.0</td></tr>
<tr><td>Feet, arms, breasts</td><td>335</td><td>1.4 (1.1–1.6)</td></tr>
<tr><td>Genital/ rectal</td><td>161</td><td>1.5 (1.2–2.0)</td></tr>
<tr><td>Sanitary napkin</td><td>77</td><td>1.6 (1.1–2.3)</td></tr>
<tr><td>Underwear</td><td>70</td><td>1.7 (1.2–2.4)</td></tr>
<tr><td>Diaphragm/ cervical cap</td><td>10</td><td>0.6 (0.3–1.2)</td></tr>
<tr><td>Male partner</td><td>56</td><td>1.0 (0.7–1.4)</td></tr>
<tr><td colspan="3">Duration of use (years)</td></tr>
<tr><td>Never</td><td>401</td><td>1.0</td></tr>
<tr><td><1</td><td>17</td><td>2.0 (1.0–4.0)</td></tr>
<tr><td>1–4</td><td>76</td><td>1.6 (1.1–2.3)</td></tr>
<tr><td>5–9</td><td>40</td><td>1.2 (0.8–1.9)</td></tr>
<tr><td>≥10</td><td>233</td><td>1.2 (1.0–1.5)</td></tr>
</table>
Comments by IARC (2010): Risk for ovarian cancer compared with 50 women with primary peritoneal cancers; no control for confounding; analysis of duration examined risk for cases reporting use of talc on the feet, genital and rectal areas.
</td>
<td></td>
</tr>
<tr>
<td>Nested case-control study

Limitations: small number of cases, small percentage of cases and controls who were interviewed to obtain information on the covariates of interest and use of surrogate respondents to obtain</td>
<td>Exposure to asbestos, talc (purity unknown) and total dust from work histories, questionnaires by industrial hygienists/ senior employees and international database; personal use of talc: 76% of cases, 57% of</td>
<td>35 (invasive and borderline tumours) selected from cohort of 4247 female pulp and paper workers; cohort follow-up, 1953–99; histological review and confirmation of diagnosis; 121 selected from the cohort by incidence density sampling; matched by birth (year ±2 years); controls had no</td>
<td>Talc-exposed women did not have an increased risk of ovarian cancer.

<u>Ovarian cancer:</u>
<table>
<tr><th>Exposure category</th><th>No. of exposed cases</th><th>Odds ratio (95% CI)</th></tr>
<tr><td>Ever use of talc for personal hygiene</td><td>12</td><td>1.2 (0.4-3.2)</td></tr>
</table>
The questions on hygienic talc use resulted in many missing values among the proxy respondents. Thus the odds ratios for some of the variables were the highest in the</td>
<td>Langseth and Kjaerheim (2004)[12]</td>
</tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td>information on covariates for the deceased cases and controls.

35 women selected from cohort of female pulp and paper workers (see also Occupational exposure – user industries) from Norway between 1953-1999</td><td>controls; personal interviews.</td><td>ovarian cancer and had intact ovaries.

<u>Exposure assessment:</u>

In-person interviews conducted at mills or by telephone; information collected on occupational history, household exposure to asbestos, menstrual and reproductive history, hereditary risk of cancer, as well as talc use on sanitary napkins, underwear or diapers or by husband in genital area.

<u>Adjustment for:</u>

Adjusted for possible confounders, but not explicitly stated.</td><td>unknown categories, indicating a possible uncertainty in the results.

Comments by IARC (2010): Nested case–control study conducted in a cohort study of 10 pulp and paper mills; many missing values among proxy respondents. The Working Group noted that hygienic exposure to talc was assessed retrospectively in the nested case–control study.</td><td></td></tr>
<tr><td>Case-control study

Limitations: low participation rate and relatively small number of cases. In addition, pathology was not confirmed for all cases, which may have resulted in some misclassification of histological subtype.

249 incident cases in central California between 2000-2001</td><td>Talc powder (purity unknown)</td><td>249 incident cases from 22 counties diagnosed in two regional cancer registries, using rapid case ascertainment procedures; histological confirmation of diagnosis for a subset of cases; 1105 population-based controls identified by random-digit dialling; frequency-matched by age, race, ethnicity.

<u>Exposure assessment:</u>

Telephone interview to obtain information on medical history, menstrual and reproductive history, family history of cancer, history of</td><td>This study provides some support for the hypothesis that perineal talc use is associated with an increased risk of epithelial ovarian cancer. No dose response association was found.

<u>Epithelial ovarian cancer:</u>

<table><tr><th>Exposure category</th><th>No. of exposed cases</th><th>Odds ratio (95% CI)</th></tr><tr><td colspan="3">Perineal use of talc</td></tr><tr><td>Never</td><td>143</td><td>1.0</td></tr><tr><td>Ever</td><td>106</td><td>1.4 (1.0–1.9)</td></tr><tr><td colspan="3">Frequency of use</td></tr><tr><td>Never</td><td>143</td><td>1.0</td></tr><tr><td><1/week</td><td>34</td><td>1.3 (0.9–2.1)</td></tr><tr><td>1–3/week</td><td>31</td><td>1.6 (0.7–1.8)</td></tr><tr><td>4–7/week</td><td>41</td><td>1.7 (1.1–2.6)</td></tr><tr><td>p for trend</td><td colspan="2">0.015</td></tr><tr><td colspan="3">Duration of use (years)</td></tr><tr><td>Never</td><td>143</td><td>1.0</td></tr></table></td><td>Mills et al. (2004)[12]</td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td>perineal talc exposure (frequency, duration and calendar years of use); ‘cumulative’ use calculated by multiplying frequency (categorical variable) by duration in months.

<u>Adjustment for:</u>

Age, race/ethnicity, duration of oral contraceptive use, breastfeeding. Additional covariates considered to be potential confounders included family history of breast or ovarian cancer, parity, history of pregnancy, body mass index, hysterectomy, tubal ligation, duration of post-menopausal use of hormones.</td><td>
<table>
<tr><td>≤3</td><td>18</td><td>1.0 (0.6–1.8)</td></tr>
<tr><td>4–12</td><td>32</td><td>1.9 (1.2–3.0)</td></tr>
<tr><td>13–30</td><td>29</td><td>1.5 (0.9–2.3)</td></tr>
<tr><td>>30</td><td>21</td><td>1.2 (0.7–2.1)</td></tr>
<tr><td>p for trend</td><td colspan="2">0.045</td></tr>
<tr><td colspan="3">Cumulative use</td></tr>
<tr><td>Never</td><td>143</td><td>1.0</td></tr>
<tr><td>1st quartile (lowest)</td><td>18</td><td>1.0 (0.6–1.8)</td></tr>
<tr><td>2nd quartile</td><td>28</td><td>1.8 (1.1–3.0)</td></tr>
<tr><td>3rd quartile</td><td>34</td><td>1.7 (1.1–2.7)</td></tr>
<tr><td>4th quartile (highest)</td><td>20</td><td>1.1 (0.6–1.8)</td></tr>
<tr><td>p for trend</td><td colspan="2">0.051</td></tr>
</table>

<u>Per histologic subtype ovarian cancer[a]:</u>
<table>
<tr><th>Histology</th><th>No. of cases</th><th>Relative risk (95% CI)</th></tr>
<tr><td>Serous invasive</td><td>42</td><td>1.8 (1.1–2.8)</td></tr>
<tr><td>Mucinous invasive</td><td>10</td><td>2.6 (0.9–7.4)</td></tr>
<tr><td>Endometrioid</td><td>14</td><td>1.3 (0.6–2.6)</td></tr>
</table>
[a] Any or ever use of talc

Comments by IARC (2010): Cumulative use calculated as frequency (categorical weighting from 0–3) multiplied by duration.</td><td></td></tr>
<tr><td>Case-control study

Limitations: limited sample size in NHS cohort, the use of common exposure and covariate definitions in both cohorts resulted in the loss of some detail (particularly for the NECC), recall</td><td>Talc powder (purity unknown)</td><td>1,385 ovarian cancer cases and 1,802 controls from the New England Case-Control (NECC) Study and Nurses' Health Study (NHS). Characteristics of the cases were generally similar between cohorts. P-values for tests for heterogeneity comparing the NECC</td><td>A statistically significant trend ($p < 0.001$) between frequency of talc use and risk of total and serous invasive ovarian cancer strengthens the evidence for an association.

<u>Epithelial ovarian cancer:</u>
<table>
<tr><th>Exposure category</th><th>No. of exposed cases</th><th>Odds ratio (95% CI)</th></tr>
<tr><td colspan="3">Regular genital talc use (≥1/week)</td></tr>
</table></td><td>Gates et al. (2008)</td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr>
<td>or selection bias (NECC cohort)

1,385 incident cases in New England, USA between 1976-2004</td>
<td></td>
<td>and NHS results were all >0.38

NECC: 1,845 (79%) of these cases were eligible and 71% of the eligible cases were enrolled in the study. Study investigators identified potential controls using random-digit dialling, drivers' license records, and Massachusetts' town resident lists. Controls were frequency matched to cases by age and state of residence. 1,175 cases and 1,202 frequency-matched controls were included.

NHS: 121,701 female registered nurses between ages 30 and 55 years responded to a mailed questionnaire about known and suspected risk factors for disease in 1976. Study participants completed follow-up questionnaires every 2 years between 1976 and 2004, the percentage of follow-up information obtained (questionnaire responses plus deaths) was 95.3%. Information on deaths due to ovarian cancer was obtained through family members, the National Death Index, and the U.S. Postal Service. All cases were diagnosed</td>
<td>
<table>
<tr><td>No</td><td>997</td><td>1.0</td></tr>
<tr><td>Yes</td><td>371</td><td>1.4 (1.1-1.6)</td></tr>
<tr><td colspan="3">Frequency of genital talc use</td></tr>
<tr><td>Never</td><td>952</td><td>1.0</td></tr>
<tr><td><1/week</td><td>45</td><td>0.8 (0.6-1.2)</td></tr>
<tr><td>1–6/week</td><td>145</td><td>1.3 (1.0-1.6)</td></tr>
<tr><td>Daily</td><td>226</td><td>1.4 (1.1-1.8)</td></tr>
<tr><td>p for trend</td><td colspan="2"><0.001</td></tr>
</table>
<u>Serous invasive ovarian cancer:</u>
<table>
<tr><td>Exposure category</td><td>No. of exposed cases</td><td>Odds ratio (95% CI)</td></tr>
<tr><td colspan="3">Regular genital talc use (≥1/week)</td></tr>
<tr><td>No</td><td>370</td><td>1.0</td></tr>
<tr><td>Yes</td><td>167</td><td>1.6 (1.3-2.0)</td></tr>
<tr><td colspan="3">Frequency of genital talc use</td></tr>
<tr><td>Never</td><td>353</td><td>1.0</td></tr>
<tr><td><1/week</td><td>17</td><td>0.7 (0.4-1.2)</td></tr>
<tr><td>1–6/week</td><td>68</td><td>1.6 (1.1-2.2)</td></tr>
<tr><td>Daily</td><td>99</td><td>1.6 (1.2-2.1)</td></tr>
<tr><td>p for trend</td><td colspan="2"><0.001</td></tr>
</table>
</td>
<td></td>
</tr>
</table>

Type of study/data	Test substance (composition and particle size)	Relevant information about the study (as applicable)	Observations	Reference
		before June 1, 2004 and had no history of a prior cancer, other than nonmelanoma skin cancer. 210 cases and 600 matched controls were included. Participants completed a detailed questionnaire on potential risk factors for ovarian cancer and covariates of interest during an in-person interview with a trained interviewer. <u>Exposure assessment:</u> The NECC questionnaires included multiple questions about regular use of talcum, baby, or deodorizing powder as an adult. Specific questions asked about type of use (as a dusting powder to the genital area, sanitary napkins, underwear, or nongenital areas), frequency of use, age at first use, number of years used, and brand of powder used. The 1982 NHS questionnaire requested information on whether the participant had ever commonly applied talcum, baby, or deodorizing powder to the perineal area (no, less than once a week, 1-6 times a week, or daily) or to sanitary napkins		

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td>(yes/no). For this analysis, we defined regular genital talc use as application of powder to the genital/perineal region at least once a week.

<u>Adjustment for:</u>

Age, study centre (NECC only), duration of oral contraceptive use (months), parity (continuous), tubal ligation, body mass index (continuous), and duration of postmenopausal hormone use (months).</td><td></td><td></td></tr>
<tr><td>Case-control study

Limitations: self-reported information on the main exposure of interest, recall bias (retrospective analysis), missing information

481 incident cases in Hawaii, USA between 1993-2008</td><td>Talc powder (purity unknown)</td><td>481 incident cases and 755 controls. Incident cases were identified through the rapid-reporting system of the Hawaii Tumour Registry, which is part of the Surveillance, Epidemiology, and End-Results Program of the National Cancer Institute. Information on tumour histology was obtained from pathology and surgical reports. Interview information were obtained from ovarian cancer cases eligible for participation in the study.

The control pool consisted of population-based lists of female Oahu residents who were interviewed by the</td><td>No statistically significantly increased risk of ovarian cancer and genital use of powder.

<u>Epithelial ovarian cancer:</u>
<table><tr><th>Exposure category</th><th>No. of exposed cases</th><th>Odds ratio (95% CI)</th></tr><tr><td colspan="3">Powder use</td></tr><tr><td>No</td><td>326</td><td>1.0</td></tr><tr><td>Non-genital use only</td><td>81</td><td>0.7 (0.5-1.0)</td></tr><tr><td>Genital use</td><td>74</td><td>1.0 (0.7-1.4)</td></tr></table>
<u>Per histologic subtype ovarian cancer[a]:</u>
<table><tr><th>Histology</th><th>No. of cases</th><th>Odds ratio (95% CI)</th></tr><tr><td>Borderline cancers</td><td>89</td><td>1.3 (0.7-2.4)</td></tr><tr><td>Invasive cancers</td><td>392</td><td>1.0 (0.7-1.4)</td></tr><tr><td>Invasive serous cancers</td><td>222</td><td>1.3 (0.8-2.0)</td></tr></table></td><td>Goodman et al. (2008) as analysed by Terry et al. (2013)</td></tr>
</table>

Type of study/data	Test substance (composition and particle size)	Relevant information about the study (as applicable)	Observations	Reference
		Health Surveillance Program of the Hawaii Department of Health. Potential controls were randomly selected from the pool so that the ethnic (e.g., Japanese) and 5-year age group distribution would match that of the case group with an approximate 1:1.6 ratio. Eligibility criteria for controls included age 18 years or older, residency in Hawaii for a minimum of 1 year, no prior history of ovarian cancer, and having at least one intact ovary. The response rate was 65% for cases and 68% for controls. <u>Exposure assessment:</u> Socio-demographic, life style, and health-related information were collected during a ~2.5h interview using a structured pre-tested questionnaire. History of talc use: ever use of talc, baby or deodorizing powder dusted or sprayed on body or genital/rectal area. Use as a dusting powder to sanitary napkins, underwear, diaphragm or cervical cap. Regular use defined as ≥once a month for 6 months or more. <u>Adjustment for:</u>	<table><tr><td>Invasive endometrioid cancers</td><td>69</td><td>0.5 (0.2-1.2)</td></tr><tr><td>Invasive clear cell cancers</td><td>47</td><td>0.5 (0.2-1.6)</td></tr><tr><td>Invasive mucinous cancers</td><td>87</td><td>0.8 (0.3-2.3)</td></tr></table>[a] genital powder use	

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td>Age (continuous), oral contraceptive duration, parity, tubal ligation history, body mass index, race/ethnicity.</td><td></td><td></td></tr>
<tr><td>Case-control study

Limitations: low response rate for controls (47%), which could have resulted in selection bias and possibly led to an over-representation of healthy subjects among the controls, analyses of medical conditions were based entirely on self-reported medical history, missing data

1,576 incident cases in Australia between 2002-2005</td><td>Talc powder (purity unknown)</td><td>1,576 incident cases and 1,509 controls in Australia. Incident cases of invasive and low malignant potential ovarian cancer diagnosed in women (aged 18–79 years) between January 2002 and June 2005. A total of 3,553 women were identified with suspected ovarian cancer. Two researchers independently abstracted information on tumour site, histological subtype and tumour behaviour (invasive vs. low malignant potential) from the diagnostic histopathology reports. 1,685 eligible participants with invasive or low malignant potential cancers of the ovary, peritoneum or fallopian tube, 1,576 (94%) returned a questionnaire and comprised the case population.

Control participants were identified from the Australian Electoral Roll (all citizens are required by law to enrol). Controls were frequency-matched to the entire case</td><td>A significantly elevated risk of ovarian cancer overall and of the serous subtype associated with perineal talc use was identified.

Increased risk of serous ovarian cancer was not restricted to perineal talc use in the oldest age groups, who were more likely to have been exposed to asbestos-contaminated talc, but was also observed in the youngest (less than 50 years) and the 50–59 year old age group.

Ovarian cancer risk was only related to talc use in women with no surgical closure of the fallopian tubes or those who had used talc presurgery. These findings support the hypothesis that talc particles are transported to the ovaries via unobstructed fallopian tubes.

<u>Epithelial ovarian cancer:</u>
<table>
<tr><th>Exposure category</th><th>No. of exposed cases</th><th>Odds ratio (95% CI)</th></tr>
<tr><td colspan="3">Perineal use of talcum powder</td></tr>
<tr><td>Never</td><td>821</td><td>1.0</td></tr>
<tr><td>Ever</td><td>702</td><td>1.2 (1.0-1.4)</td></tr>
<tr><td colspan="3">Use pre- or no-surgery</td></tr>
<tr><td>None</td><td>821</td><td>1.0</td></tr>
<tr><td>>0-10 years</td><td>200</td><td>1.1 (0.9-1.4)</td></tr>
<tr><td>>10-25 years</td><td>213</td><td>1.1 (0.9-1.3)</td></tr>
<tr><td>>25 years</td><td>289</td><td>1.3 (1.0-1.6)</td></tr>
<tr><td>p for trend</td><td colspan="2">0.021</td></tr>
<tr><td colspan="3">Use post-surgery</td></tr>
<tr><td>None</td><td>1,340</td><td>1.0</td></tr>
</table></td><td>Merritt et al. (2008)</td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr>
<td></td>
<td></td>
<td>series based on age and state of residence. The response rate was 47% and after exclusion (previous ovarian cancer or bilateral oophorectomy) 1,509 controls were included. The response rate was 84% for cases and 47% for controls.

<u>Exposure assessment:</u>

Study participants filled in a health and lifestyle questionnaire (personal details, physical characteristics, family history, medical and surgical history, lifestyle habits and reproductive factors). Participants were asked regarding use of talcum powder in the perineal region (ever used powder or talc in the genital area or on underwear or sanitary pads/diaphragm), age at first use, years of talc use. Duration of talcum powder use prior to and after hysterectomy/tubal ligation was calculated and in all analyses perineal talc use was defined as use occurring while the reproductive tract was patent (i.e., prior to hysterectomy/tubal ligation for those women who had undergone</td>
<td>
<table>
<tr><td>>0-10 years</td><td>50</td><td>1.1 (0.7-1.6)</td></tr>
<tr><td>>10-25 years</td><td>87</td><td>1.1 (0.8-1.6)</td></tr>
<tr><td>>25 years</td><td>46</td><td>1.0 (0.6-1.5)</td></tr>
<tr><td>p for trend</td><td colspan="2">0.61</td></tr>
<tr><td colspan="3">Ever vs. never use stratified by age at diagnosis/recruitment (years)</td></tr>
<tr><td><50</td><td>137</td><td>1.2 (0.9-1.6)</td></tr>
<tr><td>50-59</td><td>237</td><td>1.2 (0.9-1.6)</td></tr>
<tr><td>60-69</td><td>207</td><td>0.9 (0.7-1.2)</td></tr>
<tr><td>≥70</td><td>121</td><td>1.6 (1.1-2.4)</td></tr>
</table>

<u>Per histologic subtype ovarian cancer[a]:</u>
<table>
<tr><th>Histology</th><th>No. of cases</th><th>Odds ratio (95% CI)</th></tr>
<tr><td>Serous</td><td>994</td><td>1.2 (1.0-1.4)</td></tr>
<tr><td>Mucinous</td><td>191</td><td>1.1 (0.8-1.5)</td></tr>
<tr><td>Endometrioid</td><td>141</td><td>1.2 (0.8-1.7)</td></tr>
<tr><td>Clear cell</td><td>88</td><td>1.1 (0.7-1.7)</td></tr>
</table>
[a] Ever perineal use of talcum powder
</td>
<td></td>
</tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td>gynaecological surgery). Information on talc use under the arms or on the chest or abdomen was also collected.

<u>Adjustment for:</u>

Age (except age-stratified analysis), education, parity and oral contraceptive pill use. Analysis restricted (except use post-surgery) to use while the genital tract was unobstructed (i.e. prior to hysterectomy).</td><td></td><td></td></tr>
<tr><td>Case-control study

Limitations: small sample size, participation bias, limited information available on talc use and missing data on talc use

1,086 incident cases from North Carolina, USA between 1999-2008</td><td>Talc powder (purity unknown)</td><td>1,114 cases were enrolled, of whom 943 (84.6%) were white, 143 (12.8%) were African-American, and 28 (2.5%) were of other races/ethnicities. For the analysis, 1,086 cases were studied.

Among the 1,086 controls, 868 (79.9%) were white, 189 (17.4%) were African-American, and 29 (2.7%) were of other races/ethnicities. For the analysis, 1,057 controls were studied. The response rate was 67% for cases and 60% for controls. Response rates were lower for African Americans than for whites (56.6% and 68.3%, respectively, for cases and 49.7% and 63.7%, respectively, for controls).

Newly diagnosed</td><td>No statistically increased risk epithelial ovarian cancer observed upon use of talc in white or African-American women.

However, in a meta-analysis an increased risk of epithelial ovarian cancer (1.4 (1.1-1.8)) was observed upon genital powder use (Terry et al. 2013).

<u>Epithelial ovarian cancer:</u>
<table><tr><th>Exposure category</th><th>No. of exposed cases</th><th>Odds ratio (95% CI)</th></tr><tr><td colspan="3">Whites, talc use</td></tr><tr><td>No</td><td>328</td><td>1.0</td></tr><tr><td>Yes</td><td>222</td><td>1.0 (0.8-1.3)</td></tr><tr><td>Missing data</td><td>196</td><td>-</td></tr><tr><td colspan="3">African-Americans, talc use</td></tr><tr><td>No</td><td>45</td><td>1.0</td></tr><tr><td>Yes</td><td>38</td><td>1.2 (0.7-2.1)</td></tr><tr><td>Missing data</td><td>28</td><td>-</td></tr></table>
<u>Per histologic subtype ovarian cancer[a]:</u>
<table><tr><th>Histology</th><th>Odds ratio (95% CI)</th></tr><tr><td>Borderline cancers</td><td>1.5 (0.9-2.4)</td></tr></table></td><td>Moorman et al. (2009)</td></tr>
</table>

Type of study/data	Test substance (composition and particle size)	Relevant information about the study (as applicable)	Observations	Reference
		cases of epithelial ovarian cancer were identified through the North Carolina Central Cancer Registry. Eligible cases (aged 20–74 years at diagnosis, had no prior history of ovarian cancer, resided in the study area) were sent to the study office at Duke University Medical Center. All cases underwent standardised histopathologic review by the study pathologist for confirmation of the diagnosis. Control women were frequency-matched by age and race/ethnicity to the cases and were recruited from the same geographic region using list-assisted random digit dialling. The eligibility criteria were the same as those for the cases; in addition, the controls could not have had a bilateral oophorectomy. <u>Exposure assessment:</u> Information obtained with questionnaire which included family history of cancer; menstrual characteristics such as age at menarche and cycle length; reproductive history, including age at each pregnancy,	<table><tr><td>Invasive cancers</td><td>1.4 (1.1-1.9)</td></tr><tr><td>Invasive serous cancers</td><td>1.6 (1.1-2.2)</td></tr><tr><td>Invasive endometrioid cancers</td><td>1.2 (0.7-2.1)</td></tr><tr><td>Invasive clear cell cancers</td><td>1.0 (0.5-2.0)</td></tr><tr><td>Invasive mucinous cancers</td><td>0.9 (0.3-2.8)</td></tr></table> [a] genital powder use, analysed as North Carolina Ovarian Cancer Study (NCO) by Terry et al. (2013).	

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td>pregnancy duration and outcome, and duration of breastfeeding; type, timing, and duration of hormone and contraceptive use; and lifestyle characteristics such as smoking history, alcohol consumption during the 5 years before interview, and physical activity. Information on talc use not further specified for this study.

<u>Adjustment for:</u>

Age</td><td></td><td></td></tr>
<tr><td>Case-control study

Limitations: history of endometriosis is not validated

609 incident cases from Los Angeles county, USA between 1998-2002</td><td>Talc powder (purity unknown)</td><td>609 ovarian cancer cases and 688 control women.

Eligible patients with ovarian cancer were English speaking residents of Los Angeles County between the ages of 18-74 inclusive who had histologically confirmed invasive or borderline (low malignant potential) ovarian cancers that were first diagnosed from 1998 to 2002. The cases were identified by the Cancer Surveillance Program.

Controls were identified through a neighbourhood recruitment algorithm. Controls were women with at least one intact ovary, with no history of cancer, except possibly</td><td>This study show a significant trend of ovarian cancer with increasing number of total applications of talc. Risk increased significantly with lifetime total times of talc use, but the association was limited to those who started talc use before 1975.

<u>Epithelial ovarian cancer:</u>
<table>
<tr><th>Exposure category</th><th>No. of exposed cases</th><th>Odds ratio (95% CI)</th></tr>
<tr><td colspan="3">Talc use</td></tr>
<tr><td>No</td><td>363</td><td>1.0</td></tr>
<tr><td>Yes</td><td>242</td><td>1.5 (1.2-1.9)</td></tr>
<tr><td>Yes, non-perineal</td><td>112</td><td>1.4 (1.0-2.0)</td></tr>
<tr><td>Yes, perineal area</td><td>130</td><td>1.5 (1.1-2.1)</td></tr>
<tr><td colspan="3">Frequency and duration of talc use</td></tr>
<tr><td>No</td><td>363</td><td>1.0</td></tr>
<tr><td>1 ≤20 yrs and ≤10 times/month</td><td>35</td><td>1.4 (0.8-2.3)</td></tr>
<tr><td>1 ≤20 yrs and >10 to ≤30 times/month</td><td>23</td><td>1.2 (0.6-2.1)</td></tr>
<tr><td>1 ≤20 yrs and >30</td><td>21</td><td>1.2 (0.6-</td></tr>
</table></td><td>Wu et al. (2009)</td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr>
<td></td>
<td></td>
<td>nonmelanoma skin cancer, and individually matched with patients on race/ethnicity (non-Hispanic White, African-American, Hispanic, Asians) and date of birth (+/−5 years). The response rate was modest according to study authors.

<u>Exposure assessment:</u>

Patients were asked questions about medical gynaecological, reproductive, and lifestyle histories, family history of breast or ovarian cancer, oral contraceptive use, tubal ligation or hysterectomy, use of talc or non-steroidal anti-inflammatory drugs. To determine the use of talcum powder, participants were asked if they ever used talc at least once per month for 6 months or more. If the response was positive, researchers then asked whether they had ever used talc in nonperineal areas (feet, arms, chest or back), perineal areas, or on underwear or sanitary pads/diaphragm. Questions on talc use included age at first use, frequency of use (times per month) and years of talc use.

<u>Adjustment for:</u></td>
<td>
<table>
<tr><td>times/month</td><td></td><td>2.4)</td></tr>
<tr><td>>20 yrs and ≤10 times/month</td><td>45</td><td>1.3 (0.8-2.0)</td></tr>
<tr><td>>20 yrs and >10 to ≤30 times/month</td><td>51</td><td>1.6 (1.0-2.5)</td></tr>
<tr><td>>20 yrs and >30 times/month</td><td>67</td><td>2.1 (1.3-3.2)</td></tr>
<tr><td>p for trend</td><td colspan="2">0.032</td></tr>
<tr><td colspan="3">Total times of talc use</td></tr>
<tr><td>No</td><td>363</td><td>1.0</td></tr>
<tr><td>≤5200</td><td>49</td><td>1.2 (0.8-1.9)</td></tr>
<tr><td>>5200 to ≤15600</td><td>46</td><td>1.4 (0.9-2.2)</td></tr>
<tr><td>>15,600 to ≤52000</td><td>63</td><td>1.3 (0.9-2.0)</td></tr>
<tr><td>>52000</td><td>84</td><td>2.0 (1.3-3.0)</td></tr>
<tr><td>p for trend</td><td colspan="2">0.0004</td></tr>
<tr><td colspan="3">Total times of talc use, before 1975</td></tr>
<tr><td>≤5200</td><td>24</td><td>0.8 (0.5-1.5)</td></tr>
<tr><td>>5200 to ≤15600</td><td>29</td><td>1.4 (0.8-2.5)</td></tr>
<tr><td>>15,600 to ≤52000</td><td>49</td><td>1.5 (0.9-2.3)</td></tr>
<tr><td>>52000</td><td>82</td><td>1.9 (1.3-2.9)</td></tr>
<tr><td>p for trend</td><td colspan="2"><0.001</td></tr>
<tr><td colspan="3">Total times of talc use, after 1975</td></tr>
<tr><td>≤5200</td><td>25</td><td>2.0 (1.0-3.9)</td></tr>
<tr><td>>5200 to ≤15600</td><td>17</td><td>1.2 (0.6-2.5)</td></tr>
<tr><td>>15,600</td><td>16</td><td>1.0 (0.5-2.1)</td></tr>
</table>
Elevated risks were found among those who used talc on sanitary napkins (odds ratio, 1.6; 95% CI, 0.9–2.8), underwear (odds ratio, 1.7; 95% CI, 1.0-3.0) and on diaphragm/cervical caps (odds ratio, 1.1; 95% CI, 0.5–2.9).
</td>
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</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td>Race/ethnicity, age, education, tubal ligation, family history of breast/ovarian cancer, menopausal status, use of oral contraceptives and parity.</td><td><u>Per histologic subtype ovarian cancer[a]:</u>
<table><tr><th>Histology</th><th>Odds ratio (95% CI)</th></tr><tr><td>Serous</td><td>1.7 (1.3-2.3)</td></tr><tr><td>Mucinous</td><td>1.0 (n.d.)</td></tr><tr><td>Clear/endometrioid</td><td>1.2 (n.d.)</td></tr><tr><td>Other cell types</td><td>1.5 (n.d.)</td></tr><tr><td>Invasive, localised</td><td>1.3 (0.9-2.0)</td></tr><tr><td>Invasive, advanced stage</td><td>1.7 (1.2-2.3)</td></tr><tr><td>Low malignant potential</td><td>1.3 (0.9-2.2)</td></tr></table>[a] Talc use; n.d. 95% CI not stated in publication</td><td></td></tr>
<tr><td>Case-control study
Limitations: potential for misclassification (differential and non-differential)
of exposure status
812 incident cases in Washington State, USA between 2002-2005</td><td>Talc powder (purity unknown)</td><td>812 women with epithelial ovarian cancer and 1,313 controls in western Washington State.
Female residents in western Washington State, 35–74 years of age, who were diagnosed with a primary invasive or borderline epithelial ovarian tumour between 1 January 2002 and 31 December 2005, were considered eligible as cases, . identified through a population-based cancer registry (Cancer Surveillance System). Cases were restricted to English-speaking women who had residential telephones at the time of diagnosis. Of the 1,058 eligible women identified, 812 (76.6%) were interviewed.
Controls were selected by random</td><td>A modest association of ovarian cancer with perineal exposure to talc (via the application of genital powders) was seen in this study.
<u>Epithelial ovarian cancer (all tumours):</u>
<table><tr><th>Exposure category</th><th>No. of exposed cases</th><th>Odds ratio (95% CI)</th></tr><tr><td colspan="3">Used powder after bathing</td></tr><tr><td>No</td><td>699</td><td>1.0</td></tr><tr><td>Yes</td><td>112</td><td>1.3 (1.0-1.7)</td></tr><tr><td colspan="3">Used powder on sanitary napkins</td></tr><tr><td>No</td><td>753</td><td>1.0</td></tr><tr><td>Yes</td><td>55</td><td>0.8 (0.6-1.2)</td></tr><tr><td colspan="3">Used powder on diaphragm</td></tr><tr><td>No</td><td>160</td><td>1.0</td></tr><tr><td>Yes</td><td>46</td><td>0.7 (0.5-1.1)</td></tr><tr><td colspan="3">Used vaginal deodorant spray</td></tr><tr><td>No</td><td>726</td><td>1.0</td></tr><tr><td>Yes</td><td>84</td><td>1.2 (0.9-1.6)</td></tr><tr><td colspan="3">Duration of use (years)</td></tr><tr><td>Never</td><td>699</td><td>1.0</td></tr><tr><td>1–9.9</td><td>33</td><td>1.4 (0.9-</td></tr></table></td><td>Rosenblatt et al. (2011)</td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr>
<td></td>
<td></td>
<td>digit dialling using stratified sampling in 5-year age categories, 1-year calendar intervals, and two county strata in a 2:1 ratio to women with invasive cancer. The response proportion was 69%.

<u>Exposure assessment:</u>

Information was collected during in-person interviews. Data were collected on demographic and lifestyle characteristics; medical history; and detailed reproductive history, including menstrual, pregnancy, contraceptive history, use of contraceptive and menopausal hormone preparations. Sources of genital powder exposure were assessed: direct perineal application after bathing, its use on sanitary napkins and contraceptive diaphragms, and the use of feminine (vaginal) deodorant spray. For powder use on sanitary napkins and use of feminine deodorant sprays, we recorded the total number of months or years in which these products were used (with a minimum of at least 1 month of regular use). For the use of powder on the perineum after</td>
<td>
<table>
<tr><td></td><td></td><td>2.3)</td></tr>
<tr><td>10–19.9</td><td>29</td><td>1.5 (0.9-2.5)</td></tr>
<tr><td>20–34.9</td><td>30</td><td>1.3 (0.8-2.1)</td></tr>
<tr><td>35+</td><td>19</td><td>0.9 (0.5-1.6)</td></tr>
<tr><td colspan="3">Lifetime number of applications</td></tr>
<tr><td>1–1,599</td><td>26</td><td>1.2 (0.7-2.1)</td></tr>
<tr><td>1,600–4,799</td><td>45</td><td>2.1 (1.3-3.3)</td></tr>
<tr><td>4,800–9,999</td><td>20</td><td>0.9 (0.5-1.5)</td></tr>
<tr><td>10,000+</td><td>18</td><td>0.9 (0.5-1.6)</td></tr>
<tr><td colspan="3">Calendar year of first use</td></tr>
<tr><td>≤1959</td><td>19</td><td>0.9 (0.5-1.5)</td></tr>
<tr><td>1960–1969</td><td>24</td><td>1.1 (0.7-1.9)</td></tr>
<tr><td>1970–1979</td><td>26</td><td>1.1 (0.7-1.9)</td></tr>
<tr><td>1980+</td><td>43</td><td>2.0 (1.3-3.2)</td></tr>
<tr><td colspan="3">Time since first use (years)</td></tr>
<tr><td>≤25</td><td>42</td><td>1.8 (1.2-2.8)</td></tr>
<tr><td>25–<38</td><td>38</td><td>1.5 (0.9-2.3)</td></tr>
<tr><td>38–<45</td><td>16</td><td>0.9 (0.5-1.6)</td></tr>
<tr><td>45+</td><td>16</td><td>0.8 (0.4-1.5)</td></tr>
</table>
Use defined as regular use after bathing for at least 1 year.

<u>Per histologic subtype ovarian cancer[a]:</u>
<table>
<tr><th>Histology</th><th>No. of exposed cases</th><th>Odds ratio (95% CI)</th></tr>
<tr><td>Serous, borderline tumours</td><td>17</td><td>1.5 (0.8-2.6)</td></tr>
<tr><td>Mucinous, borderline tumours</td><td>15</td><td>1.8 (1.0-3.2)</td></tr>
</table>
</td>
<td></td>
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</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td>bathing, only intervals of at least 1 year when powder was usually used were recorded. Age when began and ended, the number of weeks or months of use per year, and the average days per week used was also recorded. Type of powder(s) used was asked including talcum, baby, corn-starch, deodorant, body/bath, and other or unknown.

<u>Adjustment for:</u>

Age, county of residence, calendar year of diagnosis/reference date, number of full-term pregnancies, duration of hormonal contraception.</td><td><table><tr><td>Serous, invasive tumours</td><td>40</td><td>1.0 (0.7-1.5)</td></tr><tr><td>Clear/endometrioid, invasive tumours</td><td>21</td><td>1.5 (0.9-2.6)</td></tr><tr><td>Other nonmucinous, invasive tumours</td><td>17</td><td>1.5 (0.9-2.6)</td></tr></table>[a] Use defined as regular use after bathing for at least 1 year.</td><td></td></tr>
<tr><td>Case-control study

Limitations: self-reported information on the main exposure of interest, recall bias (retrospective analysis), missing information

902 incident cases from Western Pennsylvania, Eastern Ohio, and Western New York State, USA between 2003-2008</td><td>Talc powder (purity unknown)</td><td>902 cases and 1,802 controls from the Hormones and Ovarian Cancer Prediction (HOPE) study.

All cases were histologically confirmed to have primary epithelial ovarian, peritoneal, or fallopian tube cancers diagnosed between 2003 and 2008. Eligible women were at least 25 years old and were within 9 months of initial diagnosis at the time of recruitment. A total of 902 cases were enrolled.

Controls were</td><td>Genital use of talc was associated with increased ovarian cancer risk in the HOPE study.

<u>Epithelial ovarian cancer:</u><table><tr><td>Exposure category</td><td>No. of exposed cases</td><td>Odds ratio (95% CI)</td></tr><tr><td>No</td><td>439</td><td>1.0</td></tr><tr><td>Non-genital use only</td><td>102</td><td>1.2 (0.9-1.6)</td></tr><tr><td>Genital use</td><td>194</td><td>1.3 (1.1-1.7)</td></tr></table><u>Per histologic subtype ovarian cancer[a]:</u><table><tr><td>Histology</td><td>Odds ratio (95% CI)</td></tr><tr><td>Borderline cancers</td><td>1.5 (0.9-2.7)</td></tr><tr><td>Invasive cancers</td><td>1.3 (1.0-1.7)</td></tr></table></td><td>Lo-Ciganic et al. (2012)

analysed by Terry et al. (2013)</td></tr>
</table>

Type of study/data	Test substance (composition and particle size)	Relevant information about the study (as applicable)	Observations	Reference
		frequency matched to cases (~2:1) by 5-year age group and telephone area code through random-digit dialling. Women who had undergone a bilateral oophorectomy were ineligible. Response rate for the screening and interview phase was 64% and 72%, respectively. <u>Exposure assessment:</u> Data were collected through questionnaires that included detailed reproductive, gynaecologic, and medical histories as well as information about lifestyle and family medical history; a reference date of 9 months before the interview date was used for all participants. Perineal talc use was defined as ever using talc or baby powder, deodorizing powder with talc at least once a month for 6 months or more. Use in any of the following ways: as a dusting powder or deodorizing spray to genital or rectal areas, sanitary napkins, underwear, diaphragm or cervical cap. <u>Adjustment for:</u> Age (continuous), oral contraceptive	Invasive serous cancers: 1.1 (0.8-1.5) Invasive endometrioid cancers: 1.3 (0.7-2.4) Invasive clear cell cancers: 1.8 (0.9-3.4) Invasive mucinous cancers: 3.0 (1.3-7.2) [a] genital powder use	

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td>duration, parity, tubal ligation history, body mass index, race/ethnicity.</td><td></td><td></td></tr>
<tr><td>Case-control study

Limitations: inability to identify infertile women that never sought medical attention and reliance on self-reported fertility drug use

Same as Lo-Ciganic et al. (2012).</td><td>Talc powder (purity unknown)</td><td>902 cases and 1,802 controls from the Hormones and Ovarian Cancer Prediction (HOPE) study. Same as Lo-Ciganic et al. (2012).

<u>Exposure assessment:</u>

Data were collected through questionnaires that included detailed reproductive, gynaecologic, and medical histories as well as information about lifestyle and family medical history; a reference date of 9 months before the interview date was used for all participants.

Perineal talc use was defined as ever using dusting powder or deodorizing spray on the genital or rectal areas, on sanitary napkins, on underwear, or on diaphragms or cervical caps.

<u>Adjustment for:</u>

Age, race, and education</td><td>Perineal talc use increased risk of ovarian cancer in this study population.

<u>Ovarian cancer:</u>
<table><tr><th>Exposure category</th><th>No. of exposed cases</th><th>Odds ratio (95% CI)</th></tr><tr><td>No</td><td>653</td><td>1.0</td></tr><tr><td>Yes</td><td>249</td><td>1.4 (1.2-1.7)</td></tr></table></td><td>Kurta et al. (2012)</td></tr>
<tr><td>Case-control study

Limitations:

1,701 incident cases in Los Angeles County, USA between 1992-2008</td><td>Talc powder (purity unknown)</td><td>1,701 cases and 2,391 controls; among Hispanics (308 cases and 380 controls), African Americans (128 cases and 143 controls), and non-Hispanic whites</td><td>Genital talc use is considered a risk factor for invasive ovarian cancer in all studied groups.

<u>Invasive ovarian cancer (all groups):</u>
<table><tr><th>Exposure category</th><th>No. of exposed cases</th><th>Odds ratio (95% CI)</th></tr></table></td><td>Wu et al. (2015)</td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td>(1,265 cases and 1,868 controls).

Eligible patients were female residents of Los Angeles County of self-reported non-Hispanic white, Hispanic, or African-American race/ethnicity. Cases were eligible for inclusion in the study if they were between 18-74 years of age at diagnosis (up to age 79 for cases diagnosed between 2003-2008). Patients who had previous cancer (excl. nonmelanoma skin cancer) or had prior bilateral oophorectomy were excluded.

Controls were residents of Los Angeles County with at least one intact ovary identified using a well-tested neighbourhood control selection algorithm. Neighbourhood controls were individually matched to cases on race/ethnicity and year of birth (±5 years); they represented essentially all the controls interviewed.

Overall response rates were between 61-70%.

<u>Exposure assessment:</u>

In-person interviews were conducted using</td><td><table><tr><td colspan="3">Genital talc use</td></tr><tr><td>None/<1 year</td><td>1,000</td><td>1.0</td></tr><tr><td>Yes</td><td>701</td><td>1.5 (1.3-1.7)</td></tr><tr><td>Per 5 years talc</td><td>-</td><td>1.1 (1.1-1.2)</td></tr></table></td><td></td></tr>
</table>

Type of study/data	Test substance (composition and particle size)	Relevant information about the study (as applicable)	Observations	Reference
		standardised questionnaires that included the use of a life calendar. The demographic, lifestyle, and medical history variables considered in this analysis include race/ethnicity, age at diagnosis, parity, oral contraceptive use, tubal ligation, self-reported physician-diagnosed endometriosis, first-degree family history of ovarian cancer, and genital talc use. Data on genital talc use was collected as yes or no (including never and <1 year of use). <u>Adjustment for:</u> Age, race/ethnicity, interviewer, study, menopausal status, age at menarche, hormone therapy use, body mass index, income, education, live-births, oral contraceptive use, tubal ligation, endometriosis, first-degree family history of ovarian cancer.		
Case-control study Limitations: recall bias (misclassification of in retrospective data), lack of metrics for how much talc is in an "application", how much enters the vagina/upper genital tract to identify a dose-	Talc powder (purity unknown)	2,041 cases of epithelial ovarian cancer and 2,100 age- and-residence-matched controls. Data come from three enrolment phases: 1 (1992–1997; Cramer et al. (1999)), 2 (1998–2002; Gates et al. (2008)), and 3 (2003–2008; Terry et al. (2013)). Women	Genital talc use was associated with an increased risk of ovarian cancer, with a trend for increasing risk by talc-years. Risks for epithelial ovarian cancer from genital talc use vary by histologic subtype, menopausal status at diagnosis, hormone therapy use, weight, and smoking. These observations suggest that oestrogen and/or prolactin may play a role via macrophage activity and inflammatory response to talc. <u>Epithelial ovarian cancer:</u>	Cramer et al. (2016)

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr>
<td>response

2,041 incident cases in Massachusetts and New Hampshire, USA between 1992-2008</td>
<td></td>
<td>residing in Eastern Massachusetts and New Hampshire diagnosed with ovarian cancer between ages 18 and 80 were identified through tumour boards and registries. Women were excluded when: they had died, moved outside study area, did not have a working phone number, had nonovarian primary tumour or nonepithelial or mesodermal tumours. Pathology reports were reviewed and histologic subtype, grade, and stage recorded. Mixed epithelial ovarian cancer was classified as the predominant type. Undifferentiated, transitional cell, fallopian tube, or primary peritoneal tumours were counted as serous.

Controls were identified through random digit dialling, driver-license lists, and town-resident lists. Controls were ineligible if they had died, moved, or were seriously ill or if they did not have a working telephone, speak English, or have ovaries. 54% of eligible controls were enrolled. Controls were frequency matched to cases by 5-year age groups</td>
<td>
<table>
<tr><th>Exposure category</th><th>No. of exposed cases</th><th>Odds ratio (95% CI)</th></tr>
<tr><td colspan="3">Any genital powder use</td></tr>
<tr><td>No</td><td>1,399</td><td>1.0</td></tr>
<tr><td>Yes</td><td>642</td><td>1.3 (1.2-1.5)</td></tr>
<tr><td colspan="3">Personal use</td></tr>
<tr><td>None</td><td>1,001</td><td>1.0</td></tr>
<tr><td>Body use only</td><td>398</td><td>1.0 (0.8-1.2)</td></tr>
<tr><td>Genital use only</td><td>94</td><td>1.4 (1.0-2.0)</td></tr>
<tr><td>Body + genital use</td><td>548</td><td>1.3 (1.1-1.5)</td></tr>
<tr><td colspan="3">Type of genital powder used</td></tr>
<tr><td>No genital use</td><td>1,394</td><td>1.0</td></tr>
<tr><td>Corn-starch use only</td><td>5</td><td>0.6 (0.2-1.7)</td></tr>
<tr><td>Johnson and Johnson Baby Powder or Shower to Shower</td><td>363</td><td>1.3 (1.1-1.5)</td></tr>
<tr><td>Other brand(s)</td><td>279</td><td>1.4 (1.1-1.6)</td></tr>
<tr><td colspan="3">Frequency of use (per month)</td></tr>
<tr><td>No genital use</td><td>1,399</td><td>1.0</td></tr>
<tr><td>1-7 days</td><td>227</td><td>1.2 (1.0-1.4)</td></tr>
<tr><td>8-29 days</td><td>133</td><td>1.4 (1.1-1.8)</td></tr>
<tr><td>≥30 days</td><td>267</td><td>1.5 (1.2-1.8)</td></tr>
<tr><td>p for trend</td><td colspan="2"><0.0001</td></tr>
<tr><td colspan="3">Years used</td></tr>
<tr><td>Never</td><td>1,399</td><td>1.0</td></tr>
<tr><td><8</td><td>152</td><td>1.3 (1.0-1.7)</td></tr>
<tr><td>8-19</td><td>145</td><td>1.3 (1.0-1.7)</td></tr>
<tr><td>20-35</td><td>178</td><td>1.4 (1.1-</td></tr>
</table>
</td>
<td></td>
</tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td>and region of residence.

Exposure assessment:

Subjects were personally interviewed about potential ovarian cancer risk factors that occurred more than 1 year before diagnosis, for cases, and interview, for controls. Subjects were asked whether they “regularly” or “at least monthly” applied powder to the genital or rectal area, sanitary napkins or tampons, underwear, or areas other than the genital-rectal area. Condom and diaphragm use as potential sources of talc exposure were also recorded.

Adjustment for:

Age, study centre and study phase.</td><td>
<table>
<tr><td></td><td></td><td>1.7)</td></tr>
<tr><td>>35</td><td>1.3</td><td>1.3 (1.0-1.7)</td></tr>
<tr><td>p for trend</td><td colspan="2">0.002</td></tr>
<tr><td colspan="3">Total genital talc applications[a]</td></tr>
<tr><td>No genital use</td><td>1,399</td><td>1.0</td></tr>
<tr><td>≤360</td><td>138</td><td>1.2 (0.9-1.5)</td></tr>
<tr><td>361-1,800</td><td>148</td><td>1.4 (1.1-1.8)</td></tr>
<tr><td>1,801-7,200</td><td>156</td><td>1.4 (1.1-1.8)</td></tr>
<tr><td>>7,200</td><td>185</td><td>1.4 (1.1-1.8)</td></tr>
<tr><td>p for trend</td><td colspan="2">0.003</td></tr>
</table>
[a] This includes talc users from phase 1 and part of phase 2 where data on months/year of use was not collected. 12 months/year was assumed when missing months per year of use.</td><td></td></tr>
<tr><td>Case-control study

Limitations: recall bias may have caused some inflation of the odds ratios; possibility of misclassification of exposure, residual confounding, or a chance finding cannot be ruled out as an explanation for the associations with nongenital powder use</td><td>Talc powder (purity unknown)</td><td>584 cases and 745 controls, African-American women from 11 US states.

Cases include African-American women 20 to 79 years of age with newly diagnosed epithelial ovarian cancer.

Controls were African-American women identified through random digit dialling, with at least one intact ovary and no history of ovarian cancer, and</td><td>Application of genital powder is associated with serous and nonserous epithelial ovarian cancer in African-American women.

The association with any occupational talc exposure and epithelial ovarian cancer (OR = 1.31; data not shown), though not statistically significant, is also consistent with the results for “only” nongenital powder use and suggest other routes of exposure, aside transvaginal, may effect epithelial ovarian cancer risk.

Epithelial ovarian cancer:
<table>
<tr><th>Exposure category</th><th>No. of exposed cases</th><th>Odds ratio (95% CI)</th></tr>
<tr><td colspan="3">Body powder use (by location)</td></tr>
</table></td><td>Schildkraut et al. (2016)</td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr>
<td>584 incident cases in Alabama, Georgia, Illinois, Louisiana, Michigan, New Jersey, North Carolina, Ohio, South Carolina, Tennessee, and Texas, USA between 2010-2015</td>
<td></td>
<td>frequency matched to cases on region of residence and 5-year age categories. The overall response rate was 43-61% (Schildkraut et al. 2014).

<u>Exposure assessment:</u>

Participants complete a baseline telephone interview, which includes detailed questions on demographic characteristics; reproductive, gynaecologic, and medical history; hormone therapy and oral contraceptive use; cancer family history and lifestyle characteristics including smoking, alcohol consumption, and physical activity.

Participants were asked whether they had ever regularly used talc, corn-starch, baby, or deodorizing powders. Participants were considered “regular users” if they reported using any of these powders at least one time per month for at least 6 months, and “never users” if they did not. Regular users were asked about their frequency and duration of use, age at first use, and whether they applied powders to genital areas (including on underwear or sanitary</td>
<td>
<table>
<tr><td>Never use</td><td>217</td><td>1.0</td></tr>
<tr><td>Ever use</td><td>367</td><td>1.4 (1.1-1.8)</td></tr>
<tr><td>Only nongenital use</td><td>119</td><td>1.3 (1.0-1.8)</td></tr>
<tr><td>Any genital use</td><td>248</td><td>1.4 (1.1-1.9)</td></tr>
<tr><td colspan="3">Frequency of any genital use</td></tr>
<tr><td>Never</td><td>217</td><td>1.0</td></tr>
<tr><td>Less than daily</td><td>61</td><td>1.2 (0.8-1.7)</td></tr>
<tr><td>Daily</td><td>58</td><td>1.5 (1.0-2.4)</td></tr>
<tr><td>p for trend</td><td colspan="2"><0.01</td></tr>
<tr><td colspan="3">Duration of any genital use (years)</td></tr>
<tr><td>Never</td><td>217</td><td>1.0</td></tr>
<tr><td><20</td><td>101</td><td>1.3 (1.0-1.9)</td></tr>
<tr><td>≥20</td><td>144</td><td>1.5 (1.1-2.1)</td></tr>
<tr><td>p for trend</td><td colspan="2">0.02</td></tr>
<tr><td colspan="3">Lifetime body powder applications (any genital use)</td></tr>
<tr><td>Never</td><td>217</td><td>1.0</td></tr>
<tr><td><3,600 applications</td><td>92</td><td>1.2 (0.8-1.6)</td></tr>
<tr><td>≥3,600 applications</td><td>152</td><td>1.7 (1.2-2.3)</td></tr>
<tr><td>p for trend</td><td colspan="2"><0.01</td></tr>
</table>

<u>Per histologic subtype ovarian cancer[a]:</u>
<table>
<tr><td>Exposure category</td><td>No. of exposed cases</td><td>Odds ratio (95% CI)</td></tr>
<tr><td colspan="3">Serous</td></tr>
<tr><td>Never</td><td>156</td><td>1.0</td></tr>
<tr><td>Only nongenital use</td><td>71</td><td>1.1 (0.8-1.6)</td></tr>
<tr><td>Any genital use</td><td>165</td><td>1.4 (1.0-1.9)</td></tr>
<tr><td colspan="3">Nonserous</td></tr>
<tr><td>Never</td><td>44</td><td>1.0</td></tr>
</table>
</td>
<td></td>
</tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td>napkins, or on birth control devices like diaphragms) and/or nongenital areas. Lifetime number of applications was calculated by multiplying the number of body powder applications per month by the number of months used. Occupational exposure to talc was also assessed. In the short questionnaire, data on occupational exposure to talc was not available (49 cases and 16 controls).

<u>Adjustment for:</u>

Age at diagnosis/interview, study site, education, tubal ligation, parity, body mass index, duration of oral contraceptive use, first-degree family history of breast or ovarian cancer, and interview year</td><td><table><tr><td>Only nongenital use</td><td>42</td><td>2.3 (1.4-3.7)</td></tr><tr><td>Any genital use</td><td>58</td><td>1.6 (1.0-2.6)</td></tr></table>[a] any genital talc use</td><td></td></tr>
<tr><td colspan="5">Cosmetic use – cohort studies</td></tr>
<tr><td>Prospective cohort study

Limitations: availability of exposure information at a single time-point only, the relatively short follow-up period after exposure assessment and the lack of information on age at first use of talc, duration of use of talc,</td><td>Talc powder (purity unknown)</td><td>Cohort of 121,700 female registered nurses who had been followed since 1976. All participants were between the ages of 30 and 55 years and lived in one of 11 states of the USA at study enrolment. 78,630 women were eligible for the analysis. 307 cases of epithelial ovarian cancer were found. Mortality follow-up is estimated to be</td><td>Little support for any substantial association between perineal talc use and ovarian cancer risk overall was found. However, perineal talc use may modestly increase the risk of invasive serous ovarian cancer.

<u>Epithelial ovarian cancer:</u><table><tr><th>Exposure category</th><th>No. of exposed cases</th><th>Relative risk (95% CI)</th></tr><tr><td colspan="3">Ever perineal talc use</td></tr><tr><td>No</td><td>179</td><td>1.0</td></tr><tr><td>Yes</td><td>128</td><td>1.1 (0.9-1.4)</td></tr><tr><td colspan="3">Talc use on perineum</td></tr></table></td><td>Gertig et al. (2000)</td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr>
<td>current use of talc in 1982 and use of talc before tubal ligation or pregnancy, all of which are potentially important parameters based on previous studies

121,700 female nurses in the USA reported between 1982-1996</td>
<td></td>
<td>98% complete in this cohort.

<u>Exposure assessment:</u>

Questionnaires were mailed to participants every 2 years beginning in 1976 to obtain information on the medical history of each woman and potential risk factors for cancer, heart disease and other conditions. The 1982 questionnaire requested information on history and frequency of application of powder to the perineal area (none, daily, one to six times a week, less than once a week) and history of application of powder to sanitary napkins (no/yes). ‘Ever talc use’ was classified as ever use on either the perineal area or on sanitary napkins. The study population included 78,630 women who responded to the questions on powder use in 1982 and who were not excluded from the analysis for another reason (cancer other than non-melanoma skin cancer before 1982, bilateral oophorectomy, surgery with unknown number of ovaries removed or radiation therapy) and entailed 984 212</td>
<td>
<table>
<tr><td>Never</td><td>186</td><td>1.0</td></tr>
<tr><td><1/week</td><td>43</td><td>1.1 (0.8-1.6)</td></tr>
<tr><td>1-6/week</td><td>30</td><td>1.0 (0.7-1.5)</td></tr>
<tr><td>Daily</td><td>48</td><td>1.1 (0.8-1.6)</td></tr>
<tr><td colspan="3">Talc use on sanitary napkins</td></tr>
<tr><td>No</td><td>242</td><td>1.0</td></tr>
<tr><td>Yes</td><td>32</td><td>0.9 (0.6-1.3)</td></tr>
<tr><td colspan="3">Talc use, perineal and sanitary napkins</td></tr>
<tr><td>None</td><td>179</td><td>1.0</td></tr>
<tr><td>Perineal or sanitary napkins</td><td>103</td><td>1.2 (0.9-1.5)</td></tr>
<tr><td>Both</td><td>25</td><td>0.9 (0.6-1.4)</td></tr>
</table>
In 1982, 40.4% of the cohort reported a history of perineal talc use (n = 31,789) and 14.5% reported a history of daily use (n = 11,411).

<u>Per histologic subtype ovarian cancer:</u>
<table>
<tr><th>Exposure category</th><th>No. of exposed cases</th><th>Relative risk (95% CI)</th></tr>
<tr><td colspan="3">All serous cancers, ever perineal talc use</td></tr>
<tr><td>No</td><td>101</td><td>1.0</td></tr>
<tr><td>Yes</td><td>84</td><td>1.3 (0.9-1.7)</td></tr>
<tr><td colspan="3">Serous invasive cancers, ever perineal talc use</td></tr>
<tr><td>No</td><td>84</td><td>1.0</td></tr>
<tr><td>Yes</td><td>76</td><td>1.4 (1.0-1.9)</td></tr>
<tr><td colspan="3">Endometrioid cancers, ever perineal talc use[a]</td></tr>
<tr><td>No</td><td>26</td><td>1.0</td></tr>
<tr><td>Yes</td><td>16</td><td>0.9 (0.5-1.9)</td></tr>
<tr><td colspan="3">Mucinous cancers, ever perineal talc use[a]</td></tr>
<tr><td>No</td><td>30</td><td>1.0</td></tr>
<tr><td>Yes</td><td>20</td><td>0.9 (0.5-1.7)</td></tr>
</table>
[a] Adjusted only for age (years), parity, duration of oral contraceptive use and tubal ligation history
</td>
<td></td>
</tr>
</table>

Type of study/data	Test substance (composition and particle size)	Relevant information about the study (as applicable)	Observations	Reference
		person–years of follow-up. Between 1982 and June 1996, 307 incident cases of epithelial ovarian cancer were identified by self-reporting in a biennial questionnaire, by deaths that were reported by relatives or postal authorities or through the National Death Index. Physicians blinded with respect to exposure status reviewed pathology reports to confirm each case and to determine the histological subtype for each tumour as reported by the woman's pathologist. Pooled logistic regression was used to model the incidence rate ratio of ovarian cancer for the exposed versus unexposed participants. <u>Adjustment for:</u> The reported results were adjusted for age in years, parity (defined as the number of pregnancies lasting 6 months or more), duration of oral contraceptive use, body mass index, history of tubal ligation, tobacco smoking status and postmenopausal use of hormones. Additional covariates		

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td>considered as potential confounders included age at menarche, duration of breastfeeding and age at menopause. Family history of ovarian cancer was not considered to be a confounder, since information on this covariate was not collected until 1992.</td><td></td><td></td></tr>
<tr><td>Prospective cohort study

Limitations: incomplete data for talc exposure (only available for part of the cohort)

121,700 female nurses in the USA between 1982-2006</td><td>Talc powder (purity unknown)</td><td>See Gertig et al. (2000).

Study consists of two cohorts (NHS and NHSII) but data on talc use was only available for NHS cohort. 108,870 women were included in the analysis of the NHS cohort with 797 incident cases of epithelial ovarian cancer identified.

Follow-up rate through 2006 was 95.2%.

<u>Exposure assessment:</u>

See Gertig et al. (2000).

Study participants completed follow-up questionnaires every 2 years between 1976 and 2006. Data on regular genital talc use was reported as ≥once/week vs. <once/week.
Between 1982 and 2006, 797 incident cases of epithelial ovarian cancer were identified (NHS cohort only). Cox</td><td>No significant association between regular exposure to talc and increased incidence rate ratio of epithelial ovarian cancer. A nonsignficiant positive association between talc use and mucinous tumours was noted.

<u>Epithelial ovarian cancer:</u>
<table><tr><th>Exposure category</th><th>Incidence rate ratio (95% CI)</th></tr><tr><td><once/week</td><td>1.0</td></tr><tr><td>≥once/week</td><td>1.1 (0.9-1.3)</td></tr></table>
<u>Per histologic subtype ovarian cancer:</u>
<table><tr><th>Histology</th><th>Incidence rate ratio (95% CI)</th></tr><tr><td>Serous invasive</td><td>1.1 (0.8-1.4)</td></tr><tr><td>Endometrioid</td><td>1.1 (0.7-1.7)</td></tr><tr><td>Mucinous, borderline and invasive tumours</td><td>1.5 (0.8-2.7)</td></tr></table></td><td>Gates et al. (2010)</td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td>proportional hazards regression was used to model the incidence rate ratio of ovarian cancer for the exposed versus unexposed participants.

<u>Adjustment for:</u>

Age, parity, breastfeeding, oral contraceptive use, tubal ligation, hysterectomy, age at natural menopause, oestrogen use, body mass index, activity, smoking (current/past), family history of breast and ovarian cancer.</td><td></td><td></td></tr>
<tr><td>Prospective cohort study

Limitations: lack of information regarding oophorectomy after baseline, potential for nondifferential misclassification of the exposure, no information regarding powder use after baseline, no data regarding the frequency of powder use, unknown during which years the perineal powder was used.

93,676 women in the USA between 1993-2012</td><td>Talc powder (purity unknown)</td><td>Cohort of 93,676 women enrolled between 1993-1998, aged 50-79. Characteristics of 61,285 postmenopausal women according to perineal powder use status were included. 429 adjudicated incident ovarian cancer cases were reported. Exclusion factors were: participation other clinical trials, unlikely to survive 3 years or interfering factors due to medical conditions, oophorectomy or unknown number of ovaries, history of any cancer (except nonmelonoma skin cancer). Follow-up rate through 2012 was 99.2%. The mean follow-up time was 12.4 years.</td><td>Perineal powder use does not appear to influence ovarian cancer risk. Combined ever powder use was not associated with individual subtypes of ovarian cancer.

<u>Ovarian cancer:</u>
<table>
<tr><th>Exposure category</th><th>No. of exposed cases</th><th>Hazard ratio (95% CI)</th></tr>
<tr><td colspan="3">Combined ever powder use [a]</td></tr>
<tr><td>Never</td><td>197</td><td>1.0</td></tr>
<tr><td>Ever</td><td>232</td><td>1.1 (0.9-1.3)</td></tr>
<tr><td><9 years</td><td>135</td><td>1.1 (0.9-1.4)</td></tr>
<tr><td>≥10 years</td><td>97</td><td>1.0 (0.8-1.3)</td></tr>
<tr><td colspan="3">Powder use on genitals</td></tr>
<tr><td>Never</td><td>247</td><td>1.0</td></tr>
<tr><td>Ever</td><td>181</td><td>1.1 (0.9-1.4)</td></tr>
<tr><td><9 years</td><td>112</td><td>1.2 (1.0-1.5)</td></tr>
<tr><td>≥10 years</td><td>68</td><td>1.0 (0.8-1.3)</td></tr>
<tr><td colspan="3">Powder use on sanitary napkins</td></tr>
<tr><td>Never</td><td>336</td><td>1.0</td></tr>
<tr><td>Ever</td><td>93</td><td>1.0 (0.8-1.2)</td></tr>
<tr><td><9 years</td><td>62</td><td>1.0 (0.7-1.3)</td></tr>
<tr><td>≥10 years</td><td>30</td><td>1.0 (0.7-1.4)</td></tr>
</table></td><td>(Houghton et al. 2014)</td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td>Exposure assessment:

Annual questionnaires on information regarding risk factors and outcomes, including ovarian cancer. Information on perineal powder (never or ever use, application, duration) was collected.

Adjustment for:

Age, race, oral contraceptive use, postmenopausal hormone use, family history of ovarian or breast cancer, age at last birth, body mass index, smoking, tubal ligation, parity</td><td>
<table>
<tr><td colspan="3">Powder use on diaphragm</td></tr>
<tr><td>Never</td><td>373</td><td>1.0</td></tr>
<tr><td>Ever</td><td>52</td><td>0.9 (0.7-1.2)</td></tr>
<tr><td><9 years</td><td>35</td><td>0.9 (0.6-1.3)</td></tr>
<tr><td>≥10 years</td><td>17</td><td>1.0 (0.6-1.6)</td></tr>
</table>
[a] Combined ever powder use is the longest duration of use among the applications to genitals, sanitary napkins, and diaphragms.

Per histologic subtype ovarian cancer[a] :
<table>
<tr><th>Exposure category</th><th>No. of exposed cases</th><th>Relative risk (95% CI)</th></tr>
<tr><td colspan="3">Serous cancers (includes borderline cancers)</td></tr>
<tr><td>Never</td><td>87</td><td>1.0</td></tr>
<tr><td>Ever</td><td>117</td><td>1.2 (0.9-1.5)</td></tr>
<tr><td colspan="3">Serous invasive cancers</td></tr>
<tr><td>Never</td><td>80</td><td>1.0</td></tr>
<tr><td>Ever</td><td>105</td><td>1.1 (0.8-1.5)</td></tr>
<tr><td colspan="3">Mucinous</td></tr>
<tr><td>Never</td><td>12</td><td>1.0</td></tr>
<tr><td>Ever</td><td>13</td><td>1.0 (0.5-2.3)</td></tr>
<tr><td colspan="3">Endometrioid</td></tr>
<tr><td>Never</td><td>13</td><td>1.0</td></tr>
<tr><td>Ever</td><td>20</td><td>1.3 (0.6-2.6)</td></tr>
<tr><td colspan="3">Other</td></tr>
<tr><td>Never</td><td>47</td><td>1.0</td></tr>
<tr><td>Ever</td><td>54</td><td>1.0 (0.7-1.5)</td></tr>
</table>
[a] Combined ever perineal powder use</td><td></td></tr>
<tr><td>Prospective cohort study

Limitations: latency of ovarian cancer not accounted for, the relative risk for douching in relation to ovarian cancer could be underestimated</td><td>Talc powder (purity unknown)</td><td>The Sister Study (2003–2009) enrolled and followed 50,884 women in the USA and Puerto Rico who had a sister diagnosed with breast cancer; aged 35-74; never had breast cancer but each had a full or half-sister who had</td><td>No association between recent talc use and ovarian cancer risk was found, but a strong positive association between douching and ovarian cancer risk was observed.

Ovarian cancer:
<table>
<tr><th>Exposure category</th><th>No. of exposed cases</th><th>Hazard ratio (95% CI)</th></tr>
<tr><td colspan="3">Douching past 12 months</td></tr>
<tr><td>No</td><td>121</td><td>1.0</td></tr>
</table></td><td>(Gonzalez et al. 2016)</td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr>
<td>50,884 women in the USA and Puerto Rico between 2003 and 2009</td>
<td></td>
<td>been diagnosed with breast cancer. More than one sister per family could participate.

Participants with bilateral oophorectomies or ovarian cancer before enrolment or who had no follow-up information were excluded. 41,654 participants were included in this analysis with a median follow-up of 6.5 years. 154 participants reported a diagnosis of ovarian cancer.

Tumours of the ovary, fallopian tubes, peritoneum or of uncertain origin but likely from one of the three aforementioned primary sites were included. Updated information on oophorectomies was collected in follow-up questionnaires administered every 2–3 years. Information on any new cancers was collected via an annual health update and the follow-up questionnaires.

<u>Exposure assessment:</u>

Participants completed computer-assisted telephone interviews, which included questions about reproductive history (including any oophorectomies),</td>
<td>
<table>
<tr><td>Yes</td><td>30</td><td>1.8 (1.2-2.8)</td></tr>
<tr><td colspan="3">Talc use past 12 months</td></tr>
<tr><td>No</td><td>130</td><td>1.0</td></tr>
<tr><td>Yes</td><td>17</td><td>0.7 (0.4-1.2)</td></tr>
<tr><td colspan="3">Douched and used talcum powder past 12 months</td></tr>
<tr><td>Neither</td><td>106</td><td>1.0</td></tr>
<tr><td>Talc use/no douching</td><td>10</td><td>0.6 (0.3-1.1)</td></tr>
<tr><td>Douching/no talc use</td><td>23</td><td>1.9 (1.2-2.9)</td></tr>
<tr><td>Both</td><td>7</td><td>1.8 (0.8-3.9)</td></tr>
</table>
Missing values: douching (3 cases), talc use (7 cases).
</td>
<td></td>
</tr>
</table>

Type of study/data	Test substance (composition and particle size)	Relevant information about the study (as applicable)	Observations	Reference
		health conditions, and lifestyle factors. Participants also completed a self-administered questionnaire about personal care products used in the 12 months before enrolment, which included questions about frequency of douching and about genital talc use in the form of powder or spray applied to a sanitary napkin, underwear, diaphragm, cervical cap, or vaginal area. Response categories were: did not use, used less than once a month, used 1–3 times per month, 1–5 times per week, or more than 5 times per week. <u>Adjustment for:</u> Race, body mass index, parity, duration of oral contraceptive use, baseline menopause status and patency		
HRR: hazard rate ratio; mppcf: million particles per cubic foot; NMRD: non-malignant respiratory disease; OR: odds ratio; RR: relative risk; SIR: standardised incidence ratio; SMR: standardised mortality ratio; TLV: threshold limit value; WL: working levels				

10.9.1 Short summary and overall relevance of the provided information on carcinogenicity

In vitro studies

Numerous in vitro studies investigating effects of talc were found which provide information on mechanism of action, a brief summary is provided below. More detailed study summaries can be found in Annex I.

Talc did not induce mutations in bacterial reverse mutation tests (in Salmonella and Saccharomyces), and chromosomal aberrations, unscheduled DNA synthesis (UDS), sister chromatid exchanges (SCE) in rat pleural mesothelial cells or human embryonic lung cells (Endo-Capron et al. 1993; Fujita et al. 1988; Litton Bionetics Inc. 1974). However, talc caused malignant transformation in primary human ovarian epithelial

cells, although only a poster abstract is available for this study (Harper et al. 2021). Other studies provide evidence that talc enhanced cell survival and proliferation in normal and cancer ovarian cells (Fletcher et al. 2019; Mandarino et al. 2020). Furthermore, exposure to talc resulted in altered gene expression and activity of antioxidant and prooxidant enzymes, possibly due to point mutations, in normal and cancer ovarian cells, and induced gene expression which may contribute to tumour growth and metastasis in murine ovarian cells (Fletcher et al. 2019; Mandarino et al. 2020).

A general cytotoxic response upon exposure to talc was observed in multiple cell types (mouse peritoneal macrophages, hamster tracheal epithelial cells and human mesothelial cells), but talc was not always found to be cytotoxic (Davies et al. 1983; Shukla et al. 2009; Woodworth et al. 1982; Chamberlain and Brown 1978; Toledano-Magana et al. 2021). Talc induced apoptosis in lung cancer cells, but not in normal pleural mesothelial cells (Lee et al. 2010; Nasreen et al. 2000). Talc triggered inflammation and/or oxidative stress in human mesothelial cells, human monocyte-derived macrophages and in murine macrophages (Mandarino et al. 2020; Mierzejewski et al. 2021; Nasreen et al. 1998; Shukla et al. 2009; Toledano-Magana et al. 2021).

Some evidence for a link between talc and inflammation was found in vitro studies. Enhanced survival or proliferation in bone-marrow derived macrophages may contribute to talc-induced inflammation and granuloma formation (Hamilton et al. 2001). Furthermore, talc compromised immunosurveillance function of murine macrophages (Mandarino et al. 2020). A haemolytic effect (50% haemolysis of red blood cells) of talc (6.5 mg/ml) was demonstrated by Woodworth et al. (1982), although at a much higher concentration (50-fold) as compared to chrysotile.

In vitro studies together provide evidence of cytotoxicity and haemolytic activity of talc. In addition, exposure to talc increased oxidative stress and inflammation which together could provide information on the mode of action for carcinogenicity of talc.

Animal studies

Multiple animal carcinogenicity and chronic toxicity studies are available (Table 9) for talc (not containing asbestos or asbestiform fibres) and most have been reviewed by the IARC (IARC 2010). There is, however, only one study with rats and mice available that is similar to a test guideline (OECD TG 453) and was performed in compliance with GLP. Other studies have limitations in methodology and reliability. Inhalation, oral, perineal and intravaginal exposure to talc are considered relevant to human and animal studies investigating these routes are summarised here. No dermal carcinogenicity (or dermal chronic toxicity) animal studies are available for talc. Other exposure routes (intraperitoneal, subcutaneous, intrapleural, intratracheal or intrathoracic) are considered less relevant to human and are briefly discussed in this CLH report. However, a summary of these studies can be found in Annex I.

F344 rats (n = 50/group/sex) were exposed to talc (≥96% pure) via inhalation (aerosols; 0, 6 and 18 mg/m^3; MP10-52 grade; MMAD 6/18 mg/m^3: 2.7/3.2 µm; whole body), 6 h per day, 5 days per week in a lifetime study until mortality in any exposure group reached 80% (113 weeks for males and 122 weeks for females), as part of a carcinogenicity study performed under the National Toxicology Program (NTP 1993), see Annex I for details. In addition, satellite groups (n = 22/group/sex) were included for control and exposure groups for interim evaluation (6, 11, 18 and 24 months) of pathology, lung burden measurements, serial pulmonary function measurements, lung biochemistry, cytology, and phagocytosis measurements. No clinicals signs and exposure-related mortality were noted in male and female rats. In female rats, body weight was reduced (-14% compared to control), no body weight changes were noted in male rats (Table 11). Lung burdens were in general proportional to exposure concentration at each interim timepoint (6 to 24 months; normalised to exposure concentration) in all exposed female rats and at 6 mg/m^3 in male rats (see Annex I Table 3). In males at 18 mg/m^3, lung burdens remained similar at 18- and 24-month interim evaluations. This indicated clearance of talc from the lungs was either not substantially impaired by increased exposure concentrations or impaired similarly at both dose levels. It is not likely lung clearance was impaired as viability and phagocytic activity of macrophages recovered from lavage fluid were not statistically significantly affected in any dose group in male or female rats compared to controls (see Annex I Table 12). However, a concentration-related impairment in respiratory function was observed starting mostly at the 11-month

interim evaluation with increasing severity and duration of exposure, at 18 mg/m^3 in male and female rats (see Annex I Figure 1).

Inflammation (granulomatous inflammation in all exposed rats), reparative and proliferative processes (peribronchial and alveolar epithelial hyperplasia, interstitial fibrosis) were noted in the lungs in all exposed male and female rats at interim evaluations, progressing in severity over time, and at final sacrifice (Table 11). For a summary on histopathological changes observed in the lungs, see 10.12.1. A statistically significantly increased incidence of lung tumours (alveolar/bronchiolar adenoma and/or carcinoma) was observed at the highest dose in females (Table 11 and Annex I Table 18; first incidence at 716 days in exposed groups) compared to controls and historical control data. Lung tumours developed late in life in rat. In both male and female rats a statistically significantly increase and dose-dependent incidence of adrenal medulla pheochromocytoma were noted (Table 11 and Annex I Table 20; first incidence at 544 days in exposed groups). The study authors concluded that there was clear evidence of carcinogenic activity in female rats, while some evidence was found in male rats.

Table 11: Summary of the lifetime and 2-year carcinogenicity studies of talc. Adopted from summary table (p. 8) from NTP (1993).

	Male F344/N Rats	Female F344/N Rats	Male B6C3F$_1$ Mice	Female B6C3F$_1$ Mice
Exposure levels	0, 6, or 18 mg/m^3 (equivalent to 0, 2.8, or 8.4 mg/kg per day)	0, 6, or 18 mg/m^3 (equivalent to 0, 3.2, or 9.6 mg/kg per day)	0, 6, or 18 mg/m^3 (equivalent to 0, 2, or 6 mg/kg per day)	0, 6, or 18 mg/m^3 (equivalent to 0, 1.3, or 3.9 mg/kg per day)
Body weights	18 mg/m^3 group slightly lower than controls	18 mg/m^3 group slightly lower than controls	Exposed groups similar to controls	Exposed groups similar to controls
Survival rates	9/49, 14/50, 16/50	11/50, 13/49, 9/50	30/47, 28/48, 32/49	30/49, 23/48, 25/50
Nonneoplastic effects	Lung: granulomatous inflammation (2/49, 50/50, 49/50); interstitial fibrosis (1/49, 16/50, 33/50); alveolar epithelial hyperplasia (5/49, 26/50, 38/50); cyst (0/49, 0/50, 3/50); alveolar squamous metaplasia (0/49, 0/50, 2/50)	Lung: granulomatous inflammation (2/50, 47/48, 50/50); interstitial fibrosis (1/50, 24/48, 44/50); alveolar epithelial hyperplasia (2/50, 27/48, 47/50); cyst (0/50, 1/48, 7/50); alveolar squamous metaplasia (0/50, 0/48, 8/50)	Lung: chronic inflammation (0/45, 16/47, 40/48); macrophage hyperplasia (3/45, 46/47, 48/48)	Lung: chronic inflammation (0/46, 25/48, 38/50); macrophage hyperplasia (2/46, 45/48, 43/50)
Neoplastic effects	Adrenal medulla: benign or malignant pheochromocytoma (26/49, 32/48, 37/47)	Lung: alveolar/ bronchiolar adenoma (1/50, 0/48, 9/50); alveolar/bronchiolar carcinoma (0/50, 0/48, 5/50); alveolar/bronchiolar adenoma or carcinoma (1/50, 0/48, 13/50) Adrenal medulla: benign or malignant pheochromocytoma (13/48, 14/47, 23/49)	None	None
Level of evidence of carcinogenic activity	Some evidence	Clear evidence	No evidence	No evidence

Several methodological limitations regarding the NTP study have been raised. Aerosol concentrations were not properly controlled throughout the experiment (week 11-18: higher than 18 mg/m^3 target; week 70-82:

lower than 6 or 18 mg/m^3 targets) and micronized talc (2.7 to 3.2 µm) was used, which has a smaller particle size distribution than cosmetic talc and talc used in other animal studies (6.0-6.9 µm). However, the particle size distribution of talc used in the NTP study is slightly higher than the recommend standard (MMAD of ≤ 2 µm with a σg of 1-3) for repeated exposure studies according to the current OECD guideline for inhalation toxicity studies (point 76, OECD Guidance Document 39[14]). The micronized talc used is thus not considered a limitation for hazard evaluation and is in fact within limits of current OECD guidelines.

Background incidence of adrenal medulla pheochromocytoma in F344 rat strain was increased in multiple studies in the NTP program (ECHA 2017). However, the incidence of (benign, malignant or combined) pheochromocytoma (Annex I Table 20) in the highest dose group was greatly increased compared to control and historical control data in both sexes. (The historical control[15] males range was: benign: 4/50 – 27/54; malignant: 0/53 – 3/49; benign, malignant or complex: 4/48 – 27/54; females: 0/50 – 6/47; 0/47 – 2/50; 0/50 – 6/47 [see also Annex I Table 21]). The increased incidence of pheochromocytomas appears to be talc-related. The increased incidence mainly concerned benign neoplasms and no supporting increase in hyperplasia incidence was noted. Pheochromocytomas are known in rats exposed to particulates through inhalation (secondary to hypoxemia) and considered less relevant to humans (Ozaki et al. 2002). Lung function was impaired in both sexes at the highest dose level from 11 months of exposure onwards, see 10.12.1. On the other hand, no clinical signs or haematology data related to hypoxemia were found or reported, respectively. It is unclear if lung damage was the primary cause of the formation of pheochromocytomas.

Another limitation raised is that the lung tumours in female rats were observed at the highest dose level (18 mg/m^3) which was possibly above maximum tolerable dose (MTD); based on body weight changes in female rats, and lower respiratory function from 11 months and onwards and high lung burden in male and female rats. A notable reduction in body weight (>10%) was only observed in female rats in the highest dose group (compared to control), while chronic lung toxicity was observed in both sexes. Viability of macrophages and phagocytic activity of alveolar macrophages, recovered from lavage fluid, were not statistically significantly different at 6 and 18 mg/m^3 compared to control in rats of both sexes. No evidence of lung overload was thus found. In regard to lung burden, Morrow (1988, 1992) stated that 6% particle volume loading of alveolar macrophages (AM) “a progressive prolongation of pulmonary dust retention apparently developed”, and if 60% particle volume loading of AM is reached “pulmonary dust clearance appeared to cease almost completely”. Morrow roughly estimated the levels of lung burdens related to the 6% and 60% particle volume loading of AM: he calculated a total AM pool volume of 25 mm³ in a rat lung of about 1.5 g (about 2.5×10^7 alveolar macrophages with an AM volume of about 1000 µm³). A volume of 6% of the AM pool then corresponds to 1.5 mm³ or 1.5 mg of particles with unit density (AM volume loading of 60% corresponds to 15 mm³ or 15 mg of particles with unit density; Table 12). For talc 6% or 60% volume loading of AM would correspond to 4.1 or 41 mg talc/rat lung (Table 12). Following this principle, it can be calculated that the talc exposure resulted in 20-50% average (male and female rats) volume loading (13.5-36.5 mg/rat lung) in alveolar macrophages (Table 13), and shows that 60% volume loading was slightly exceeded in male rats (43 mg/rat lung) but not in female rats (30 mg/rat lung) at the highest dose level. The comparable viability of macrophages, AM phagocytic activity and volume loading all indicate that the increased induction of benign and malignant lung tumours in female rats cannot be attributed to lung overload conditions. Alveolar clearance rates and half-times were not measured in the NTP (1993) study, but Oberdörster (1995) derived crude estimates of clearance rates and half-times based on the pulmonary talc accumulation data in the NTP study (Table 14). The alveolar clearance half-times did not reach or exceed one year upon exposure to talc at any dose level in rats. This is in line with the recommendation in the current OECD guidance document on the conduct and design of chronic toxicity and carcinogenicity studies

[14] OECD Guidance Document 39: https://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2009)28/rev1&doclanguage=en

[15] Historical control data based on historical control data in F344/N rats in NTP studies performed between 1984 and 1994. Data from NTP historical controls database: https://ntp.niehs.nih.gov/data/controls/index.html.

guidance for chronic toxicity and carcinogenicity studies (point 135, OECD Guidance Document 116).[16] It should be noted, however, that AM volume loading and alveolar clearance half-times are estimates and it cannot be excluded that actual AM volume loading and clearance rates might have been different in rats in the NTP study. On the other hand, the measured viability of macrophages and phagocytic activity of alveolar macrophages in the NTP study (not statistically significantly different compared to control) indicated no lung overload. Taken all together, lung tumours in female rats thus developed under inhalation exposure conditions associated with marked particle loading of AM, but this is not considered excessive.

Table 12: Substance-specific lung burden and degree of alveolar macrophages (AM) particle volume loading. Adopted from (RAC 2017).

Density of substance	Substance-specific lung burden in the rat lung corresponding to a 6% volume loading of alveolar macrophages	Substance-specific lung burden in the rat lung corresponding to a 60% volume loading of alveolar macrophages
1	1.5 mg/rat lung	15 mg/rat lung
2.7 (talc)	4.1 mg/rat lung	41 mg/rat lung

Table 13: Calculation of lung burden upon exposure to talc in rats in the NTP study[17].

	Exposure levels	
	6 mg/m^3 (180 mg/h/m^3 per week)	18 mg/m^3 (540 mg/h/m^3 per week)
Talc burden after 23-24 months in rats (mg per lung)	• 18 (male) • 9 (female) • 13.5 (average)	• 43 (male) • 30 (female) • 36.5 (average)
Particle volume loading in alveolar macrophages	~20%	~50%

Table 14: Average pulmonary retention halftimes and average clearance rates for talc in rats estimated from measured pulmonary talc burdens in the chronic NTP study. Adopted from Table 4 from Oberdörster (1995).

	(mg/m^3)	$T_{1/2}$, days	Clearance rate/day
Males	6	300	2.31×10^{-3}
	18	300	2.31×10^{-3}
Females	6	250	2.77×10^{-3}
	18	280	2.48×10^{-3}

In another study, Wistar rats (n = 12/group/sex) were exposed (whole body) to Italian talc (92% pure) via inhalation (about 40% as respirable dust [definition of respirable not specified]; 0 or 10.8 mg/m^3; 00000 grade; mean particle size 25 µm; upper particle size of 70 µm), 7.5 h per day, 5 days per week for 6 or 12 months (Wagner et al. 1977). The documentation in this study is very limited and therefore not further specified in the Annex of this proposal. Rats were sacrificed ten days after the end of each exposure period or one year after the exposure had discontinued. Per group: 12 rats died, 10 rats were sacrificed, and 2 rats were unaccounted for. Survival of exposed rats (6 and 12 month group combined: 24/48) were similar to the

[16] OECD Guidance Document 116: https://www.oecd-ilibrary.org/docserver/9789264221475-en.pdf?expires=1642505883&id=id&accname=ocid49027884&checksum=DB32A59DFC7FACD54DC7D49CAA1CD78B

[17] Based on calculations from: Nikula (2000)

control group (27/48). No lung neoplasms were noted in the 6-month and control group; one small lung adenoma (1/24) was noted in the 12-month group but this was likely an incidental finding.

$B6C3F_1$ mice (n = 50/group/sex) were exposed (whole body) to talc (≥96% pure) via inhalation (aerosols; 0, 6 and 18 mg/m^3; MP10-52 grade; MMAD 6/18 mg/m^3: 3.3/3.6 µm), 6 h per day, 5 days per week in a 2-year study (103-104 weeks) and then sacrificed as part of a lifetime carcinogenicity study (NTP 1993), see Annex I for details. In addition, satellite groups (n = 40/group/sex) were included for control and exposure groups for interim evaluation (6, 12 and 18 months) of pathology, lung burden measurements, lung biochemistry, cytology, and phagocytosis measurements. Aerosol concentrations were not properly controlled throughout the experiment (week 70-82: lower than 6 or 18 mg/m^3 targets). No clinical signs or differences in survival rates were noted in mice (Table 11). The exposure-normalised data show that lung talc burdens of mice exposed to 18 mg/m^3 were disproportionately greater at 12 and 24 months compared to mice exposed to 6 mg/m^3 (Annex I Table 24). This was statistically significant at 12 and 24 months in both sexes, but not at 6 or 18 months (both sexes). The lack of statistical significance at 18 months might be explained, in part, by the small sample size. Clearance of talc from the lungs was either not substantially impaired by increased exposure concentrations or impaired similarly at both dose levels. In addition, lung burden was disproportionately greater at 18 mg/m^3 in comparison to 6 mg/m^3, explained by the statistically significantly reduced phagocytic activity in both sexes at 18 mg/m^3 (Annex I Table 30). Absolute and relative lung weights were increased at the highest dose at final sacrifice in both sexes (Annex I Table 31). Chronic active inflammation (minimal to mild) and accumulation of macrophages in the alveoli surrounding terminal bronchioles (hyperplasia, macrophage; minimal to mild) were observed in the lungs at ≥6 mg/m^3 in both sexes (for a more detailed summary see 10.12.1). No other histological findings were noted in the lungs. No carcinogenic effects were observed in mice.

Golden Syrian hamsters (n = 25-50/group/sex) were exposed (whole body, 5 days/week) to talc-based baby powder via inhalation (aerosols, ≥95% w/w platy talc from Vermont) for 30 days (3, 30 or 150 min/day; 37.1 mg/m^3, mean respirable fraction 9.8 mg/m^3, MMAD of 4.9 µm) or 300 days (30 or 150 min/day; 27.4 mg/m^3, mean respirable fraction 8.1 mg/m^3, MMAD of 6.0 µm), see Annex I for details (Wehner et al. 1977c). Corresponding control groups were exposed to air. After completion of the exposures, the hamsters were maintained for observations for the remainder of their natural lifespan. The experiments were concluded by the killing of all surviving animals when the number of deaths in the group with the most survivors exceeded 90%. It should be noted the MMAD of talc particles used here is larger than recommended by the OECD.[14] No statistically significantly differences or dose-response in survival rates, clinical toxicity or body weights related to exposure to talc were noted. Mean survival of females was statistically significantly lower compared to males in all groups. A few neoplasms were noted in all groups, but incidences were not related to exposure. No primary neoplasms were found in the respiratory system of any hamster.

Two oral studies in are available for talc, both conducted in Wistar rats. In one study rats (n = 8-16/group/sex) were fed 0 or 100 mg Italian talc (92% pure, 00000 grade) per day on 101 days during 5 months via diet, followed by basal diet for life (Wagner et al. 1977). The documentation in this study is very limited and therefore not further specified in the Annex of this proposal. No significant differences on the average survival (614 days vs. 641 days in control) and tumour incidences were noted in the exposed group compared to control. In the other study rats (n = 25/group/sex) were fed 0 or 50 mg talc (commercial type, not further specified)/kg bw/day for life (Gibel et al. 1976). No significant differences on the average survival (649 days vs. 702 days in control) and tumour incidences were noted in the exposed group compared to control.

No carcinogenicity or chronic toxicity animal studies for the perineal or vaginal route are available for talc. Other animal studies investigating perineal and intravaginal exposure to talc are discussed below.

In an experimental study, female Sprague-Dawley rats (n = 7/group) were exposed to 100 mg talc (purity unknown)/day in saline via intravaginal (group 3) or perineal (group 4) application for 3 months (Keskin et al. 2009). Two control groups were included; one group did not receive any intervention (group 1) and one group received intravaginal application of saline (group 2). Animals were sacrificed after the completion of the experiment. Evidence of foreign body reaction and infection (vulvovaginitis, endometritis, pelvic

infection (PID), ovarian infection and salpingitis and tubal occlusion), along with an increase in inflammatory cells, were found in all the genital tissues upon intravaginal or perineal application of talc (Table 15). There was an increase in the number of follicles in animals in the exposure and control groups. The study authors concluded that talc resulted in a foreign body reaction in the female genital system but no neoplastic reaction was observed. The test period of this study is not sufficient to study tumour development and the infection observed was likely unrelated to talc exposure, both important limitations of this study.

Table 15: Groups of histopathological changes observed in the genital system of experimental animals. Adopted from Table 1 from Keskin et al. (2009).

	Normal	Vulvovaginitis	Endometritis	P ID	Findings of ovarian infection ($n = 2 \times 7 = 14$)	Salpingitis and tubal occlusion ($n = 2 \times 7 = 14$)	Neoplastic changes	Preneoplastic changes
Group 1 ($n = 7$)	5	2	0	1	1 (2 ovaries)	1 (2 fallopian tubes)	0	0
Group 2 ($n = 7$)	6	0	1	0	0	0	0	0
Group 3 ($n = 7$)	0	5	6	4	7 ($2 \times 3 + 1$)*	8 (2×4)	0	0
Group 4 ($n = 7$)	0	7	4	5	8 (2×4)	5 ($2 \times 2 + 1$)**	0	0

Statistical comparisons of the groups were done by using Fischer exact test. Following positive correlations were found between groups: Group 3 and Group 1, $P = 0.021$, $P < 0.05$; Group 3 and Group 2, $P = 0.005$, $P < 0.05$; Group 4 and Group 1, $P = 0.021$, $P < 0.05$, Group 4 and Group 2, $P = 0.005$, $P < 0.05$. Other comparisons did not reveal statistically significant results ($P > 0.05$)

Group 1: control group with no intervention, Group 2: control group receiving intravaginal saline administration, Group 3: study group receiving intravaginal talc application, Group 4: study group receiving perineal talc application

* In this group, one rat had infection findings in only one ovary. For the remaining, both ovaries were involved, ** In this group, one rat had infection findings in only one fallopian tube

In another experimental study female Sprague-Dawley rats (n = 3-10/group) were administered implants consisting of Italian talc (purity unknown, 00000 grade, size 0.3-14 µm) via intrabursal injection. Animals were sacrificed 1, 3, 6, 12 and 18 months after implantation (Hamilton et al. 1984). Two controls groups were included: 3 sham-operated animals and 3 unexposed animals. Cystic appearance of the ovaries and associated tissue was noted 1-18 months after exposure, but did not appear time-dependent. Histological changes included decreased amount and spread of ovarian tissue as a remnant on the inner wall of the bursa and focal areas of papillary change (4/10 vs. 0/6 in control) after 12 months, these were considered preneoplastic. There was no evidence of cellular atypia or neoplastic changes in the ovaries in exposed females. Talc particles were present in the surface of the ovarian epithelium, cortex and connective tissue matrix of the bursa. The study authors noted that histological changes observed might be related to constant exposure to high concentrations of steroid hormones, which is entrapped in follicular fluid within the distended bursa.

Wistar rats (n = 7/group) were exposed to talc powder (purity not stated; 100 mg/kg bw) via an incision made in the uterine horn, applied during the proliferative phase of the menstrual cycle (Yumrutas et al. 2015). No operation or application were performed in the control group. All animals were sacrificed after one month. Gene expression levels of *Gsr* and *Sod1* (markers for oxidative stress) were statistically significantly ($p < 0.05$) increased upon exposure to talc compared to control. Gene expression levels of other antioxidant, antiapoptotic and apoptotic genes were changed, but not statistically significant. In addition, statistically significant ($p < 0.05$) changes in miRNA levels were observed compared to control. This study is of limited reliability (RL 3) as no appropriate control groups (sham-operated and sham-exposed groups) were included and no information on body weight, survival, clinical signs or gross pathology was provided in this study.

In extension of the inhalation NTP study (1993), ovarian exposure in female F344/N rats and female $B6C3F_1$ mouse (n = 10/group) to talc was investigated as according to the study authors (Boorman and Seely 1995): "*there was ample opportunity for perineal exposure as assumed by the study authors, as talc was covering fur and the cage bars*." There were no exposure-related lesions in the ovaries of rats or mice (see Annex I for details). No talc particles were found in the ovaries or ovarian bursa in rats, findings in mice were not further specified. It is questionable if talc particles have reached the ovaries and therefore the study has limited value.

Multiple studies are available investigating other routes of administration of talc and include intrapleural, intratracheal, intrathoracic, subcutaneous or intraperitoneal administration (see Annex I for summary table).

In one study (reported as an abstract) tumours (one lymphosarcoma and one reticulum-cell sarcoma in the peritoneal cavity, one cystadenoma of the liver) were noted in female Evans rats (3/27 vs. 0/26 in saline-exposed controls) upon a single intraperitoneal injection of 100 mg USP-grade talc. In male Marsh mice, tumours (two adenocarcinomas and three lymphoid tumours of the lung) were also noted (5/47 vs. 0/48 in saline-exposed controls) upon a single intrathoracic injection of 10 mg USP-grade talc (Bischoff and Bryson 1976). In another study malignancies were observed in Golden Syrian hamsters (33 out of 45) upon exposure (intratracheal administration) with talc plus benzo[*a*]pyrene, while no malignancies were noted in talc-exposed animals or in the control groups (Stenback and Rowlands 1978). In the other studies no increased incidence of tumour formation was observed upon exposure to talc compared to the control.

Animal studies – summary

Based on these animal studies it can be concluded that there is evidence of carcinogenicity (alveolar/bronchiolar carcinoma and malignant pheochromocytoma) for talc from one lifetime (inhalation) study in rat. The benign and malignant lung tumours were only observed in female rats, developed late in life and were induced in the absence of overload, as indicated by normal viability and phagocytic activity of lung macrophages as well as the calculated macrophage loading. On the other hand, inhalation exposure conditions in the NTP study were associated with marked particles loading of macrophage, but not excessive. The pheochromocytomas observed in male and female rats could be related to talc, although a plausible mechanism is unknown. A similar study in mice was negative for tumour formation. Other carcinogenicity inhalation studies for talc have several limitations regarding the adequacy of the study design (in particular regarding the MMAD of particles within the exposure atmosphere) and, most importantly, did not study chronic exposure (exposures of 30 days or up to 12 months). No tumours were observed upon oral exposure to talc.

For perineal and intravaginal exposure to talc, no adequate carcinogenicity animal studies are available. No evidence of carcinogenicity was found in the limited available animal studies. Importantly, no chronic toxicity studies are available for this route and preneoplastic changes in the ovaries (in rat) were described in one animal study.

Human epidemiological studies – occupational exposure

Multiple epidemiological studies have been published where occupational exposure to talc (not containing asbestos or asbestiform fibres) in millers and miners from multiple countries was investigated and summarised in Table 10. The IARC has reviewed most studies published up to 2010 (IARC 1987, 2010), see Annex I for studies summarised by IARC. IARC concluded that there was little or inconsistent evidence of an increased risk of cancer and occupational exposure to talc (IARC 2010). Inhaled talc (not containing asbestos or asbestiform fibres) was not classifiable as to its carcinogenicity (Group 3). A literature review has been published by the Cosmetic Ingredient Review Expert Panel regarding the safety assessment of talc used in cosmetics (Fiume et al. 2015), and a literature review addressing inhalation toxicity of talc (Johnson 2020). These sources were used here as main sources for published epidemiological studies investigating occupational exposure to talc. The cohort studies assessed here in general included relatively small populations and limited information on exposure levels, previous occupation and confounders (smoking and alcohol consumption). Cohort studies of talc miners and millers from sources containing talc (fibrous to platy) and amphiboles were not included by the IARC workgroup (2010) and in this CLH report (Honda et al. 2002; Brown et al. 1990; Brown and Wagoner 1978; Stille and Tabershaw 1982; Lamm et al. 1988). Amphiboles, such as tremolite and anthophyllite, have been detected in talc from a mine (Gouverneur District) in New York state, USA. Tremolite and anthophyllite fibres are known to cause mesotheliomas in animals and humans (Finkelstein 2012), and these studies were therefore not included in this CLH report.

Observations related to any non-malignant respiratory diseases (NMRDs) are discussed in 10.12.1.

Occupational exposure – talc miners and millers

Multiple epidemiological studies have examined talc miners and millers in various geographical regions. Retrospective cohort studies by Rubino et al. describe mortality in 1678 or 1992 male talc mines and millers in Piedmont, Italy (Rubino et al. 1979; Rubino et al. 1976). IARC (2010) noted that the term silica used by

Rubino et al. (1976) was in fact quartz. Talc from this site contains high levels of respirable quartz and small amounts of tremolite (respirable range 0.5 – 5 µm, as defined by British Medical Research Council criteria). Rock-type inclusions were removed before milling so that silica or quartz content was <2%. Cumulative exposure levels (in million particles per cubic foot (mppcf)-year) to talc was estimated from dust content measurements in the period of 1948-1974 and miners and millers were classified in three different levels (miners: 566–1699, 1700–566, 5666–12750; millers: 25–141, 142–424, 425–906). No increased standardised mortality ratio (SMR) was observed for all cancers or lung cancer in miners or millers. In addition, no increased SMR associated with higher cumulative exposure was observed. However, statistically significantly increased SMR rates for all causes in miners and millers were found (SMR (95% CI)[18] miners: 1.3 (1.2-1.4); millers: 1.2 (1.0-1.4)). In a follow-up study, respirable (not specified) dust levels of 0.5-2.5 mg/m^3 (mean 1.1 mg/m^3) and talc levels between 0.3-2.0 mg/m^3 (mean 1.0 mg/m^3) were reported (Coggiola et al. 2003), and similar respirable (not specified) dust levels were reported in a more recent follow-up study (Pira et al. 2017). No excess SMR was found for total cancer mortality, nor mortality for lung cancer in the total cohort in follow-up studies (Ciocan et al. 2022; Coggiola et al. 2003; Pira et al. 2017), although slight (not statistically significant) increased SMRs were noted for stomach cancer in the total cohort (1822 to 1974 workers) and in miners for all cancers or lung cancer (Coggiola et al. 2003; Pira et al. 2017). However, statistically significant increased SMRs for oral cavity, pharyngeal, and oesophagus cancers were observed in the total cohort. No linear trends were observed between cancer mortality and first exposure (latency). The authors stated that the excess mortality for oral cavity and oesophageal cancers is likely due to alcohol consumption and cigarette smoking. However, no or limited information on smoking habits and alcohol consumption for the talc miners and millers was provided by the study authors to confirm this.

Selevan et al. (1979) studied mortality in male talc workers (392 workers) from Vermont, USA. Talc from this site contains chlorite and dolomite but no detectable asbestiform fibres and no significant quantities of free silica (respirable crystalline silica <0.25%, defined as free silica by study authors). Miners were also exposed to radon daughters which is a cofactor. No exposure data were available in this cohort, but past exposure levels exceeded levels of 20 mppcf in both miners and millers. An excess mortality (statistically significant) from respiratory cancer was noted for miners (SMR 4.3 (1.4-10.1)) but not for millers. In a recent follow-up study, Fordyce et al. (2019) found a border-line nonsignificant excess of lung cancer (SMR 1.4 (1.0-2.0)). One case of mesothelioma was noted in talc worker who also had been exposed to asbestos, following employment of 30 years or more. No trend in latency and risk of respiratory cancer was noted. The authors concluded that there is no evidence of increased risk of respiratory cancer from these data.

In a cohort study of Katsnelson and Mokronosova (1979) consisting of male and female miners and millers from the former USSR (number unknown), a high and statistically significantly increased mortality ratios were found for all cancers combined, lung and stomach cancer. Study authors reported that talc of this area does not contain tremolite or fibrous materials. Levels of quartz ranged from 0.2-1.6%. However, this study has important limitations; the number of workers are lacking in this study and IARC noted a discrepancy in the study author's calculations (denominator only included current employed persons and not current and past workers).

In a French cohort, no significant excess mortality from cancer in general or specifically from respiratory and digestive cancers was found in 470 talc workers (Leophonte et al. 1983; Leophonte and Didier 1990). No asbestos was found in French talc but various amounts of chlorites and small amounts of dolomite and quartz (0.5-3%) were reported. Exposure to respirable (not specified) dusts ranged from 1 to 30 mg/m^3. In a follow-up study by Wild (2000), mortality from lung cancer was not significantly increased in subgroups of employees who were under 60 years of age (SMR 2.0 (0.8-4.0)), had a latency period of < 20 years (2.4 (0.8-5.6)) or had a duration of employment of < 10 years (2.1 (0.9-4.1)). A modest excess risk (not statistically significant) for stomach cancers was observed in male workers (1.2 (0.4-2.8)). No increasing trend of incidences of lung cancer with increasing cumulative exposure to talc (in mg/m^3-years) was observed. This French cohort was expanded with an Austrian cohort (Wild et al. 2002); one site in France (1070 male workers) and three sites from Austria (542 male workers). Mortality from lung cancer was non-significantly

[18] 95% confidence interval (95% CI) reported in parentheses, if available, throughout this CLH report

increased in the French and Austrian cohort (SMR 1.2 (0.8-1.9) and 1.1 (0.4-2.2), respectively), while mortality from stomach cancer was non-significantly increased in the French cohort only (1.2 (0.4-2.8). Austrian talc from all sites was a talc-dolomite mixture and contained 1-4% quartz. Dust levels in the 1990s were <5 mg/m^3. However, exposures before 1985 could be higher; there were cases of exposure to levels higher than 50 mg/m^3. The study was expanded with a nested case-control study for lung cancer: 88 control subjects were selected from the two cohorts and matched based on age, calendar period and site. Groups were categorised based on exposure group of job type (no exposure, < 5 mg/m^3, 5–30 mg/m^3 and > 30 mg/m^3), smoking habits, exposure to quartz and job history. No or slightly elevated odds ratios (ORs) were noted (ORs: 0.6-1.1) and no trend with increasing cumulative exposure was observed. Results upon adjustment for smoking, quartz exposure and underground work were similar. The analyses of the case-control studies on lung cancer did not find any dose-response relation, be it by maximal dose, latency, duration of exposure, or cumulative exposure.

Wergeland et al. (1990) investigated morbidity and mortality in 94 miners and 295 millers between 1953-1987. Personal air samples collected in the early 1980s showed that total dust levels varied greatly by job category and workplace (mine, 0.9–97 mg/m^3; mill, 1.4–54 mg/m^3). Peak exposures occurred during drilling in the mine (319 mg/m^3) and in the store house in the mill (109 mg/m^3). Talc contained magnesite and trace quantities of quartz (<1%) and fibres (tremolite, anthophyllite, talc particles; 0.2-0.9 fibres/ml). No association between lung cancer morbidity or other cancer and exposure to non-asbestiform talc was found. In the highest exposure subgroup, no increased incidence of cancer was noted (standardised incidence ratio (SIR 0.4 (0.2-1.0)) and no cases of lung cancer were observed. In a follow-up (1953-2011; 390 male workers), slightly increased SIRs (not statistically significant) for all cancers in total cohort and bladder cancer in millers were reported, specifically in workers employed during the 1960s (Wergeland et al. 2017). The temporary increased SIR for bladder cancer could not be explained by occupational exposure and/or environmental pollution based on available data. A statistically significant SIR for colorectal cancer was noted in the total cohort (1.6 (1.1-2.3)), but was according to the authors related to the way of counting cases and random variation in a small cohort.

Occupational exposure – user industries

A case report of lung adenocarcinoma was described in a patient with talcosis linked to occupational exposure to talc in a confectionary factory (Kobayashi et al. 2019). Talc crystals were found in lung tissue. However, authors stated it was difficult to elucidate whether talc directly contributed to carcinogenesis.

Case-control and cohort studies of workers in user industries (ceramics, pulp and paper, rubber) exposed to talc, investigated ovarian, lung and stomach cancers. A significant association between stomach cancer and exposure to talc materials was demonstrated in a case-control study in a rubber factory workers (17000 workers) in the USA (Blum et al. 1979). The incidence of stomach cancer was related to duration of exposure, and cases commonly were exposed 10 years earlier than the comparisons. However, increased risk was observed in one site only (company A). No clear elevation of odds ratio reported for other site (company B). No information was available on the purity and asbestos content of talc in this study.

Exposure to nonfibrous talc in ceramic plumbing fixture factory workers (2055 males) and its relation to lung cancer and other diseases were investigated in two studies (Thomas 1982; Thomas and Stewart 1987). Nonfibrous steatite talc from Montana and prior 1976 fibrous talc in some glazes were used. In the preliminary study an increased frequency of lung cancer was found in male workers. In a follow-up study, a SMR of 1.4 (1.1-1.9) was found for lung cancer. Mortality due to lung cancer increased upon duration of exposure to nonfibrous talc and latency. Furthermore, mortality was specifically increased in workers exposed to high levels of silica dust and nonfibrous talc. The role of silica as cofactor or a promoting agent cannot be ruled out according to the study authors.

Straif et al. (1999) described an excess mortality for stomach (SMR 1.2 (0.8-1.6)) and lung cancer (1.2 (1.0-1.4)) and employment in early production stages of rubber manufacturing in rubber plant workers (11633 males) from five different locations in Germany. No information is available on the type or purity of talc. An aetiologic role of asbestos, carbon black, dusts and talc (asbestos contaminated talc for lung cancer) was suggested by the study authors. In a follow-up study, similar SMRs were found for stomach and lung cancer

(Straif et al. 2000). In addition, an increased SMR (1.2 (0.5-2.3)) for larynx cancer was noticed. When comparing to a low exposure group, SMRs were increased in groups exposed to higher levels of talc for these cancers. Increased lung cancer risk among rubber workers may be associated with exposure to asbestos and talc. Exposure-specific results tend to support an association between exposure to asbestos, talc, or carbon black and increased mortality from laryngeal cancer, but the study authors noted the small number of observed deaths.

Langseth and Andersen (1999) found an increased risk of ovarian cancer in 4247 women in Norway who worked in paper mills and where talc was used as filler. The authors noted that talc may have contributed to this increased risk, among exposure to other substances. In a follow-up study, occupational exposure to talc or dust did not increase incidence of ovarian cancer, while asbestos did (Langseth and Kjaerheim 2004). This estimate was unchanged after adjustment for multiple potential confounders, including parity, breastfeeding, tobacco smoking habits and family history of breast or ovarian cancer. The odds ratios for occupational exposure to talc and total dust were similarly unchanged after adjustment for confounding.

Occupational exposure – meta-analyses

Multiple meta analyses are available based on aforementioned cohort studies in talc miners, millers and user industries. Wild (2006) [adopted from IARC (2010)] performed a meta-analysis of lung cancer mortality among miners and millers from industries that produced non-asbestiform talc in Vermont, USA (Selevan et al. 1979), Norway (Wergeland et al. 1990), Italy (Coggiola et al. 2003), France (Wild 2000) and Austria (Wild et al. 2002). The purpose of the analysis was to compute risk estimates separately for talc miners, who usually have some co-exposure to silica and/or radon daughters, and talc millers, who normally have no such co-exposure. Previously unpublished risk estimates for the subgroup of millers in the French and Austrian cohorts were used and additional information on smoking habits was obtained for Italian, French and Austrian workers. Data indicated that the prevalence of smoking was higher than that in the reference populations. In the estimation of the overall risk for millers, data from all five countries were used, while only data from the USA, Norway and Italy were included in that for miners. Based on SMRs for lung cancer of 1.0 (USA; 95% CI: 0.1–3.7), 0.7 (Italy; 0.3–1.2), 1.2 (France; 0.8–1.9), 0.7 (Austria, Site B; 0.1–2.0) and 1.1 (Austria, Site C; CI, 0–6.2) and a SIR of 0.8 (Norway; 0.2– 2.0) for talc millers, a summary SMR of 0.92 (0.7–1.3) was obtained. No heterogeneity between studies was detected. Similarly, based on mortality ratios for lung cancer of 4.4 (USA; 1.4–10.2) and 1.1 (Italy; 0.7–1.5) and an incidence ratio of 1.6 (Norway; 0.2–5.7) for talc miners, a summary SMR of 1.2 (0.9–1.6) was found. Due to a significant heterogeneity of the latter data set, a random effect estimate of the overall SMR was also calculated (SMR: 1.9 (0.7–5.1)).

Finley et al. (2017) evaluated the epidemiological studies in talc miners and millers in Italy (Coggiola et al. 2003), Norway (Wergeland et al. 1990), France and Austria (Wild et al. 2002), in a meta-analysis for cosmetic talc as risk factor for pleural mesothelioma. The purpose was to assess whether existing epidemiological information supports a conclusion that cosmetic talc exposure is not associated with an increased risk of pleural mesothelioma. In this study, based on pooled analysis of aforementioned epidemiological studies, the statistical power to detect pleural mesothelioma in cosmetic talc miners and millers was evaluated. Overall, the cohort studies comprised 99,022 person-years of observation and no mesotheliomas were observed. Four mesotheliomas were expected based on the person-year of observation and the background rates in the populations. Statistical powers of 84% and 67% were calculated for a 3- or 2.5-fold greater increase in pleural mesothelioma mortality in this pooled analysis, respectively. Expanding on follow-up studies for the Italian (Pira et al. 2017) and the Norwegian cohorts (Wergeland et al. 2017), Marsh et al. (2019) performed a similar meta-analysis study. A total of 113,344 person-years were included in the cohorts and no mesotheliomas were found. Three cases of pleural mesotheliomas were expected and statistical powers of 79% and 62% for a 3- or 2.5-fold greater increase in pleural mesothelioma mortality were determined for the pooled cohort, respectively. Similar statistical powers were reported when restricting the pooled cohort to workers with a latency period of ≥30 years (observation time from first employment). Based on new information from the cohort of Vermont and Italian talc miners and millers (Fordyce et al. 2019; Ciocan et al. 2022), this meta-analysis was updated (Ierardi and Marsh 2020; Ierardi et al. 2022). Approximately 4.14 cases of pleural mesotheliomas were expected based on 135,524 person-years. One case of pleural mesothelioma was observed (Ierardi et al. 2022). The pooled cohorts had a 71% and 87%

statistical power to detect a 2.5- or 3-fold greater increase in pleural mesothelioma mortality, respectively. The authors of these studies concluded that there is no epidemiological evidence to support the hypothesis that exposure to cosmetic talc is associated with pleural mesotheliomas.

Chang et al. (2020) performed a meta-analysis study combining cohorts of talc mine workers and workers from user-industries (paper, rubber, pottery, cement) to study a possible association between talc exposure and stomach cancer. All pooled analyses were based on random-effects models. Heterogeneity was observed among studies. Workers in six cohort studies were exposed to talc not containing asbestiform fibres (Coggiola et al. 2003; Wergeland et al. 1990; Wild et al. 2002; Fu and Zhang 1992; Nie et al. 1992). A non-statistically significantly increased meta-relative risk of 1.3 (1.0-1.6, $p = 0.09$) for stomach cancer was found when combining cohorts of talc miners and millers exposed to talc not containing asbestiform fibres.

IARC (2010) assessed three community-based studies investigated occupational exposure to talc in workers in China, USA and Canada (Siemiatycki 1991; Hartge and Stewart 1994; Chen et al. 1992). The risks for ovarian and lung cancer were not increased in these studies. A borderline significant increase for prostate cancer was described; OR of 1.4 (90% CI: 1.0-2.1). For more study details, see Annex I.

Talc is commonly applied to induce fibrogenesis in the pleural space to treat pleurodesis. No increased risk between lung or pleural cancer and the use of talc in this treatment was noted in multiple clinical studies where hundreds of patients were followed for decades (BTA 1979; Lange et al. 1988; Viskum et al. 1989).

Occupational exposure – summary

In summary, no cases of lung mesothelioma were noted in the cohort studies in talc miners and millers. No increased risk for lung cancer was found, including the high exposed groups. In one epidemiological study from the USA, increased risk of lung cancer in talc miners was most likely caused by co-exposure to radon (Selevan et al. 1979). Increased incidence of ovarian cancer in female workers in pulp and paper industry was reported, but was attributed to exposure to asbestos (Langseth and Andersen 1999; Langseth and Kjaerheim 2004). In user industries cohort studies, no talc-related increased risk in cancer was observed and often co-exposure (crystalline silica or asbestos) was the main reason for increased risk of cancer. Cohort studies mostly involved relatively small populations and included limited information on exposure levels, occupational history and confounders (smoking and alcohol consumption). An association of lung cancer or ovarian cancer and occupational exposure to talc is not supported based on available epidemiological data.

Human epidemiological studies - cosmetic use

Epidemiological studies investigating the perineal route of exposure to talc-based body powder and ovarian cancer are available and summarised in Table 10. Studies up to 2010 have been assessed and summarised by the IARC (IARC 1987, 2010), see Annex I for studies summarised by IARC.

A small number in the Working Group of the IARC found there was inadequate evidence for an increased risk of cancer, but the Working Group overall concluded that there was limited evidence when taking in account the epidemiological studies regarding perineal use of talc and increased risk of ovarian cancer (IARC 2010). The IARC concluded that perineal use talc-based body powder was classified as possibly carcinogenic to humans (Group 2B). The Working Group noted, however, that exposure to body powders, baby powders, talcum powders and deodorizing powders, most of which contain cosmetic talc in varying amounts, was defined in a variety of ways and that some substances called talc may have contained quartz and other potentially carcinogenic materials. In addition, it is important to note that talc-based body powders from approximately 1970 onwards are much less likely to contain asbestos (Rohl and Langer 1974). After this, talc manufacturers claimed to voluntarily use asbestos-free talc, often referred to as cosmetic grade free of asbestos (Hildick-Smith 1976; Harlow and Hartge 1995).

The Cosmetic Ingredient Review Expert Panel and Health Canada have published more recent reviews of literature describing perineal exposure to talc and ovarian cancer (Fiume et al. 2015; Health Canada 2021). In the screening assessment of Health Canada it was concluded that the available data suggest a causal relationship as the epidemiological studies show a high degree of consistency and cover several decades and multiple geographical regions. However, the Cosmetic Ingredient Review Expert Panel determined that a causal link between cosmetic use of talc in the perineal and ovarian cancer is not supported.

Cosmetic use – case-control studies

A total number of 29 case-control studies from Australia, Canada, China, Greece, Israel, Norway, the UK and the USA, published between 1982-2016 and investigating perineal exposure to talc and ovarian cancer were included. Most studies have previously been reviewed (Fiume et al. 2015; Health Canada 2021; IARC 2010).

IARC (2010) assessed case-control studies published up to 2004 and designated eight population-based case-control studies from Australia, Canada (Ontario) and theUSA (two non-overlapping studies in Boston, MA, and one each in California, DelawareValley, eastern Massachusetts and New Hampshire, and Washington State) as being more informative (Chang and Risch 1997; Cook et al. 1997; Cramer et al. 1999; Cramer et al. 1982; Green et al. 1997; Harlow et al. 1992; Ness et al. 2000; Purdie et al. 1995; Whittemore et al. 1988). This was based on the following characteristics: the study was population-based, was of a reasonable size, had acceptable participationrates and included information to allow control for potentially important confounders. The selected studies included at least 188 cases and had participation rates that generally ranged from 60 to 75% [adopted from IARC (2010)]. Among these eight studies, the prevalence of use of body powder among controls ranged from 16 to 52%; however, information on exposure was not collected in a comparable manner across studies. In addition, the frequency and duration of use or total lifetime applications were investigated in several studies as well as consideration of prior tubal ligation or simple hysterectomy. Only sparse data were available on whether women had used body powder before or after the mid-1970s. The relative risks for ovarian cancer among users of body powder (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 case-control studies assessed by IARC (2010), most studies also reported relative risks of this magnitude or higher (Booth et al. 1989; Chen et al. 1992; Godard et al. 1998; Harlow et al. 1992; Hartge et al. 1983; Mills et al. 2004; Rosenblatt et al. 1992; Shushan et al. 1996). The subset of studies that assessed use of talc on a diaphragm were relatively uninformative due to their lack of precision in general. Results on exposure-response relationships were presented in six of the more informative case–control studies. A positive exposure-response trends was apparent in a Boston-based study that presented the most comprehensive analysis (Harlow et al. 1992). In the Canadian and Californian studies, a non-significant, weakly positive trend was observed for either duration or frequency of use, but not for both (Chang and Risch 1997; Whittemore et al. 1988). In the other three case–control studies, no consistent trend was observed and the strongest associations tended to be seen among the shorter-term or less frequent talc users (Ness et al. 2000; Cramer et al. 1999; Cook et al. 1997). Other studies showing a positive exposure-response trend include studies by Booth et al. (1989), and Mills et al. (2004). Four of the eight more informative case–control studies presented results on histological type of ovarian cancer (Chang and Risch 1997; Harlow et al. 1992; Cramer et al. 1999; Cook et al. 1997). Risks for serous ovarian cancer (relative risk; RR 1.7 (1.1-2.5) or RR 1.7 (1.2-2.4)) were somewhat greater than those for other histological types in two of the four case–control studies and borderline greater (RR 1.3 (1.0-1.9)) in one of the four case-control studies in which the contrast was reported (Cook et al. 1997; Cramer et al. 1999; Chang and Risch 1997). In addition, a greater risk for serous ovarian cancer (RR 1.8 (1.1-2.8)) was reported in the study of Mills et al. (2004), designated as a less informative study by IARC (2010). Results for other histological types were inconclusive.

Eleven case-control studies have been published since 2008 and since the assessment by IARC (2010); one study from Australia (Merritt et al. 2008), and the other studies are from the USA (Gates et al. 2008; Goodman et al. 2008; Moorman et al. 2009; Wu et al. 2015; Wu et al. 2009; Rosenblatt et al. 2011; Kurta et al. 2012; Lo-Ciganic et al. 2012; Cramer et al. 2016; Schildkraut et al. 2016). These studies are population-based and examined 1,200 participants or more. The prevalence of genital use of body powder or talc in controls and cases ranged between 15 to 48%. Participation rates were below 60% in three studies (Cramer et al. 2016; Merritt et al. 2008; Schildkraut et al. 2016), or modest (no response rate provided) according to the study authors in one study (Wu et al. 2009), but above 60% in the other studies and similar in both controls and cases. Limited information to control for confounders (e.g. limited information on talc use, missing data) is available for three studies, as reported by the study authors (Cramer et al. 2016; Kurta et al. 2012; Moorman et al. 2009). A statistically significant increased risk of ovarian cancer (30 to 50%) upon perineal exposure to talc was reported compared to non-users or non-regular users in seven studies (Gates et al. 2008;

Wu et al. 2015; Wu et al. 2009; Kurta et al. 2012; Lo-Ciganic et al. 2012; Cramer et al. 2016; Schildkraut et al. 2016), or borderline significantly increased (20 to 30%) in two studies (Merritt et al. 2008; Rosenblatt et al. 2011).

Of the aforementioned 11 case-control studies published since 2008, seven studies provided information on exposure frequency, duration, time since first use and/or number of applications (Gates et al. 2008; Merritt et al. 2008; Wu et al. 2009; Wu et al. 2015; Cramer et al. 2016; Schildkraut et al. 2016; Rosenblatt et al. 2011). One study did not find a positive exposure-response (Rosenblatt et al. 2011), but the other six studies reported a statistically significant positive exposure-response (Gates et al. 2008; Merritt et al. 2008; Wu et al. 2009; Wu et al. 2015; Cramer et al. 2016; Schildkraut et al. 2016). Risk of ovarian cancer increased significantly with lifetime total times of talc use only in women who first started using before 1975 and who were thus more likely to have been exposed to asbestos-contaminated talc (Wu et al. 2009). Merritt et al. (2008) showed mixed results; an increased risk of serous ovarian cancer in the oldest age groups (likely exposed to asbestos-contaminated talc) was found but also in younger age groups. Rosenblatt et al. (2011), on the other hand, found a higher increased risk of ovarian cancer in woman who first started using perineal powder after 1980 versus women who started using earlier, which does not suggest an association with asbestos-contaminated talc. Altogether, it is not likely other hazardous contaminants (e.g. asbestos) of talc caused increased risk estimates, as study results do not support this.

Histology data on ovarian tumours were available for eight studies. Two studies reported an increased risk for all invasive cancers (Moorman et al. 2009; Lo-Ciganic et al. 2012), five studies reported an increased risk of (among which) serous ovarian cancer (Gates et al. 2008; Merritt et al. 2008; Schildkraut et al. 2016; Wu et al. 2009; Rosenblatt et al. 2011), and one study reported a modest increase for borderline ovarian cancers and invasive serous ovarian cancers (Goodman et al. 2008). Other data on ovarian cancer histology are less conclusive.

The self-reported exposure assessment of perineal use of talc varied by study (ever use versus regular use, mode of application, frequency or duration). Non-differential misclassification of talc use could be expected due to the crude exposure assessment definitions and attenuate a positive association. On the other hand, recall bias, which is an issue in case-control studies, could possibly result in inflated risk estimates. Widespread publicity regarding a possible association between perineal use of body powder and ovarian risk could overestimate perineal use of talc and thus inflate risk estimates. IARC (2010) considered it unlikely that such a bias could explain the consistency in estimated risks of ovarian cancer and this substantially influenced the results. Case-control studies published since 2008 do not suggest otherwise (Merritt et al. 2008; Rosenblatt et al. 2011; Wu et al. 2009). Unrecognised risk factors or chance could have resulted in the increased risk estimates. However, the diversity of social and cultural contexts of the available data do not suggest an unknown confounder or chance could explain the increased risk estimates. The data from case-control studies together are consistently showing an excess risk and provide limited evidence of ovarian cancer upon perineal use of talc.

Cosmetic use – cohort studies

Four cohort studies investigated perineal use of talc and the risk of ovarian cancer in cohorts from Puerto Rico and the USA.

Gertig et al. (2000) carried out a prospective cohort analysis that reported an association between perineal use of talcum, baby or deodorant powder and the risk for ovarian cancer. This analysis was conducted among participants in the Nurses' Health Study (NHS), a cohort of 121,700 female registered nurses (aged 30-55 years living in one of 11 states of the USA). The 1982 questionnaire requested information on history and frequency of application of powder to the perineal area (none, daily, one to six times a week, less than once a week) and history of application of powder to sanitary napkins (no/yes). 'Ever talc use' was classified as ever use on either the perineal area or on sanitary napkins. This study has been assessed and summarised by IARC, see Annex I. Overall, no association between 'ever use' of talcum powder and total risk for epithelial ovarian cancer (RR 1.1 (0.9–1.4)) and no trend of increased risk for ovarian cancer with increasing frequency of talc use were observed. However, an increase in risk for serous invasive cancers was associated with any history of talc use (RR 1.4 (1.0–1.9)) and a borderline significant trend was found with increasing frequency

of use (*p* for trend = 0.05). Among women without a history of tubal ligation, no association was observed between history of talc use and total risk for epithelial ovarian cancer (RR 1.0 (0.7–1.3)). Similarly, history of tubal ligation did not modify the association between the use of talc and risk for serous invasive cancers. A follow-up of this cohort was published by Gates et al. (2010). Two cohorts were investigated in this study, but data on talc use was only available for the NHS cohort. This cohort was followed-up to 2006 (follow-up rate 95.2%). Between 1982 and 2006, 797 incident cases of epithelial ovarian cancer were identified, including 307 incident cases identified by Gertig et al. (2000). Study participants completed follow-up questionnaires every 2 years between 1976 and 2006. Information on frequency of genital talc use was collected in 1982 and data were reported as ≥once/week vs. <once/week. Regular exposure (≥once/week) was not significantly associated (incidence rate ratio 1.1 (0.9-1.3)) with increased incidence rate ratio of epithelial ovarian cancer compared to no or not regular exposure to talc. There was a nonsignificant positive association (incidence rate ratio 1.5 (0.8-2.7)) between talc use and mucinous tumours (includes borderline and invasive tumours). The study authors stated that a stronger positive association between genital talc use with serous or serous invasive cancers (451 cases of total of 797 epithelial ovarian cancer cases) was observed in other studies compared to this study. This may be due to the limited number of cases of endometrioid or mucinous histology; 115 and 69 out of total of 797 epithelial ovarian cancer cases, respectively. The incomplete data for a few exposures, in particular talc use and family history of ovarian cancer (not further specified), also are weaknesses because the limited data may have influenced the observed associations for these exposures. Furthermore, exposure information of talc was available at a single time-point only. The association with talc use in this analysis differed from the association in the previous analysis of the same group studied by Gertig et al. (2000), possibly because of a greater degree of exposure misclassification over 24 years of follow-up. The suggestive positive association with the mucinous subtype may reflect a longer latency period between talc exposure and development of mucinous tumours.

In another cohort study (Houghton et al. 2014), perineal powder use and risk of ovarian cancer was assessed prospectively in the Women's Health Initiative Observational Study (WHI-OS) cohort. The WHI-OS enrolled 93,676 women from 40 clinical centres across the USA from 1993 to 1998. Women were eligible if they were aged 50 to 79 at enrolment, postmenopausal, and planned to reside in the area for at least three years. Perineal powder use (ever use on private parts) was assessed at baseline only by self-report regarding application to genitals, sanitary napkins, or diaphragms and duration of use (<1 year, 1–4 years, 5–9 years, 10–19 years, or ≥20 years). Ovarian cancer cases were initially self-reported by participants in annual mailed questionnaires. Medical records (hospital discharge summaries and pathology reports) were requested for each self-reported case and adjudicated by a physician. Data were also stratified by age at baseline, because older women may have had more potential for exposure to talc contaminated with asbestos. Cox proportional hazard regression was used to estimate risk, adjusting for covariates, including person-time until diagnosis of ovarian cancer, death, loss to follow-up or missing information (n = 516), or September 17, 2012. After applying the exclusion criteria (participating in another clinical trial, unlikely to survive three years due to medical conditions, had conditions that would interfere with study participation, bilateral oophorectomy or an unknown number of ovaries at baseline, history of any cancer at baseline except nonmelanoma skin cancer), 61,576 participants with 429 adjudicated incident ovarian cancer cases remained. These women were followed for a mean of 12.4 years without a history of cancer or bilateral oophorectomy, 52.6% reported ever using perineal powder. Ever use of perineal powder (hazard ratio (HR) 1.1 (0.9-1.3)) was not associated with risk of ovarian cancer compared with never use. Individually, ever use of powder on the genitals (HR 1.1 (0.9-1.4)), sanitary napkins (HR 1.0 (0.8-1.2)), or diaphragms (HR 0.9 (0.7-1.2)) was not associated with risk of ovarian cancer compared with never use, nor were there associations with increasing durations of use. Combined ever powder use was not associated with individual subtypes of ovarian cancer; the HR for serous ovarian cancer was 1.2 (0.9-1.5). Estimates did not differ when stratified by age or tubal ligation status. The authors concluded that perineal powder use does not appear to influence ovarian cancer risk.

In the Sister Study 50,884 women in the USA and Puerto Rico were enrolled between 2003 and 2009 who had a sister diagnosed with breast cancer (Gonzalez et al. 2016). Enrolled participants were aged 35 to 74 years and never had breast cancer but each had a full or half-sister who had been diagnosed with breast cancer. More than one sister per family could participate. Participants who had bilateral oophorectomies,

ovarian cancer before enrolment or who had no follow-up information were excluded. After exclusion, 41,654 participants were enrolled in this study. Telephone interviews were conducted at the start of the study, which included questions about reproductive history, health conditions, and lifestyle factors. At baseline, participants completed a self-administered questionnaire about personal care products used in the 12 months before enrolment, which included questions about frequency of douching and about genital talc use in the form of powder or spray applied to a sanitary napkin, underwear, diaphragm, cervical cap, or vaginal area. Response categories were: did not use, used less than once a month, used 1–3 times per month, 1–5 times per week, or more than 5 times per week. Information on oophorectomies was updated via follow-up questionnaires conducted every 2-3 years. Information on new cancers were collected through an annual health update and follow-up questionnaire. Adjusted HRs and 95% CIs for the association of talc use and douching with ovarian cancer risk using Cox proportional hazards models, with age as the primary time scale. The median follow-up duration was 6.5 years, with 154 incident ovarian cancer cases. There was little association between baseline perineal talc use and subsequent ovarian cancer (HR 0.73 (0.4-1.2)). Douching was more common among talc users (OR 2.1 (2.0-2.3)), and douching at baseline was associated with increased subsequent risk of ovarian cancer (HR 1.8 (1.2-2.8)). Douching with no talc use was also associated with increased risk of ovarian cancer compared with use of neither talc nor douching (HR 1.9 (1.2-2.9)). No modifications of effect estimates (patency, hysterectomy, tubal ligation, parity, menopause status) for either douching or talc use were found. Restriction to medically confirmed serous ovarian cancer attenuated effect estimates (HR 1.4 (0.6-3.2)). No association between recent talc use and ovarian cancer risk was found, but a strong positive association between douching and ovarian cancer risk was noted.

The cohort studies available on perineal use of talc and ovarian cancer may not cover the latency period of ovarian cancer. A minimum latency period of 15-20 years has been reported for radiation-induced ovarian cancer (Tokuoka et al. 1987). Other studies estimate a latency period of ovarian cancer of 20 to 40 years (Purdie et al. 2003; Tung et al. 2005; Gonzalez et al. 2016; Tran et al. 2019). The studies of Gertig et al. (2000) (1982-1996; 14 years) and Gonzalez et al. (2016) (2003-2009; median follow-up of 6.5 years) do not cover such a latency period, while studies of Gates et al. (2010) (1982-2006; 24 years) and Houghton et al. (2014) (1993-2012; 19 years, mean follow-up time was 12.4 years) barely covered such a latency period to detect ovarian cancer. Another important issue is the low incidence of ovarian cancer in the cohort studies, which results in a small number of cases. This is illustrated by the low number of cases of ovarian cancer (154 to 797 cases) in relatively large cohorts (50,884 to 121,700 participants). It cannot be excluded that the inadequate study duration to cover the latency period and low number of cases of ovarian cancer in cohort studies attenuated a positive association between perineal use of talc and ovarian cancer.

Cosmetic use – meta-analyses

Recent meta-analysis studies pooled data of available case-control and cohort studies (all included in this CLH report) on perineal use of talc and ovarian cancer (Berge et al. 2018; Penninkilampi and Eslick 2018; Kadry Taher et al. 2019), as shown in Table 16 [adopted from Health Canada (2021)]. These meta-analyses demonstrate statistically significant and consistent increased risk estimates (20 to 30%) with narrow 95% CIs. These studies together consist of large populations with different social, cultural and geographical backgrounds and covering several decades. Two of these studies confirm consistency of data from the epidemiological studies analysed (Kadry Taher et al. 2019; Penninkilampi and Eslick 2018). In the other study causality of the association was not supported due to heterogeneity of results between case-control and cohort studies, but such a statistically significant association was supported when considering case-control studies (RR 1.3 (1.2-1.4)) only (Berge et al. 2018). A weak positive exposure-response relationships (duration and frequency of talc use) was demonstrated in two studies (Berge et al. 2018; Penninkilampi and Eslick 2018). An increasing trend in ovarian cancer risk with increasing cumulative exposure to talc was also suggested by the study of Kadry Taher et al. (2019), but no statistical test for trend was attempted due to a high degree of heterogeneity among studies analysed.. Penninkilampi and Eslick (2018) and Kadry Taher et al. (2019) found a positive association of perineal talc use specifically for the serous and endometrioid histologic subtypes, but Berge et al. (2018) only found a positive association for the serous histologic subtype.

Similar results were observed in other meta-analysis studies which are not shown in Table 16 (Terry et al. 2013; Langseth et al. 2008; Huncharek et al. 2003; Huncharek et al. 2007; Gross and Berg 1995; Tanha et al.

2021; Davis et al. 2021). In one study, however, it was noted that these results did not provide a basis of causality due to substantial design limitations of the studies analysed (Gross and Berg 1995). In two other studies risk estimates were statistically significantly increased in population-based case-control studies only and not in hospital-based case-control studies (Huncharek et al. 2003; Huncharek et al. 2007). In addition, concerns were raised regarding inconsistencies of pooled studies and invalid pooled summary RR estimates in a study of by Langseth et al. (2008).

Other recent meta-analysis studies found no support of an association between perineal use of talc and ovarian or uterine cancer based on data pooled from the four cohort studies (O'Brien et al. 2020; O'Brien et al. 2021).

Table 16: Association of ovarian cancer and perineal use of talc as analysed in meta-analysis studies. Adopted from Health Canada (2021).

Reference	Sample size (number of cases)	RR (95% CI)		
		Berge et al. (2018)	Penninkilampi and Eslick (2018)	Kadry Taher et al. (2019)
Case-control studies				
Booth et al. (1989)	686 (235)	1.3 (0.9-1.8)	1.3 (0.9-1.8)	Not included
Chang and Risch (1997)	1014 (450)	1.4 (1.0-1.8)	1.4 (1.1-1.9)	1.4 (1.1-1.9)
Chen et al. (1992)	336 (112)	3.9 (0.9-10.6)	3.9 (1.4-10.6)	Not included
Cook et al. (1997)	735 (313)	1.5 (1.1-2.0)	1.5 (1.1-2.0)	1.6 (1.1-2.3)
Cramer et al. (1982)	430 (215)	1.9 (1.3-2.9)	1.6 (1.2-2.1)	1.9 (1.3-2.9)
Cramer et al. (2016)[a]	4,141 (2,041)	1.3 (1.1-1.5)	1.4 (1.0-2.0)	1.3 (1.2-1.5)
Eltabbakh et al. (1998)	516 (50)[b]	Not included	Not included	Not included
Gates et al. (2008)	3,187 (1,385)	Not included	Not included	1.4 (1.1-1.6)
Godard et al. (1998)	305 (153)	2.5 (0.9-6.6)	2.5 (0.9-6.6)	2.5 (0.9-6.6)
Goodman et al. (2008)	1,236 (481)	1.0 (0.7-1.4)	Not included	Not included
Green et al. (1997); Purdie et al. (1995)	1,684 (824)	1.3 (1.0-1.5)	1.3 (1.1-1.6)	1.3 (1.1-1.6)
Harlow and Weiss (1989)	274 (116)	1.1 (0.7-2.1)	1.1 (0.6-2.1)	1.1 (0.7-1.7)
Harlow et al. (1992)	474 (235)	1.5 (1.0-2.1)	Not included	1.5 (1.0-2.3)
Hartge et al. (1983)	306 (135)	2.5 (0.7-10.0)	2.5 (0.7-9.5)	0.7 (0.4-1.2)
Kurta et al. (2012)	2,704 (902)	Not included	1.4 (1.2-1.7)	1.4 (1.2-1.7)
Langseth and Kjaerheim (2004)	225 (46)	Not included	Not included	1.2 (0.4-3.2)
Lo-Ciganic et al. (2012)	2,704 (902)	1.3 (1.1-1.7)	Not included	Not included
Merritt et al. (2008)	3,085 (1,576)	1.1 (0.9-1.4)	1.2 (1.0-1.4)	1.2 (1.0-1.4)
Mills et al. (2004)	1,354 (249)	1.4 (1.0-1.9)	1.4 (1.0-1.9)	1.4 (1.0-1.9)
Moorman et al. (2009)	2,143 (1,086)	1.4 (1.1-1.8)	Not included	1.1 (0.9-1.3)

Ness et al. (2000)	2,134 (767)	1.5 (1.1-2.0)	1.5 (1.1-2.0)	1.5 (1.1-2.0)
Rosenblatt et al. (1992)	123 (77)	1.7 (0.7-3.9)	1.7 (0.7-4.0)	1.0 (0.2-5.0)
Rosenblatt et al. (2011)	2,125 (812)	1.1 (0.9-1.4)	1.3 (1.0-1.7)	1.3 (1.0-1.7)
Schildkraut et al. (2016)	1,329 (584)	1.4 (1.1-1.9)	1.4 (1.1-1.9)	1.4 (1.1-1.9)
Shushan et al. (1996)	608 (200)	Not included	2.0 (1.1-3.6)	Not included
Tzonou et al. (1993)	389 (189)	1.1 (0.3-4.0)	1.1 (0.3-4.0)	1.1 (0.3-3.9)
Whittemore et al. (1988)	727 (188)	1.4 (0.9-2.0)	1.4 (1.0-2.0)	1.5 (0.8-2.6)
Wong et al. (1999)	1,155 (462)	1.0 (0.8-1.3)	0.9 (0.2-3.6)	1.0 (0.8-1.3)
Wu et al. (2009)	1,297 (609)	Not included	Not included	1.5 (1.1-2.1)
Wu et al. (2015)	4,092 (1,701)	1.5 (1.3-1.7)	1.3 (1.1-1.5)	1.5 (1.3-1.7)
Cohort studies				
Gates et al. (2010)	108,870 (797)	1.1 (0.9-1.3)	Not included	Not included
Gertig et al. (2000)	78,630 (307)	Not included	1.1 (0.9-1.4)	1.1 (0.9-1.4)
Gonzalez et al. (2016)	41,654 (154)	0.7 (0.4-1.2)	0.7 (0.4-1.2)	0.7 (0.4-1.2)
Houghton et al. (2014)	61,285 (429)	1.1 (0.9-1.3)	1.1 (0.9-1.4)	1.1 (0.9-1.4)
Overall OR		1.2 (1.1-1.3)	1.3 (1.2-1.4)	1.3 (1.2-1.4)

[a] This includes data from Cramer et al. (1999); [b] 'Cases' for this study were women diagnosed with primary peritoneal cancers. 'Controls' were women diagnosed with primary epithelial ovarian cancer.

Cosmetic use – summary

Data from case-control studies consistently show an unusual consistent excess risk of ovarian cancer upon perineal use of talc. The variety of social, cultural and geographical backgrounds is high, limiting the influence of unknown confounders or chance potentially explaining increased risk estimates. A positive exposure-response was shown in most case-control studies. In general, risk estimates for the serous histological subtype was higher as compared to other histological subtypes, although data were not always conclusive. Methodology on self-reported exposure assessment varied by study, making it difficult to compare. In addition, talc content in products used (e.g. body powder, baby powder) was not always known. Confounders and biases, such as recall bias or other contaminants in talc (e.g. asbestos), could have influenced risk estimates. This cannot be ruled out, but it is considered unlikely due to the variety of social, cultural and geographical background.

Two cohort studies demonstrate a non-statistically significant association between perineal talc use and serous or mucinous ovarian cancers (Gates et al. 2010; Gertig et al. 2000). Two other cohort studies do not show an association (Gonzalez et al. 2016; Houghton et al. 2014). It is uncertain whether the follow-up time of the cohort studies was sufficient to detect a (statistically significant) association due to the relatively long latency period and low number of cases of ovarian cancer. Recent meta-analysis studies found a positive association (20 to 30% increased risk) between perineal talc use and ovarian cancer (Penninkilampi and Eslick 2018; Berge et al. 2018; Kadry Taher et al. 2019). Data together provide limited evidence of a positive association between perineal use of talc and ovarian cancer, but confounders and biases cannot be ruled out.

Mode of action

The adverse effects observed upon exposure to talc, in both human and animals, appear to be triggered by an inflammatory response as well as induction of oxidative stress, and depends on the chemical features of talc (Johnson 2020; Leophonte and Didier 1990; Shim et al. 2015; Wild et al. 1995). Moreover, in vitro studies show that talc has inherent toxicity, is haemolytic and triggers a pro-inflammatory response (Davies et al. 1983; Mierzejewski et al. 2021; Nasreen et al. 1998; Nasreen et al. 2000; Shukla et al. 2009; Woodworth et al. 1982).

Reactive hydroxyl groups in talc may play an important role in its cytotoxicity and haemolytic activity. Silica and kaolinite (both have hydroxyl groups) are phagocytosed by alveolar macrophages and then interact with the lysosomal membrane (Allison 1977; Brody and Davis 1982). As a result, lysosomal enzymes are released in the cytoplasm resulting in oxidative stress, cytotoxicity and cell death of the alveolar macrophages. It is likely talc interacts with cell surfaces of epithelial cells and macrophages and triggers an inflammatory response. This will increase lung burden as the clearance of these particles from the lung is inhibited or delayed. However, it is less clear to what extent this mechanism plays a role in pulmonary lesions. A potential mechanism for pulmonary neoplasms in vivo is linked to increased cell replication due to cell injury and release of mitogenic growth factors from alveolar macrophages. Hyperplasia of the alveolar epithelium was observed in rats after 6 months which became more severe over time (NTP 1993). Morphologic changes were observed in the epithelial layer (epithelial hyperplasia and dysplasia) and were particularly evident in areas of fibrosis. Alveolar/bronchiolar adenomas and carcinomas were noted in female rats, and benign and malignant pheochromocytomas were present in both sexes. Tumours at both sites were exposure related. The lung tumours likely developed via inflammation and enhanced cell replication. No convincing mode of action is at hand for the formation of pheochromocytomas in rats, as incidence of hyperplasia of the adrenal medulla was similar in exposed rats versus controls. On the other hand, a plausible mechanism demonstrating these talc-induced pheochromocytomas in rats are not relevant to humans is absent.

Upon perineal or intravaginal administration talc a foreign body reaction and infection was observed in rat ovaries and a cystic appearance of the ovaries was induced (Hamilton et al. 1984; Keskin et al. 2009). Talc particles were found in ovarian tissues in multiple studies (Egli and Newton 1961; De Boer 1972; Venter and Iturralde 1979; Henderson et al. 1971; Henderson et al. 1979; Henderson et al. 1978). In addition, talc particles or compounds containing magnesium and silicate (mostly asbestos and talc) were found in ovarian (9-75%) and cervical (50%) tumours (Henderson et al. 1971; Mostafa et al. 1985).

Clear mode of actions for lung and ovarian tumours are not available, but data suggest carcinogenicity is triggered via inflammation, oxidative stress and increased cell replication. A plausible mechanism for pheochromocytomas in rats remains to be elucidated but no conclusive evidence formation of these tumours is not operative in humans is available.

Factors for consideration in the hazard assessment

Factors taken into account from available animal and human data for the hazard assessment of carcinogenicity of talc is shown in Table 17.

Upon (chronic) exposure to talc, incidence of lung tumours was increased in (female) rats compared to controls and historical control data, but not in mice or hamster (NTP 1993; Wehner et al. 1977c). This is in line with observations of lung tumours upon exposure to other nonfibrous particles (diesel soot, carbon black, quartz) via inhalation, also demonstrating that hamsters and mice were less susceptible (Driscoll et al. 2002). It should be pointed out, however, that although the main study protocol of the inhalation studies in mice and rats were very comparable (MMAD of 2.7 to 3.6 µm, 6 h per day, 5 days per week, lifetime exposure), the protocol of the inhalation study in hamster was substantially different (MMAD of 6.0 µm, 3 to 150 min per day, 5 days per week, 30 or 300 days). Alveolar/bronchiolar adenoma and/or carcinoma developed late in life and upon exposure to 18 mg/m^3 respirable talc and were observed in female rats only (NTP 1993). Particle loading in the lungs was marked in rats, but not excessive, and therefore not regarded a confounding effect of excessive toxicity. For other nonfibrous particles (carbon black, diesel exhaust or titanium dioxide) both late development of lung tumours in rats and a higher incidence in female rats compared to male rats were also observed (Nikula 2000).

The exposure to respirable dust and talc reported in epidemiological studies was in general considerably lower than reported in the rat study. In humans, no lung tumours in talc miners and millers have been reported, although the exposure levels to respirable dust in talc workers are often not provided and, if so, greatly varied; ranging between 0.94-134 mg/m^3 (reported as total dust) in measurements collected between 1960 and 1990 (Wergeland et al. 1990; Wild et al. 2002). Recent studies described exposure levels of respirable (definition of respirable mostly not specified by study authors) dust between 0.2-2.5 mg/m^3 in measurements collected after 1990s (Coggiola et al. 2003; Pira et al. 2017), and exposure levels of respirable talc in talc miners and millers of ≤2 mg/m^3 talc (mean 1.0 mg/m^3) (Coggiola et al. 2003). No specifications on methodology (e.g. static or personal air sampling) were provided. The dose levels applied in rats where carcinogenic effects were observed (18 mg/m^3, 6 h per day, 5 days per week) are calculated to be considerably higher as compared to known exposure levels in humans: when considering correction for time (6 to 8 h of 0.75) and activity (respiratory volume for 8 h exposure (6.7 m^3/person) to respiratory volume light activity for worker (10 m^3/person) of 0.67), in correspondence with REACH guidance (ECHA 2012), this results in a worker exposure of (18 mg/m^3 * 0.75 * 0.67) 9 mg/m^3. These extrapolated exposure levels are at least 4- to 9-fold lower compared to (mean) exposure to respirable talc in miners and millers. Note that the exposure levels for humans is also referring to total dust, not just respirable dust. Therefore the exposure to respirable talc is likely even lower in the human studies as compared to the rat study described by the NTP (NTP 1993). In conclusion, human data on lung tumours do not exclude a carcinogenic potential of talc or question the positive evidence for lung tumours in female rats.

The suggestive mode of action of lung carcinogenicity in rats (inflammation, oxidative stress and increased cell replication) is considered relevant to human. An analogous mode of action has been described for talc in open wounds (inflammatory response to particles with low potential of degradation by macrophages). However, accumulation of nonfibrous particles, response and type of lung cells which come in contact with the particles may be different in humans compared to rats, and could also be the case for talc (Nikula et al. 2001).

Increased incidence of pheochromocytomas (benign and malignant) was noted in rats exposed to talc compared to controls and historical control data. No pheochromocytomas were noted in other species. The formation of pheochromocytomas in rats could be secondary to hypoxemia, as observed upon exposure to particles via inhalation (Ozaki et al. 2002). No data supporting a mode of action for the pheochromocytomas in rats upon exposure to talc via inhalation are available. Therefore also no data are available supporting potential non-human relevance.

Ovarian tumours were noted upon perineal exposure to talc in humans in case-control studies. No adequate animal studies are available for this route. A mode of action similar to the formation of lung tumours is likely, based on foreign body reaction, infection and cystic appearance observed in rat ovaries.

Summary of weight of evidence:

- Rat lung tumours (alveolar/bronchiolar carcinoma and adenoma) developed late in life and were observed in one lifetime inhalation study in female rats. These findings are similar to described upon inhalation of other nonfibrous particles.
- The rat lung tumours developed under inhalation exposure conditions associated with marked, but not excessive particle loading and is deemed relevant to humans. Moreover, viability and phagocytic activity of macrophages were not impaired at any dose level in rats indicating absence of lung overload conditions.
- The mode of action of lung carcinogenicity involves inflammation, oxidative stress and increased cell replication, and is considered relevant to humans. It is acknowledged that nonfibrous particles accumulation and response in the lungs are different in rats versus humans.
- The pheochromocytomas (benign, malignant or complex) were observed in male and female rats and related to exposure to talc. The increased incidence of predominantly benign pheochromocytomas was not supported by an increased incidence of hyperplasia in the adrenal medulla. Pheochromocytomas might be less relevant to humans as these types of tumours are known in rats

exposed to particulates through inhalation (secondary to hypoxemia). It is unclear whether lung damage was the primary cause of the pheochromocytomas and there is no evidence the talc-induced pheochromocytomas in rats are not relevant to humans. Overall, the relevance of these tumours remains unclear.

- No talc-induced carcinogenicity was observed in mice (or other animal species) or via other exposure routes (oral, intrapleural, intraperitoneal). However, no adequate animal studies are available for routes other than inhalation exposure.
- No evidence of lung cancer is demonstrated in epidemiological studies in talc workers. Cohort studies involved relatively small populations and included limited or no information on exposure levels and confounders. Extrapolated exposure levels from the rat study suggest at least a 4- to 9-fold lower (mean) exposure to respirable talc in miners and millers as compared to the rat study. Therefore, epidemiological studies in talc workers do not exclude a carcinogenic potential of talc or question the positive evidence for lung tumours in female rats.
- Limit evidence of a carcinogenic potential upon perineal use of talc is demonstrated in epidemiological studies investigating ovarian cancer. Case-control studies show an unusual consistent excess risk of ovarian cancer upon perineal use of talc, but confounders and biases (e.g. recall bias, content of talc in used products and contaminants) cannot be ruled out. A weak but non-statistically significant positive association of certain histological subtypes of ovarian cancer is found in two cohort studies, but not in two other cohort studies. Cohort studies might have been inadequate to detect a positive association due to the relatively long latency period and low number of cases of ovarian cancer.

Table 17: Factors to be taken into consideration in the hazard assessment

Species and strain	Tumour type and background incidence	Multi-site responses	Progression of lesions to malignancy	Reduced tumour latency	Responses in single or both sexes	Confounding effect by excessive toxicity?	Route of exposure	MoA and relevance to humans
Rat, F344/N	Alveolar/bronchiolar adenoma and carcinoma, increased vs historical control data	Yes (females)	Incidence hyperplasia increased, tumours developed into malignant tumours	First incidence at 716 days (exposed groups)	Females	Marked particles loading of macrophage, but not excessive	Inhalation	Relevant for humans
	Benign and malignant pheochromocytomas, increased vs historical control data	Yes (females)	No increased incidence of hyperplasia, mostly benign tumours.	First incidence at 544 days (exposed groups)	Both sexes	Possibly secondary to hypoxemia	Inhalation	Less relevant to humans if hypoxemia related. However, no conclusive data these tumours are not relevant for humans.
Mouse, $B6C3F_1$	No statistically significant carcinogenic effects noted	No	No	No	No	Clearance of talc from the lung was impaired in highest dose group	Inhalation	N/A
Hamster, Golden Syrian	Observed neoplasms (in all groups) were not related to exposure	No	No	No	No	No	Inhalation	N/A
Human	No statistically significant increased incidence of lung tumours noted	No	No	No	No	Other contaminants	Inhalation	N/A
	Ovarian cancer	No	Yes	15 to 40 years (based on other studies)	Females	Other contaminants	Perineal	N/A

10.9.2 Comparison with the CLP criteria

Classification in Category 1A is based on sufficient human evidence and is not applicable for lung tumours as the evidence available for talc in humans does not show an association with lung cancer in talc workers. Nonetheless, these epidemiological studies do not exclude carcinogenicity or overrule the animal carcinogenicity study because of lower (and limited information on) exposure levels. There is evidence for an association between perineal use of talc and ovarian cancer in humans. However, confounders and biases cannot be ruled out and, accordingly, this association is not considered strong while the evidence is regarded as limited. Therefore, a classification in category 1A is not justified.

Classification in Category 1B is mostly based on sufficient evidence from animal data. In the CLP Guidance sufficient evidence is described as:

- two or more animal species, or
- two or more independent studies in one species, or
- both sexes of a single species in a well-conducted study (ideally conducted under GLP), or
- single study in one species and sex when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset or when there are strong findings of tumours at multiple sites.

For talc, neither of these conditions seems to be met. One well-conducted rat study (conducted under GLP) is available indicating lung tumour formation in female rats only (single species, single sex, both benign and malignant). In addition, pheochromocytomas (predominantly benign; both sexes) upon inhalation were noted. However, incidence of hyperplasia of the adrenal medulla was not increased, tumours were mostly benign and there is no plausible mechanism for the pheochromocytomas. Thus these tumours are considered barely supportive for classification and are not taken into account. The lung tumours developed are not considered occurring at an unusual degree, as an 10% increased incidence of alveolar/bronchiolar carcinoma which developed late in life do not fulfil this requirement. The animal data on lung tumours is therefore considered as limited evidence and do not fulfil the criteria for classification in category 1B

In addition to the limited animal evidence, case-control studies demonstrate an unusual consistent excess risk of ovarian cancer upon perineal use of talc, but confounders (e.g. recall bias, content of talc in used products and contaminants) cannot be ruled out. The human data on ovarian cancer and perineal use of talc are therefore also considered as limited evidence. Limited evidence of lung tumours in rats and limited evidence of ovarian cancer in humans may warrant classification in Category 1B (CLP Guidance Table 3.6.1) on a case-by-case basis. However, this is not regarded applicable as the routes (inhalation or perineal) and type (predominantly continuous or peak exposure) of exposure are different, site of tumour formation is different (lung or ovarian) and no conclusive information on the mechanisms for both cancers is available. Therefore, a classification in category 1B is not justified.

Classification in Category 2 is based on limited evidence from human and/or animal studies and considered applicable for talc. Limited evidence of carcinogenicity (ovarian cancer) upon perineal use of talc in humans and limited evidence of lung tumours in one animal study (female rats; NTP carcinogenicity study) are available. Therefore, a classification in Category 2 is warranted.

Route of exposure

Classification as a carcinogen in Category 2 is based on both effects observed in rats after inhalation exposure and in humans after perineal exposure. Therefore, specification of a route is not proposed.

Particle size

The induction of lung tumours after inhalation exposure in rats is limited to particles that can reach the alveoli. Therefore, a particle size relevant for such effects could be included in the Annex VI entry. However, there is no evidence for a clear-cut border for talc via inhalation, based on animal or human data,

and no information on the relevance of the particle size on the ovary tumours after perineal exposure. Therefore, no particle size limitation is proposed.

Asbestiform talc

Asbestiform talc may induce carcinogenicity via a mechanism comparable to other insoluble fibres such as asbestos, silicon carbide and multi-wall carbon nanotubes. IARC classified talc containing asbestiform fibres in Group 1, carcinogenic to humans (IARC 1987, 2010). Asbestiform talc were not assessed in this CLH proposal. As a more severe classification for this type of talc cannot be excluded, inclusion of Note V was considered: "*If the substance is to be placed on the market as fibres (with diameter < 3 µm, length > 5 µm and aspect ratio ≥ 3:1) or particles of the substance fulfilling the WHO fibre criteria or as particles with modified surface chemistry, their hazardous properties must be evaluated in accordance with Title II of this Regulation, to assess whether a higher category (Carc. 1B or 1A) and/or additional routes of exposure (oral or dermal) should be applied*." However, as for talc the route is not specified, it is suggested to include a new note as follows: "*If the substance is to be placed on the market as fibres (with diameter < 3 µm, length > 5 µm and aspect ratio ≥ 3:1) or particles of the substance fulfilling the WHO fibre criteria or as particles with modified surface chemistry, their hazardous properties must be evaluated in accordance with Title II of this Regulation, to assess whether a higher category (Carc. 1B or 1A) and/or specification of routes of exposure should be applied*."

Quartz

Quartz is a reported impurity of talc (see Table 3 and confidential annex). It is considered unlikely quartz has influenced the results presented in this CLH proposal. Quartz as impurity of talc will thus not impact the classification of talc as a carcinogen in Category 2. This is because there is no evidence quartz influenced the NTP rat carcinogenicity study as quartz was not reported as impurity, or influenced the evidence of ovarian cancer in humans as risk estimates in earlier studies, in which exposure to contaminates was more likely, were similar to risk estimates from newer studies. Moreover, classification in Category 2 is warranted based on limited evidence from human studies, taking into account bias or confounding due to impurities.

Specific concentration limit

No specific concentration limit is proposed as the proposed classification in Category 2 is based on both animal data and human data with limited exposure data.

10.9.3 Conclusion on classification and labelling for carcinogenicity

Classification of talc as **Carc. 2, H351** is proposed, based on carcinogenic effects in the lungs (animal study) and ovaries (epidemiological data), without an indication of the exposure route and a specific concentration limit.

10.10 Reproductive toxicity

Not evaluated in this dossier.

10.11 Specific target organ toxicity-single exposure

Not evaluated in this dossier.

10.12 Specific target organ toxicity-repeated exposure

Table 18: Summary table of animal studies on STOT RE

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, route of exposure, dose levels, duration of exposure	Results	Reference
Inhalation			
Similar to OECD TG 453 with deviations: there were difficulties maintaining control of chamber concentrations; week 11-18: too high concentrations in 18 mg/m^3 chamber (30 to 40 mg/m^3); week 70-82: too low concentrations in all exposure chambers. F344/N rats (n = 50/group/sex, satellite group of 22/group/sex for measurements on lung) GLP RL 1	MP10-52 grade talc aerosols (≥96% talc, free of asbestos, virtually free of silica, 0.2-1.2% absorbed water, 1.0% iron, 0.5-0.7% aluminium, 0.35-0.5% fluorine, other impurities ≤0.1%) 0, 6 or 18 mg/m^3 (MMAD 2.7 and 3.2 µm, resp.; GSD 1.9 µm) Whole body, 6 h per day, 5 days per week Lifetime study *See Annex I for more details*	Survival and number of deaths of exposed male and female rats were similar to that of the controls. Body weight was reduced in female rats (6/18 mg/m^3: -3/-14%), no significant body weight changes were noted in males. Lung burden data suggest that either clearance of talc was not substantially impaired by increasing the exposure concentration, or that clearance of talc was impaired similarly at both exposure levels. Viability (0, 6, 18 mg/m^3 male: 64%, 67%, 58%; female: 83%, 75%, 61%) and phagocytic activity (male: 83%, 63%, 65%; female: 76%, 67%, 70%) of macrophages recovered from lavage fluid were not statistically significantly affected in any dose group after 24 months. Impaired lung function (reduced total lung capacity, vital capacity and forced vital capacity) was noted in both sexes at the highest dose level from 11 months onwards. Statistically significant increases of total lung collagen, protein and enzyme levels in lavage fluid were observed at ≥6 mg/m^3 in both sexes at the 24-month interim time point. Incidences of granulomatous inflammation (average severity minimal to moderate; 0, 6, 18 mg/m^3 male: 2/49, 50/50**, 49/50**; female: 2/50, 47/48**, 50/50**), peribronchial hyperplasia (minimal to mild; male: 0/49, 12/50**, 8/50**; female: 0/50, 8/48**, 9/50**), alveolar epithelial hyperplasia (minimal to mild; male: 5/49, 26/50**, 38/50**; female: 2/50, 27/48**, 47/50**) and interstitial fibrosis (minimal to mild; male: 1/49, 16/50**, 33/50**; female: 1/50, 24/48**, 45/50**) were increased in all exposed rats at final sacrifice. In females, an increases in alveolar squamous metaplasia (minimal; 0/50, 0/48, 8/50**) and squamous cysts (0/50, 1/48, 7/50**) were noted at the highest dose. Absolute and relative lung weights were increased, at the end of the study (6/18 mg/m^3 vs. control, males: 110/220%**, females: 193*/292%**).	NTP (1993)

Similar to OECD TG 412 F344/N rats (n = 10/group/sex, satellite group of 5/group/sex for evaluation lung burden) GLP RL 1	MP10-52 grade talc aerosols (≥96% talc, free of asbestos, virtually free of silica, 0.2-1.2% absorbed water, 1.0% iron, 0.5-0.7% aluminium, 0.35-0.5% fluorine, other impurities ≤0.1%) 0, 2, 6 or 18 mg/m^3 (MMAD 3.3 µm; GSD 1.9 µm) Whole body, 6 h per day, 5 days per week 4-week study *See Annex I for more details*	No statistically significant body weight changes or increases in any organ-weight-to-body-weight ratios in both sexes were noted. All rats survived to the end of the study. The lung burdens increased with talc exposure level; the ratio of lung burden normalised to exposure concentration was somewhat higher at ≥6 mg/m^3 in males (2, 6, 18 mg/m^3: 34.25**, 44.22**, 49.52**) and females (33.05**, 43.04**, 45.30**). A minimal increase of macrophages (containing talc-particles) in lungs were found at the highest dose level in both sexes, but no signs of adverse effects were observed. The response was minimal in the high exposure group and therefore tissues from lower exposure groups were not examined.	NTP (1993); Pickrell et al. (1989)
Experimental study, similar to OECD TG 412 Sprague-Dawley rats (n = 6/group/sex) No GLP RL 2	Talc aerosols (64.1% SiO_2, 32.6% MgO, 2.76% CaO, and 0.27% Na_2O, also including trace amounts of Fe_2O_3, Al_2O_3 and MnO) 0, 5, 50 or 100 mg/m^3 (MMAD 3.88 µm) Whole body, 6 h per day, 5 days per week 4-week study *See Annex I for more details*	There were no exposure-related adverse symptoms and deaths associated with inhaled talc during the experimental period. No statistically significant changes in body weight and relative organ weights. No dose-dependent changes in haematological or biochemical values. Infiltration of macrophages (minimal to moderate) on the alveolar wall and spaces near terminal and respiratory bronchioles were noted and occurred in a dose-dependent manner (0, 5, 50, 100 mg/m^3 males: 0/3, 0/3, 3/3, 3/3; females: 0/3, 0/3, 3/3, 3/3). No other exposure-related histopathological findings in the lungs were observed. A dose-dependent upregulation in protein expression of SOD2, an oxidative marker, was observed in lung tissue which was statistically significant in low- and high-dose in males and in high-dose females.	Shim et al. (2015)

Repeated dose toxicity study No test guideline study. Limitations: description of materials, methods and results is minimal. Wistar rats (n = 12/group/sex) Predates GLP RL 3 (limited documentation, large particle size)	Italian talc (00000 grade, 40% as respirable (not specified) dust, 92% talc; 0.5-1% quartz, mean size 25 µm, upper particle size of 70 µm) 0 or 10.8 mg/m^3 Whole body, 7.5 h per day, 5 days per week for 6 or 12 months (cumulative exposures: approx. 8200 and 16,400 mg/m^3 × h (resp.)) Ten days after the end of each exposure period rats were sacrificed or 1 year after the exposure had discontinued.	Ten days after the end of each exposure period rats were sacrificed or 1 year after the exposure had discontinued. Survival of exposed rats (6 and 12 months group combined: 24/48) were similar to the control group (27/48). Mostly minimal fibrosis (incidence not provided) was noted in exposed rats at ≥6 months, which progressed to minimal to slight fibrosis 1 year after exposure.	Wagner et al. (1977)
Similar to OECD TG 453 with deviations: there were difficulties maintaining control of chamber concentrations in week 70-82 (below target concentrations in all exposure chambers). B6C3F$_1$ mice (n = 50/group/sex, satellite group of 40/group/sex for measurements on lung) GLP RL 1	MP10-52 grade talc aerosols (≥96% talc, free of asbestos, virtually free of silica, 0.2-1.2% absorbed water, 1.0% iron, 0.5-0.7% aluminium, 0.35-0.5% fluorine, other impurities ≤0.1%) 0, 6 or 18 mg/m^3 (MMAD 3.3 and 3.6 µm, resp.; GSD 1.9 and 2.0 µm, resp.) Whole body, 6 h per day, 5 days per week 2-year study *See Annex I for more details*	Survival and number of deaths of exposed males and females were similar to control. Lung burden data suggest that clearance of talc from the lung was impaired, or impaired to a greater extent, in mice exposed to 18 mg/m^3 than in mice exposed to 6 mg/m^3. Lung burden was disproportionately greater at 18 mg/m^3 in comparison to 6 mg/m^3 in mice, explained by the statistically significantly reduced phagocytic activity at 18 mg/m^3. Increased levels of total protein, beta-glucuronidase, lactate dehydrogenase, glutathione reductase, total nucleated cells and polymorphonuclear leukocytes in bronchoalveolar lavage fluid in both sexes at 18 mg/m^3 and ≥24 month exposure. Absolute and relative lung weights were increased, at final sacrifice (6/18 mg/m^3 vs. control, males: 107/175%**, females: 105/152%**). Statistically significantly increased incidence of accumulation of alveolar macrophages in the alveoli surrounding terminal bronchioles (hyperplasia, macrophage) and inflammation were noted in the lungs at ≥6 mg/m^3 in both sexes.	NTP (1993)

Similar to OECD TG 412 $B6C3F_1$ mice (n = 10/group/sex, satellite group of 5/group/sex for evaluation lung burden) GLP RL 1	MP10-52 grade talc aerosols (≥96% talc, free of asbestos, virtually free of silica, 0.2-1.2% absorbed water, 1.0% iron, 0.5-0.7% aluminium, 0.35-0.5% fluorine, other impurities ≤0.1%) 0, 2, 6 or 18 mg/m^3 (MMAD 2.7 µm; GSD 1.9 µm) Whole body, 6 h per day, 5 days per week 4-week study *See Annex I for more details*	No statistically significant body weight changes or increases in any organ-weight-to-body-weight ratios in both sexes were noted. No clinical signs reported. Two exposed male mice died before the end of the study; one at 2 and 6 mg/m^3. Talc lung burdens increased with talc exposure level but the ratio of lung burden to exposure concentration was constant at all exposure levels in both sexes. The maximum ability of the respiratory tract to clear particles was apparently not exceeded at any dose level. Minimal changes in the lungs (increased intra-alveolar macrophages which contained talc-particles) of male and female mice were noted in the high exposure group (incidence not provided) and therefore tissues from lower exposure groups were not examined.	NTP (1993); Pickrell et al. (1989)

No test guideline study Golden Syrian hamsters (n = 25-50/group/sex) Predates GLP RL 3 (large MMAD)	Talc-based baby powder (aerosols; 95% w/w, Vermont talc), whole body exposure Three groups were exposed to 37.1 mg/m^3, mean respirable fraction 9.8 mg/m^3, MMAD of 4.9 µm; 3, 30, or 150 min/day, 5 days/week, for 30 days. Two additional groups were exposed 27.4 mg/m^3, mean respirable fraction 8.1 mg/m^3, MMAD of 6.0 µm; for 30 or 150 min/day, for 300 days. The survivors in these two groups were killed at the age of 20 months. Two groups of 25 male and 25 female hamsters were exposed to air and served as controls. *See Annex I for more details*	There were no significant differences among the survival times in exposed groups or compared to control groups. A statistically significantly ($p < 0.05$) lower mean survival was noted in females in all groups compared to males. No clinical signs or body weight changes related to exposure were observed. An exposure related effect was noted for focal alveolar cell hyperplasia upon a 300-day exposure (0, 30, 150 min/day male: 5/25, 14/49, 15/48; female: 0/25, 11/50, 9/48). No clear dose- or exposure duration-related effects on incidences were observed for other histological effects.	Wehner et al. (1977c)
Other routes			
No test guideline study Subacute toxicity test Sprague-Dawley rats (n = 5, male) Predates GLP RL 2	Talc (purity not stated; FDA 71-43; lot no. 11-16-17 (#141); 29.6% w/v suspension in saline), 5000 mg/kg bw/day for 5 days. All animals were observed for 14 days.	No deaths observed. Minimal signs of toxicity were noted, consisting of slightly rough fur, decreased activity and light coloured stools (presumably due to coloration of the compound). No gross pathologic evidence was observed at necropsy. The 14-day LD_{50} was considered >5000 mg/kg bw.	Litton Bionetics Inc. (1974)

No test guideline study. Limitations: description of materials, methods and results is minimal. Wistar rats (n = 8-16/group/sex) Predates GLP RL 3 (limited documentation, large particle size)	Italian talc (00000 grade, 92% talc, 3% chlorite, 1% carbonate minerals, 0.5-1% quartz; mean size 25 µm), 0 or 100 mg/day in diet for 5 months (talc-containing diet was actually given for 101 days) and then basal diet for life	The average survival in the control and exposed group was 641 and 614 days, respectively. This difference was not statistically significant. No histopathological changes were reported.	Wagner et al. (1977)
GSD: geometric standard deviation; MMAD: mass median aerodynamic diameter; SOD2: superoxide dismutase 2; Statistically significant vs. control, *$p \leq 0.05$, **$p \leq 0.01$			

Table 19: Summary table of human data on STOT RE

Type of study/data	Test substance (composition and particle size)	Relevant information about the study (as applicable)	Observations	Reference
Occupational exposure – talc miners and millers – case-control studies				
Case-control study 7 male talc workers from Vermont, USA. Subjects had different job functions, e.g. watchman, bagger, driller.	Talc mined in this region contains chlorites and carbonates, and only traces of quartz and fibrous silicates. X-ray crystallographic studies revealed that the predominant mineral present in the lungs in all studied cases was talc. Smaller amounts of chlorite, quartz, mice (biotite) and feldspar (oligoclase, albite) were also present. In one case, a few fibres of tremolite	Employed 4-27 years up to 1976. Lifetime exposure ranged from 12 to 5930 mppcf. Lung tissues were compared with tissues from eight adult male control subjects (age-matched) from the same region and were processed in a fashion similar to that used with specimens. Autopsy examination indicated that death of the eight controls was caused by either trauma or cardiovascular disease.	In 3/7 workers with exposure of 26-27 years chest x-rays were consistent with pneumoconiosis. In addition, the lung tissues from 4 other workers (exposure history of 4-19 years) exhibited focal and diffuse fibrosis with accumulation of talc. But the x-ray films were negative. Linear correlation was found between years of talc exposure and accumulation of dust (predominantly talc, but also small traces of chlorite and quartz) in lungs.	Vallyathan and Craighead (1981)

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td>asbestos were found in the lungs.</td><td></td><td></td><td></td></tr>
<tr><td>Nested case-control study

Limitations: information on smoking habits was available for French cohort, no specific information was given on the proportion of subjects alive among cases and controls at the date of interview.

1160 talc workers (1070 men, 90 women) from Luzenac, France (site A), only male workers were included by Wild et al. (2002); and 542 male talc workers from 3 sites (site B, C and D) in Styrian Alps, Austria</td><td>Talc from site A: pure talc, chlorite, dolomite, quartz (0.5-3%) and does not contain asbestos. Site B: talc-chlorite mixture containing quartz (0.5-4%); site C: talc-dolomite aggregation (medium talc content 25%), containing quartz in the end products (<1%), singular parts in the mine, rich in dolomite (could contain 2–3% quartz); site D: an aggregation of more or less equal proportions of mica, chlorite, and quartz.</td><td>French cohort: employees were active in 1945 or hired during the period 1945-1994 and having worked ≥1 year.

Austrian cohort: Employed >1 year during 1972-1995;

Semi-quantitative, site-specific job exposure matrix based on personal dust measurements (1988–1992) and descriptions of workplaces from management and long-term workers; workers assigned to four categories of exposure: no exposure, ambient (<5 mg/m^3), medium (5–30 mg/m^3) and high (>30 mg/m^3); other exposures coded: quartz, other carcinogens, underground work.

Nested case-control study: three randomly selected controls per case; NMRD: 39 cases, 116 controls (France); 1 case, 3 controls (Austria).

Dust levels 1960s and 1970s generally high (ranging <5 to >30 mg/m^3). In 1990s, dust levels <5 mg/m^3.

Cumulative exposure estimates (mg/m^3–</td><td>Increased mortality in the highest exposure groups (with a significant trend) with cumulative exposure to talc.

Cumulative exposure estimates (mg/m^3–years) for individual workers. The cumulative exposure to talc dust was transformed into units of 100 years.mg/m^3. One unit is for instance obtained as 40 years at 2.5 mg/m^3 (low exposure), as 10 years of medium exposure, or as 2.5 years in a highly exposed job.
<table>
<tr><th>Exposure category</th><th>No. of cases</th><th>Odds ratio (95% CI)</th></tr>
<tr><td>Unexposed</td><td>6</td><td>1.0</td></tr>
<tr><td><100 mg/m^3–years</td><td>1</td><td>0.2</td></tr>
<tr><td>100–400 mg/m^3–years</td><td>8</td><td>1.0</td></tr>
<tr><td>400–800 mg/m^3–years</td><td>9</td><td>2.0</td></tr>
<tr><td>≥800 mg/m^3–years</td><td>16</td><td>2.5</td></tr>
<tr><td colspan="3">Cumulative exposure to talc: per 100 mg/m^3–years (40 cases and 115 controls):</td></tr>
<tr><td>All cases</td><td>40</td><td>1.1 (1.0-1.2)</td></tr>
<tr><td>Pneumoconiosis</td><td>10</td><td>1.2 (1.0-1.4)</td></tr>
<tr><td>COPDs</td><td>10</td><td>1.0 (0.9-1.2)</td></tr>
<tr><td>Other (pneumonia, bronchopneumonia or other)</td><td>20</td><td>-</td></tr>
</table>
Unadjusted odds ratio, adjustment on potential confounders (smoking and exposure to quartz) did not change this trend to any extent. Most cases (39/40) of NMRDs were from the French cohort. Assumes a linear trend.</td><td>Wild et al. (2002)</td></tr>
</table>

Type of study/data	Test substance (composition and particle size)	Relevant information about the study (as applicable)	Observations	Reference
		years) assigned to individual workers by occupational physician using work histories abstracted from company records. Adjusted for age, calendar year, smoking, exposure to quartz, exposure to other carcinogens, underground work; French smoking information collected by an external interviewer blind to case-control status on basis of existing documents or via former colleagues. Limited information available; for 52% of cases and 75% of controls. Austrian smoking information obtained from unpublished mortality studies on pneumoconiosis, from colleagues, from workers' compensation records; no missing information on smoking habits in Austrian cohort.		
Occupational exposure – talc miners and millers – cross-sectional studies				
Cross-sectional study Limitations: only currently employed workers were included, time employed was relatively short for the	Free silica content of bulk samples was low (below the limit of detection in MT, 1.5% in NC, and 2.2% in TX). Dolomite content was	The average time worked was 7, 6, and 10 year and the average exposure (cumulative exposure/total time worked) was (mg/m^3 × year) 1.2, 2.6, and 0.3 in MT, TX, and NC respectively. The geometric mean	There were no significant increases in symptoms or pneumoconiosis among the study group of talc workers nor significant reductions in lung function. Prevalence (% in nonsmokers, exsmokers, smokers, total) of dyspnoea and pleural thickening: 6, 10, 3, 5 and 0, 4, 9, 5. No association with cumulative exposure. <u>Lung symptoms prevalence:</u>	Gamble et al. (1982)[19]

[19] Primary source not assessed. Adopted from Johnson (2020) and Fiume et al. (2015).

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td>development of occupationally related symptoms, estimating past exposure was a problem.

299 miners and millers from Montana (MT; 177 workers), Texas (TX; 71 workers) and North Carolina (NC; 51 workers), USA.

Lung parameters of talc workers were compared with 292 controls (blue collar workers and potash miners).</td><td>13% in TX sample and 1-3% in other samples. Under the transmission electron microscope, tremolite and antigorite fibres (0.5-3 µm length) were observed on the TX talc, acicular particles (aspect ratios 5-100 to 1 and some diameters <0.1 µm) in NC talc, and no fibres in the MT talc.</td><td>concentrations of respirable dusts (mg/m^3) in samples for miners and millers was: 0.66 and 1.1 (MT), 0.45 and 1.56 (TX), 0.14 and 0.26 (NC).</td><td><table><tr><td></td><td colspan="2">Prevalence (%)</td></tr><tr><td>Symptom</td><td>Talc workers</td><td>Controls</td></tr><tr><td>Cough</td><td>20.3</td><td>16.7</td></tr><tr><td>Phlegm</td><td>20.3</td><td>17.3</td></tr><tr><td>Dyspnoea</td><td>5.8</td><td>7.5</td></tr><tr><td>Bilateral pleural thickening</td><td>6.3</td><td>0.4</td></tr></table>
Mean percentage of predicted pulmonary function (FEV_1, FVC, peak flow, FEF_{50}, FEF_{75}: 99.7, 101.0, 97.9, 94.1, 84.5) similar in talc workers as compared to controls.

Workers with bilateral pleural thickening had lung function 10-20% below workers with no pleural thickening. In talc workers older than 40 years, the prevalence of pleural changes was 7, 16, and 14% in MT, TX, and NC, respectively. They had also worked twice as long (13 year) and an average of 13 year between beginning exposure to talc and the time of the X-ray.</td><td></td></tr>
<tr><td>Cross-sectional study

Limitations: short follow-up interval for the development of occupationally related symptoms and for the overall ranges of exposure within this study

116 miners and millers from Vermont, USA.</td><td>Talc was found to be essentially free from silica and asbestos.</td><td>Employed at ≥25 years old were included. Forced expirations after maximum inspiration were recorded for each worker. Posterioranterior chest radiographs were taken in full inspiration of 100 workers. Study included a 1-year follow-up. Measurements were taken 1975-1976.

Exposure levels were 0.2-3 mg/m^3 respirable dusts (not specified). The geometric mean exposure for the population was 1.8 mg/m^3 of respirable</td><td>Lung function was impaired, as demonstrated by statistically significant decreases FEV_1 (92.6% of control, $p < 0.001$) and MMEF (66.2% of control, $p < 0.001$) compared to predicted. Decreased FEV_1/FVC and MMEF were statistically significantly associated ($p < 0.01$) with years of employment and exposure to talc.

A 43% prevalence of any chest X-ray abnormality was observed. One-third of these abnormalities were parenchymal opacities or pleural abnormalities.

12/100 workers had small round opacities and 9/100 had small irregular opacities. There was a statistically significant ($p < 0.001$) association with x-ray abnormalities and talc years or year employed.</td><td>Wegman et al. (1982)</td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td>dust. Average years employed was 8.5 years.

No appropriate control group was available. Observed pulmonary function parameters were compared to predicted values from a standard population.</td><td></td><td></td></tr>
<tr><td>Cross-sectional study

Limitations: limited documentation (e.g. no information on years of employment) available.

176 talc workers, functional respiratory study in 39 pneumoconiotic workers, all from Luzenac, France</td><td>French talc, which contains various amounts of chlorites, small quantities of dolomite. There is no asbestos and quartz is between 0.5-3%.</td><td>Questionnaire, clinical examination, chest x-ray, vitalographic spirometry were carried out in 1978.

Exposure to respirable (not specified) dust at milling and packaging of talc drastically decreased from 1954 to 1988. Exposure during milling and packaging (respectively): 30 or 28 mg/m^3 in 1954 and 1 or 2 mg/m^3 in 1988.</td><td>Increased prevalence of pneumoconiosis 46/176 talc workers; 36 had slight pneumoconiosis (small opacities), 10 had signs of pneumoconiosis with higher profusion or large opacities. Three cases of pleural thickenings were observed.

Pulmonary function in pneumoconiotic workers was statistically significantly (p not specified) decreased; compared to reference values of the ECSC, VC and TLC were 96.8 and 94.2%, respectively.

Bronchoalveolar lavage was performed on eight pneumoconiosis patients (as result from talc exposure). Statistically significant increases in neutrophils, eosinophils and polymorphonuclear leukocytes in the lungs were reported, including talc particles (plate-like 0.5-40 µm in size).</td><td>Leophonte and Didier (1990)</td></tr>
<tr><td>Cross-sectional study

Limitations: spirometric tests were suboptimal and resulted in exclusion of 30 patients.

166 millers from talc factory in south western France.</td><td>Talc ore containing chlorite, aluminium, dolomite (<3%), quartz (<3%), and traces of calcite, apatite, pyrite and mica. No amphiboles detected.</td><td>Talc workers employed between 1989-1990.

Workers completed a standardised questionnaire regarding occupational history, smoking, symptoms etc. during annual medical check-up. Chest radiographs were taken between 1982-1987 and 139 workers had a second radiograph in 1992.

In 1986, 1989 and 1991 systematic</td><td>Increased prevalence of dyspnoea (adjusted for smoking categories) upon increasing cumulative exposure to talc.

Statistically significant downward trends for FVC (including or excluding smoking categories), and FEV and MMEF (after adjustment for smoking categories, pack-years and time since the end of smoking for ex-smokers).

<u>Lung symptoms:</u>
<table><tr><td></td><td>No. of cases</td><td>Prevalence (%)</td></tr><tr><td colspan="3">Cumulative exposure <20 y mg/m^3 (n = 46)</td></tr><tr><td>Chronic bronchitis</td><td>0</td><td>0</td></tr></table></td><td>Wild et al. (1995)</td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td>exposure measurements were taken for every workplace and job via personal dust sampling. Exposure assessment for earlier time points was based on expert quantification.
The geometric mean of estimated exposure was 1.87 mg/m^3 (range 0.5 to 50 mg/m^3, GSD was 2.5 mg/m^3). The estimated cumulative exposure at the date of spirometry was >150 y mg/m^3 for 41 subjects.</td><td>
<table>
<tr><td>Chronic cough or phlegm</td><td>4</td><td>8.7</td></tr>
<tr><td>Dyspnoea</td><td>2</td><td>4.4</td></tr>
<tr><td>Wheeze</td><td>2</td><td>4.4</td></tr>
<tr><td colspan="3">Cumulative exposure 20-50 y mg/m^3 (n = 25)</td></tr>
<tr><td>Chronic bronchitis</td><td>1</td><td>4</td></tr>
<tr><td>Chronic cough or phlegm</td><td>5</td><td>20</td></tr>
<tr><td>Dyspnoea</td><td>2</td><td>8</td></tr>
<tr><td>Wheeze</td><td>1</td><td>4</td></tr>
<tr><td colspan="3">Cumulative exposure 50-150 y mg/m^3 (n = 54)</td></tr>
<tr><td>Chronic bronchitis</td><td>7</td><td>13</td></tr>
<tr><td>Chronic cough or phlegm</td><td>14</td><td>35.7</td></tr>
<tr><td>Dyspnoea</td><td>9</td><td>17</td></tr>
<tr><td>Wheeze</td><td>2</td><td>3.7</td></tr>
<tr><td colspan="3">Cumulative exposure >150 y mg/m^3 (n = 41)</td></tr>
<tr><td>Chronic bronchitis</td><td>1</td><td>2</td></tr>
<tr><td>Chronic cough or phlegm</td><td>6</td><td>14.6</td></tr>
<tr><td>Dyspnoea</td><td>6</td><td>14.6</td></tr>
<tr><td>Wheeze</td><td>0</td><td>0</td></tr>
</table>
<u>Spirometry:</u>
<table>
<tr><td></td><td>Mean (SD)[20]</td></tr>
<tr><td colspan="2">Cumulative exposure <20 y mg/m^3 (n = 36)</td></tr>
<tr><td>FVC</td><td>1.33 (1.28)</td></tr>
<tr><td>FEV$_1$</td><td>1.22 (1.21)</td></tr>
<tr><td>FEV/FVC$_1$</td><td>0.25 (0.70)</td></tr>
<tr><td>MMEF</td><td>0.66 (1.58)</td></tr>
<tr><td colspan="2">Cumulative exposure 20-50 y mg/m^3 (n =</td></tr>
</table>
</td><td></td></tr>
</table>

[20] The measurements were expressed as standardised residuals (observed-predicted/residual SD from the European Respiratory Society)

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td colspan="2">20)</td></tr>
<tr><td>FVC</td><td>0.82 (1.04)</td></tr>
<tr><td>FEV₁</td><td>0.77 (1.22)</td></tr>
<tr><td>FEV/FVC₁</td><td>0.27 (0.79)</td></tr>
<tr><td>MMEF</td><td>0.36 (1.41)</td></tr>
<tr><td colspan="2">Cumulative exposure 50150 y mg/m^3 (n = 44)</td></tr>
<tr><td>FVC</td><td>1.10 (1.07)</td></tr>
<tr><td>FEV₁</td><td>0.74 (1.17)</td></tr>
<tr><td>FEV/FVC₁</td><td>-0.04 (0.80)</td></tr>
<tr><td>MMEF</td><td>-0.19 (1.15)</td></tr>
<tr><td colspan="2">Cumulative exposure >150 y mg/m^3 (n = 36)</td></tr>
<tr><td>FVC</td><td>0.65 (1.03)</td></tr>
<tr><td>FEV₁</td><td>0.50 (1.06)</td></tr>
<tr><td>FEV/FVC₁</td><td>0.24 (0.75)</td></tr>
<tr><td>MMEF</td><td>-0.06 (1.12)</td></tr>
<tr><td colspan="2">Slope / 100 y mg/m^3</td></tr>
<tr><td>FVC</td><td>-0.24 (p = 0.015)</td></tr>
<tr><td>FEV₁</td><td>-0.26 (p = 0.014)</td></tr>
<tr><td>FEV/FVC₁</td><td>-0.06 (p = 0.40)</td></tr>
<tr><td>MMEF</td><td>-0.26 (p = 0.032)</td></tr>
</table>

In the first radiograph, 4 pleural abnormalities were reported. In the second radiograph, 11 new opacites compatible with pneumoconiosis were observed. Smoking was positively and statistically significantly related to this increase: 10/11 pneumoconiosis-like new images were from smokers.
</td><td></td></tr>
<tr><td colspan="5">Occupational exposure – talc miners and millers – cohort studies</td></tr>
<tr><td>Retrospective cohort study

Limitations: no smoking data for exposed workers and unexposed</td><td>Pure talc used for pharmaceutical and cosmetic industry. Also exposure to dusts containing high</td><td>Employment 1 year in talc exposed job during 1921-1974; hired 1921-1950; mortality follow-up, 1921-1974 quantitative estimation of</td><td>Statistically significant increases in specific cause of death among miners were found for silicosis (62 observed; SMR, 2.0; (95% CI, 1.5–2.6) and for silicosis with superimposed tuberculosis (18 observed; SMR, 2.0; 95% CI, 1.2–3.1). These estimates were found to increase with increasing cumulative exposure. No</td><td>Rubino et al. (1976)</td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr>
<td>controls. Lack of comparability between the workers and the comparison groups could influence the mortality ratio estimates of this study (IARC 2010).

1992 male talc workers (1514 miners, 478 millers) from Val Chisone (Piedmont), Italy. Risk ratios calculated using death rates from neighbouring rural population.</td>
<td>levels of respirable dust (respirable range 0.5 – 5 µm as defined by British Medical Research Council criteria; quartz[21]). Rock-type inclusions were removed before milling so that content had quartz <2%. Small amounts of tremolite detected. Respirable dust measurements, 1948–1974;</td>
<td>cumulative exposure for individual workers, expressed as summed product of duration (years) and exposure (mppcf); classification of workers into 3 levels of exposure. Information relating to cause of death was obtained from death certificates for both exposed and controls. Vital status, 90%; cause of death: 95% of exposed workers, 95% of controls.

Adjusted for age; comparison with unexposed, age-matched controls from neighbouring rural town; controls matched on vital status at date of entry into study; miners and millers exposed to a very pure form of talc; miners also exposed to inhalable silica; significantly elevated SMRs for silicosis with and without tuberculosis among miners; estimates increased with increasing cumulative exposure; no observed cases of mesothelioma; no smoking data for exposed workers or unexposed controls.</td>
<td>information provided on other types of pneumoconiosis.

Increased mortality of respiratory diseases likely due to high exposure to silica rather than talc, as cases were higher in miners.

<u>Respiratory diseases (all except pulmonary tuberculosis)[22]:</u>
<table>
<tr><td>Exposure category</td><td>No. of cases/deaths</td><td>SMR</td></tr>
<tr><td>All miners</td><td>140</td><td>1.4 (p < 0.01)</td></tr>
<tr><td>All millers</td><td>25</td><td>1.2</td></tr>
<tr><td colspan="3">Miners (mppcf-years)</td></tr>
<tr><td>Level 1: 566–1699</td><td>26</td><td>0.7 (p < 0.05)</td></tr>
<tr><td>Level 2: 1700–5665</td><td>38</td><td>1.1</td></tr>
<tr><td>Level 3: 5666–12750</td><td>76</td><td>1.1 (p < 0.05)</td></tr>
<tr><td colspan="3">Miners (latency, years)</td></tr>
<tr><td><20</td><td>28</td><td>1.2</td></tr>
<tr><td>20-40</td><td>76</td><td>1.4 (p < 0.01)</td></tr>
<tr><td>>40</td><td>36</td><td>1.5 (p < 0.01)</td></tr>
<tr><td colspan="3">Millers (mppcf-years)</td></tr>
<tr><td>Level 1: 25–141</td><td>11</td><td>1.1</td></tr>
<tr><td>Level 2: 142–424</td><td>9</td><td>1.3</td></tr>
<tr><td>Level 3: 425–906</td><td>5</td><td>0.6</td></tr>
<tr><td colspan="3">Millers (latency, years)</td></tr>
<tr><td><20</td><td>7</td><td>0.9</td></tr>
<tr><td>20-40</td><td>17</td><td>1.5 (p < 0.05)</td></tr>
<tr><td>>40</td><td>1</td><td>0.6</td></tr>
</table>

<u>Pneumoconiosis (silicosis)[22]:</u></td>
<td></td>
</tr>
</table>

[21] IARC noted that the term silica was in fact quartz

[22] 95% CI not determined in original study

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>Exposure category</td><td>No. of cases/deaths</td><td>SMR (95% CI)</td></tr>
<tr><td>All miners</td><td>62</td><td>2.0 (1.5-2.6)[23] (p < 0.01)</td></tr>
<tr><td>All millers</td><td>3</td><td>1.4 (0.3-4.2)[23]</td></tr>
<tr><td colspan="3">Miners (mppcf-years)</td></tr>
<tr><td>Level 1: 566–1699</td><td>8</td><td>0.5 (p < 0.05)</td></tr>
<tr><td>Level 2: 1700–5665</td><td>14</td><td>0.9</td></tr>
<tr><td>Level 3: 5666–12750</td><td>40</td><td>1.3 (p < 0.05)</td></tr>
<tr><td colspan="3">Miners (latency, years)</td></tr>
<tr><td><20</td><td>11</td><td>2.0 (p < 0.01)</td></tr>
<tr><td>20-40</td><td>24</td><td>2.0 (p < 0.01)</td></tr>
<tr><td>>40</td><td>27</td><td>2.0 (p < 0.01)</td></tr>
<tr><td colspan="3">Millers (mppcf-years)</td></tr>
<tr><td>Level 1: 25–141</td><td>1</td><td>0.9</td></tr>
<tr><td>Level 2: 142–424</td><td>2</td><td>3.3</td></tr>
<tr><td>Level 3: 425–906</td><td>-</td><td>-</td></tr>
<tr><td colspan="3">Millers (latency, years)</td></tr>
<tr><td><20</td><td>-</td><td>-</td></tr>
<tr><td>20-40</td><td>2</td><td>1.3</td></tr>
<tr><td>>40</td><td>1</td><td>2.0</td></tr>
</table>
<u>Silico-tuberculosis[22]:</u>
<table>
<tr><td>Exposure category</td><td>No. of cases/deaths</td><td>SMR</td></tr>
<tr><td>All miners</td><td>18</td><td>2.0 (p < 0.01)</td></tr>
<tr><td>All millers</td><td>2</td><td>2.0</td></tr>
<tr><td colspan="3">Miners (mppcf-years)</td></tr>
</table>
</td><td></td></tr>
</table>

[23] 95% CI adopted from Ciocan et al. (2022)

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>Level 1: 566–1699</td><td>1</td><td>0.2</td></tr>
<tr><td>Level 2: 1700–5665</td><td>6</td><td>1.2</td></tr>
<tr><td>Level 3: 5666–12750</td><td>11</td><td>1.3</td></tr>
<tr><td colspan="3">Miners (latency, years)</td></tr>
<tr><td><20</td><td>3</td><td>2.1</td></tr>
<tr><td>20-40</td><td>10</td><td>2.0 (p < 0.01)</td></tr>
<tr><td>>40</td><td>5</td><td>1.9</td></tr>
<tr><td colspan="3">Millers (mppcf-years)</td></tr>
<tr><td>Level 1: 25–141</td><td>-</td><td>-</td></tr>
<tr><td>Level 2: 142–424</td><td>1</td><td>1.1</td></tr>
<tr><td>Level 3: 425–906</td><td>1</td><td>3.3</td></tr>
<tr><td colspan="3">Millers (latency, years)</td></tr>
<tr><td><20</td><td>1</td><td>2.0</td></tr>
<tr><td>20-40</td><td>1</td><td>2.0</td></tr>
<tr><td>>40</td><td>-</td><td>-</td></tr>
</table>
</td><td></td></tr>
<tr><td>Retrospective cohort study

Limitations: national death rates were available from 1951 onwards.

1678 male talc workers (1260 miners, 418 millers) from Val Chisone (Piedmont), Italy. Risk ratios calculated using national death rates.</td><td>Re-analysis, same as Rubino et al. 1976</td><td>Re-analysis, same exposure categories as Rubino et al. (1976)

SMRs recalculated using national death rates instead of comparison with neighbouring rural population; national death rates available only from 1951 onward; rates for 1951 were applied for 1946–50.</td><td>Mortality from NMRD (mainly pneumoconiosis and tuberculosis) was statistically significantly increased.

<u>NMRDs:</u>
<table>
<tr><td>Exposure category</td><td>No. of cases/deaths</td><td>SMR (95% CI)</td></tr>
<tr><td>All miners</td><td>109

(58 cases of pneumoconiosis, 23 cases of tuberculosis)</td><td>3.3 (2.7-4.0).</td></tr>
<tr><td>All millers</td><td>11 (3 cases of pneumoconiosis, 8 cases of tuberculosis)</td><td>N.D.</td></tr>
</table></td><td>Rubino et al. (1979)[24]</td></tr>
<tr><td>Retrospective cohort study</td><td>The talc in this region is a mixture of pure</td><td>Employed >1 year between 1940 and 1969; mortality</td><td>Excess NMRD mortality was observed in millers, a group thought to have greater lifetime dust exposures than millers. No</td><td>Selevan et al. (1979)</td></tr>
</table>

[24] Primary source not assessed. Adopted from IARC (2010).

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr>
<td>Limitations: no smoking data for exposed workers. IARC noted that the results for respiratory cancer were not analysed by latency (IARC 2010).

392 male talc workers (163 miners, 225 millers) from Vermont, USA.</td>
<td>talc, magnesite, chlorite and dolomite. Airborne dust samples and bulk materials were free of both asbestiform minerals and significant quantities of free silica (respirable crystalline silica <0.25%, defined as free silica)</td>
<td>follow-up: date of first radiogram, 12-month employment anniversary January 1940, whichever was later; follow-up through 1975; vital status: 99%; cause of death: 94%

To calculate risk ratios, mortality rates from Vermont were used for NMRDs and respiratory cancer. For other causes of death, rates for the USA were used.

Historical insufficient information to calculate cumulative exposure histories; cohort classification based on work area. According to the authors, past exposure levels were far exceeding 20 mppcf for miners and millers.

Miners were also exposed to radon daughters (0.12-1 WL).

Adjusted for age, sex, race, calendar year; US death rates: 1940–1967; linear extrapolation for all causes of death: 1967–1969. Vermont death rates for specific causes of death: 1949–1975; workers selected from annual radiographic survey of dusty trades; no data on smoking habits for millers or miners; exposure to radon daughters in</td>
<td>such excess was observed among miners.

<u>Mortality NMRDs:</u>
<table><tr><td>Exposure category</td><td>No. of cases/deaths</td><td>SMR (95% CI)</td></tr><tr><td>Millers</td><td>7</td><td>4.1 (1.6-8.4)</td></tr><tr><td>Miners</td><td>2</td><td>1.6 (0.2-5.9)</td></tr></table>Most workers who died from NMRD had radiographic evidence of pneumoconiosis (rounded opacities).</td>
<td></td>
</tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td>mine; radiographic evidence of pneumoconiosis in most workers who died from NMRD.</td><td></td><td></td></tr>
<tr><td>Retrospective cohort study

Limitations: limited documentation (e.g. smoking habits, no information on years of employment) available.

97 talc workers from Luzenac, France</td><td>French talc, which contains various amounts of chlorites, small quantities of carbonates. There is no asbestos and quartz is between 0.5-3%.</td><td>Retrospective cohort included workers employed between 1945-1981 and deceased between 1970-1981 and compared with 97 subjects dead at the same age from the same area.</td><td>Increased mortality as result of NMRDs (OR: 2.4) was found in talc workers as compared to controls from the same area.</td><td>Leophonte and Didier (1990)</td></tr>
<tr><td>Retrospective cohort study

Limitations: no information on smoking habits for millers; smoking habits for miners above national average.

389 male talc workers (94 miners, 295 millers) in northern Norway.

National rates were used to calculate expected numbers of cancers and deaths.</td><td>Norwegian talc contains mainly pure talc and magnesite, and only trace quantities of quartz, tremolite and anthophyllite (optical and electron microscopy; 0.2-0.9 fibres/ml).

Millers worked mostly with talc from this mine (90%), but also with talc from India (10%). In addition to talc, dolomite and mica were also processed at the mill.</td><td>Employed >1 year in mine (1944-1972) or >2 years in mill (1935-1972); mortality and cancer incidence follow-up 1953-1987.

Workers were classified by total duration of employment in jobs with low, medium, high and unknown exposure.

Personal air samples collected in the early 1980s showed that total dust levels varied greatly by job category and workplace (mine, 0.9–97 mg/m^3; mill, 1.4–54 mg/m^3). Peak exposures occurred during drilling in the mine (319 mg/m^3) and in the store house in the mill (109 mg/m^3).

Samples contained <1% quartz (X-ray</td><td>There were fewer deaths than expected from NMRDs but the numbers were too small for further conclusions. Three cases of mortality due to NMRD were recorded; silicosis was recorded twice (one miner, one miller) and talcosis once (one miller).

No association between respiratory disease mortality and exposure to non-asbestiform talc was found.

<u>Mortality NMRDs (pneumonia):</u>
<table><tr><td>Exposure category</td><td>No. of cases/deaths</td><td>SMR (95% CI)</td></tr><tr><td>Total cohort</td><td>3</td><td>0.3 (0.1-0.8)</td></tr><tr><td>Miners</td><td>1</td><td>0.4 (0-2.2)</td></tr><tr><td>Millers</td><td>2</td><td>0.2 (0-0.9)</td></tr></table></td><td>Wergeland et al. (1990)</td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td>diffractometry) and low levels of radon daughters 1.5-7.5 pCi/L (0.02-0.08 WL) radon daughters.

Smoking habits were available for 63/94 miners and rates were above the national average (76% smokers, 16% former smokers, 8% non-smokers). No information available for smoking habits for millers.

Adjusted for age, smoking (miners only); national death rates: 1953–1987; main minerals in mined talc deposit were talc and magnesite.</td><td></td><td></td></tr>
<tr><td>Retrospective cohort study

See nested case-control study Wild et al. (2002)</td><td>See nested case-control study Wild et al. (2002)</td><td>French cohort: employees were active in 1945 or hired during the period 1945-1994 and having worked ≥1 year. Mortality of the cohort was evaluated from 1 January 1945 to 31 December 1996. Vital status was obtained from the local population register and national mortality files which also included information on cause of death, in most cases, for individuals who died after 1968. Vital status 97%; cause of death: 74% pre-1968 and 98% post-1968. Partial overlap of study population with</td><td>The lower than expected mortality in both cohorts (SMR (95% CI) French cohort: 0.9 (0.8-1.0); Austrian cohort: 0.8 (0.6-1.0)) for mortality from all causes and from cardiovascular diseases hints at a healthy worker effect.

French cohort:

A non-significant excess mortality due to NMRDs found for workers compared to the control group. Three cases of mortality due to pneumoconiosis were reported. Mortality from NMRDs decreased when pre-1968 national reference rates were applied.

Austrian cohort:

Mortality from NMRDs lower than expected. No cases of pneumoconiosis observed.

<u>Mortality NMRDs (males):</u>
<table><tr><td>Exposure category</td><td>No. of cases/deaths</td><td>SMR (95% CI)</td></tr><tr><td colspan="3">French cohort</td></tr><tr><td>NMRD, post-1968 (national</td><td>26</td><td>1.1 (0.7-1.6)</td></tr></table></td><td>Wild (2000); Wild et al. (2002)</td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td>Leophonte et al. (1983); extent of overlap unknown; national mortality rates applied pre- and post- 1968; regional mortality rates applied post-1968.

Austrian cohort: Employed >1 year during 1972-1995; mortality follow-up, 1972-1995; vital status: 97%; smoking information obtained from unpublished mortality studies on pneumoconiosis, from colleagues, from workers' compensation records; no missing information on smoking habits in Austrian cohort. SMRs calculated by comparison with regional rates, 1972–1995;

Dust levels 1960s and 1970s generally high (ranging <5 to >30 mg/m^3). Mean exposure to respirable dust at French site was 3.6 to 25.6 mg/m^3 (range: 0.21-134 mg/m^3; 193 measurements) and ranged between 6.5-19.6 mg/m^3 (17 measurement) at two Austrian sites. Exposure prior to hiring also coded: none, probable exposure to quartz, certain exposure to quartz, exposure to other carcinogens.</td><td>
<table>
<tr><td>rates)</td><td></td><td></td></tr>
<tr><td>Pneumoconiosis, post-1968 (national rates)</td><td>3</td><td>5.6 (1.1-16.2)</td></tr>
<tr><td>NMRD, pre-1968 (national rates)</td><td>5</td><td>0.7 (0.2-1.6)</td></tr>
<tr><td colspan="3">Austrian cohort</td></tr>
<tr><td>NMRD</td><td>1</td><td>0.3 (0.0-1.5)</td></tr>
<tr><td>Pneumoconiosis</td><td>0</td><td>-</td></tr>
</table>
</td><td></td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr>
<td>Retrospective cohort study

Limitations: limited data on smoking and lack of information on potential confounders (e.g. alcohol consumption).

1974 male talc workers from Val Chisone (Piedmont), Italy</td>
<td>Follow-up of Rubino et al. 1976 and 1979</td>
<td>Employed >1 year in mine or mill during 1946–1995;
mortality follow- up, 1946–1995; loss to follow-up, 9%; analysis based on 1244 miners and 551 millers.

Information relating to cause of death was obtained from death certificates for both exposed and controls.
Detailed job histories from plant records; workers classified on basis of job held (miner versus miller), duration of exposure (years) and time since first exposure (years).

In later years (not further specified), exposure levels to talc dusts were monitored and the values in the mine were between 0.5 and 2.5 mg/m^3, mean 1.1 mg/m^3 for respirable fraction (not specified) and 0.3–2.0 mg/m^3, mean 1.0 mg/m^3 for talc alone.

Adjusted for age, calendar period; study population overlaps with that of Rubino et al. (1976, 1979); national death rates used for pre-1970 period; rates for early 1950s used for 1946–1949; regional rates used for 1970–1995, except for cancers of oral cavity,</td>
<td>A direct trend in risk with exposure was observed only for non-neoplastic respiratory diseases. Mortality excess for non-neoplastic respiratory diseases was mainly due to silicosis.

Excess mortality was noted for non-malignant digestive tract diseases in miners (SMR 1.4; 95% CI 1.0-1.8) and for liver cirrhosis in miners and millers (SMR 1.8; 95% CI 1.3-2.5 and SMR 1.7; 95% CI 1.0-2.7, respectively). The authors stated that the excess mortality for liver cirrhosis could be due to elevated alcohol drinking in this cohort.

<u>Mortality non-neoplastic respiratory diseases:</u>
<table>
<tr><th>Exposure category</th><th>No. of cases/deaths</th><th>SMR (95% CI)</th></tr>
<tr><td>Total cohort</td><td>127</td><td>2.3 (1.9-2.7)</td></tr>
<tr><td>Miners</td><td>105</td><td>3.1 (2.5-3.7)</td></tr>
<tr><td>Millers</td><td>22</td><td>1.0 (0.6-1.6)</td></tr>
<tr><td colspan="3">Years since first exposure (latency) for miners and millers:</td></tr>
<tr><td><20</td><td>11</td><td>1.5 (0.7-2.6)</td></tr>
<tr><td>20–30</td><td>26</td><td>2.3 (1.5-3.4)</td></tr>
<tr><td>>30</td><td>90</td><td>2.4 (1.9-3.0)</td></tr>
</table>
</td>
<td>Coggiola et al. (2003)</td>
</tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td>oesophagus and suicide (regional rates unavailable, national rates used); no information on smoking habits; no variation in lung cancer by duration of exposure.</td><td></td><td></td></tr>
<tr><td>Retrospective cohort study

Limitations: standard respiratory health questionnaire was only used about twice at the French site and less at the Austrian site. In addition, mean duration follow-up of questionnaire was <5 year and therefore the statistical power showing any exposure effect is quite weak.

398 talc workers from Styrian Alps, Austria or Pyrenees, France</td><td>Nonasbestiform talc-chlorite mixture. The quartz content of the French talc is below 1%, while the Austrian talc contains up to 3% quartz.</td><td>At least 5-year continuous employment between 1989-2001

Talc exposure had been systematically measured since 1984 and 1988 at the French and Austrian site using personal dust samplers (gravimetric dust concentration), respectively. Earlier historical semi-quantitative exposure estimates were based on expert quantification (Wild et al. 1995). A quantitative site-specific job exposure matrix for job-time period combinations was set up based on arithmetic mean of exposure measurement by 5-year periods.

Geometric mean exposure in the French mill was 1.95 mg/m^3 (GSD 3.9) in 1986 and 0.8 mg/m^3 (GSD 4.3) in 2003. In the Austrian mill geometric mean exposure was 0.75 mg/m^3 (GSD 3.67) in 1988-1995 and 0.30 mg/m^3 (GSD 3.25) in 1996. The mean duration of follow-up</td><td>No statistically significant changes based on the respiratory questionnaire were found. The prevalence of small radiological opacities and lung function parameters were statistically significantly related to cumulative exposure at inclusion but not to exposure during the study period.

The FEV_1 decreased by 66 ml per 100 years.mg/m^3 (corrected for confounding, e.g. smoking), which is less than that reported for other types of mineral dusts.

<u>Self-declared respiratory symptoms:</u>
<table><tr><td></td><td>OR (95% CI)</td></tr><tr><td colspan="2">Total cumulative exposure per 10 y mg/m^3</td></tr><tr><td>Chronic bronchitis</td><td>1.0 (1.0-1.1)</td></tr><tr><td>Usual cough or phlegm</td><td>1.0 (1.0-1.1)</td></tr><tr><td>Dyspnoea</td><td>1.0 (1.0-1.1)</td></tr><tr><td colspan="2">Cumulative exposure at inclusion per 10 y mg/m^3</td></tr><tr><td>Chronic bronchitis</td><td>1.0 (1.0-1.1)</td></tr><tr><td>Usual cough or phlegm</td><td>1.0 (1.0)</td></tr><tr><td>Dyspnoea</td><td>1.0 (1.0-1.1)</td></tr><tr><td colspan="2">Cumulative exposure since inclusion per 10 y mg/m^3</td></tr><tr><td>Chronic bronchitis</td><td>0.5 (0.2-1.2)</td></tr><tr><td>Usual cough or phlegm</td><td>1.3 (1.0-1.6)</td></tr><tr><td>Dyspnoea</td><td>1.4 (0.9-2.3)</td></tr></table>Adjusted for: pack-years of cigarettes for chronic bronchitis and usual cough and/or phlegm and age for dyspnoea.

<u>Lung function:</u>
<table><tr><td></td><td>Mean regression coefficient</td></tr></table></td><td>Wild et al. (2008)</td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td>was 14.5 years (with at least 2 examinations).

French cohort: lung function (standard forced expiratory volumes) tested during yearly medical check between 1988-2004. Standard chest x-rays were obtained at the time of recruitment and in a series of cross-sectional surveys of the population between 1987-2003. Standard respiratory health questionnaire was administered to the population in 1990/91, 1992/93 and 1999.

Austrian cohort: lung function (standard forced expiratory volumes) and standard radiographs obtained during health check-ups in 1988, 1990, 1994, 1998 and 2002. Standard respiratory health questionnaire was administered to the population in 1988 and repeated for all active employees in 2003.</td><td>
<table>
<tr><td></td><td>(95% CI)</td></tr>
<tr><td colspan="2">Total cumulative exposure per 10 y mg/m^3</td></tr>
<tr><td>FEV$_1$ (ml)</td><td>-6.58 (-13.81 to 0.65)</td></tr>
<tr><td>FVC (ml)</td><td>-7.71 (-15.45 to 0.03)</td></tr>
<tr><td>FEV/FVC</td><td>0.000 (-0.090 to 0.090)</td></tr>
<tr><td colspan="2">Cumulative exposure at inclusion per 10 y mg/m^3</td></tr>
<tr><td>FEV$_1$ (ml)</td><td>-7.26 (-14.65 to 0.13)</td></tr>
<tr><td>FVC (ml)</td><td>-8.47 (-16.38 to -0.57)</td></tr>
<tr><td>FEV/FVC</td><td>-0.004 (-0.096 to 0.087)</td></tr>
<tr><td colspan="2">Cumulative exposure since inclusion per 10 y mg/m^3</td></tr>
<tr><td>FEV$_1$ (ml)</td><td>7.75 (-25.49 to 40.99)</td></tr>
<tr><td>FVC (ml)</td><td>10.24 (-28.22 to 48.70)</td></tr>
<tr><td>FEV/FVC</td><td>0.105 (-0.364 to 0.574)</td></tr>
</table>
Adjusted for: pack-years of cigarettes, apparatus used to determine respiratory function, gender, gender-specific age and height, medical history.

<u>Radiography:</u>

Profusion in radiography presented as: profusion (concentration) of small opacities is classified on a 4-point major category scale (0, 1, 2, or 3), with each major category divided into 3, giving 12 ordered subcategories of increasing profusion; category 0 refers to the absence of small opacity and category 3 represents the most profuse.
<table>
<tr><td></td><td>OR (95% CI)</td></tr>
<tr><td colspan="2">Total cumulative exposure per 10 y mg/m^3</td></tr>
<tr><td>Profusion ≥0/1</td><td>1.0 (1.0-1.1)</td></tr>
<tr><td>Profusion ≥1/0</td><td>1.0 (1.0-1.1)</td></tr>
<tr><td>Pleural abnormalities</td><td>1.0 (1.0-1.1)</td></tr>
</table>
</td><td></td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td colspan="2">Cumulative exposure at inclusion per 10 y mg/m^3</td></tr>
<tr><td>Profusion ≥0/1</td><td>1.1 (1.0-1.1)</td></tr>
<tr><td>Profusion ≥1/0</td><td>1.1 (1.0-1.1)</td></tr>
<tr><td>Pleural abnormalities</td><td>1.0 (1.0-1.1)</td></tr>
<tr><td colspan="2">Cumulative exposure since inclusion per 10 y mg/m^3</td></tr>
<tr><td>Profusion ≥0/1</td><td>0.9 (0.8-1.0)</td></tr>
<tr><td>Profusion ≥1/0</td><td>0.9 (0.7-1.0)</td></tr>
<tr><td>Pleural abnormalities</td><td>1.1 (1.0-1.3)</td></tr>
</table>
Adjusted for: smoking and site (for pleural opacities) or obesity and site (for pleural shadows)</td><td></td></tr>
<tr><td>Retrospective cohort study

Limitations: limited data on smoking and lack of information on potential confounders (e.g. alcohol consumption).

1822 talc workers (1212 miners and 610 millers) from Val Chisone (Piedmont), Italy</td><td>Follow-up of Rubino et al. (1976 and 1979) and Coggiola et al. (2003)</td><td>Employed ≥1 month in mine or mill during 1946–1995; mortality follow- up, 1946–2013; loss to follow-up, 8%; analysis based on 1166 miners and 556 millers. The analyses was restricted to male workers, as only 2.0% (35/1757) of workers were female.

Information relating to cause of death was obtained from death certificates for both exposed and controls.
Average range respirable (not specified) dust level in 2007-2014 for miners and millers: 0.2-1.6 and 0.3-0.9 mg/m^3 (respectively).
Proportion silica over total dust starkly reduced in the mill plant from 1978 onwards in comparison to 1974. Average range silica levels in 2007-2014</td><td>Excess mortality from pneumoconiosis, in particular in miners, was noted. A high number of deaths from silicosis (69 observed vs. 2.6 expected) in the absence of an excess risk for lung cancer was found. This was associated with duration of employment and time since first employment; a linear trend was. The increased mortality for pneumoconiosis among miners is attributable to past exposure to silica.

Excess mortality was also noted for liver cirrhosis in miners and millers (SMR 1.9; 95% CI 1.3-2.5 and SMR 1.9; 95% CI 1.2-2.8, respectively). The authors stated that the excess mortality for liver cirrhosis is likely related to heavy alcohol consumption.

<u>Mortality non-neoplastic respiratory diseases:</u>
<table>
<tr><th>Exposure category</th><th>No. of cases/deaths</th><th>SMR (95% CI)</th></tr>
<tr><td>Total cohort</td><td>147</td><td>2.3 (1.9-2.7)</td></tr>
<tr><td>Miners</td><td>120</td><td>2.9 (2.4-3.5)</td></tr>
<tr><td>Millers</td><td>27</td><td>1.1 (0.7-1.6)</td></tr>
<tr><td colspan="3">Years since first exposure (latency) for miners and millers</td></tr>
<tr><td><20</td><td>9</td><td>1.2 (0.6-2.4)</td></tr>
<tr><td>20–29</td><td>26</td><td>2.4 (1.5-3.5)</td></tr>
</table></td><td>Pira et al. (2017)</td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td>for miners and millers: 0.0005-0.021 and 0.0005-0.014 mg/m^3 (respectively).

Detailed job histories from plant records; workers classified on basis of job held (miner versus miller), duration of exposure (years) and time since first exposure (years).

Adjusted for age, calendar period; study population overlaps with that of Rubino et al. (1976, 1979) and Coggiola et al. (2003); national death rates used for pre-1970 period; national death rates for early 1950s used for 1946–1949; regional rates used for 1970–2013, for cancers of oral cavity, oesophagus and suicide no regional rates were available and national rates were used instead for the whole study period.

Limited data available on smoking. Smokers in survey of 1993 (total of 200 workers): 47% of miners and 44% of millers. Smoking prevalence was similar to that of men in Italy in the mid-1990s. Smokers in survey of 2010 (total of 102 workers): 51% of total.</td><td><table><tr><td>30-39</td><td>34</td><td>2.2 (1.5-3.0)</td></tr><tr><td>≥40</td><td>78</td><td>2.5 (2.0-3.2)</td></tr></table>No linear trend observed (p = 0.068).

<u>Mortality pneumoconiosis:</u><table><tr><td>Exposure category</td><td>No. of cases/deaths</td><td>SMR (95% CI)</td></tr><tr><td>Total cohort</td><td>69</td><td>26.6 (20.7-33.7)</td></tr><tr><td>Miners</td><td>63</td><td>38.7 (29.7-49.5)</td></tr><tr><td>Millers</td><td>6</td><td>6.2 (2.3-13.6)</td></tr><tr><td colspan="3">Years since first exposure (latency) for miners and millers</td></tr><tr><td><20</td><td>3</td><td>9.0 (1.9-26.3)</td></tr><tr><td>20–29</td><td>13</td><td>24.4 (13.0-41.7)</td></tr><tr><td>30-39</td><td>15</td><td>22.3 (12.5-36.8)</td></tr><tr><td>≥40</td><td>38</td><td>36.1 (25.5-49.6)</td></tr></table>Linear trend observed (p = 0.0085).</td><td></td></tr>
<tr><td>Retrospective</td><td>Follow-up of</td><td>Employed >1 year in</td><td>No excess mortality due to NMRD were</td><td>Wergeland et</td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr>
<td>cohort study

Limitations: healthy worker effect and small cohort (low statistical power).

390 male talc workers (94 miners, 296 millers) in northern Norway

National rates were used to calculate expected numbers of cancers and deaths.</td>
<td>Wergeland et al. (1990).</td>
<td>mine (1944-1972) or >2 years in mill (1944-1972);
mortality and cancer incidence follow-up 1953-2011. None were lost to follow-up.

Workers were classified by total duration of employment in jobs with low, medium, high and not exposed. Smoking data: see Wergeland et al. (1990).

Dust measurements in the mill from 1965 varied between 1.3 and 393.9 mppcf (<5 µm); bagging room: 28.2 mppcf; sieving: 150-200 mppcf. Exposure levels 10-20 times the current TLV (20 mppcf[13] or 6 mg/m^3 for talc dust <5 µm with <1% quartz) were described. A few samples contained more quartz (3-6%).

Personal air samples were collected in the early 1980s, as described by Wergeland et al. (1990).

Rate ratios were adjusted for age according to 10-year age bands.

For the analysis of the relationship between dust exposure intensity and NMRDs the cohort was considered at risk from end of</td>
<td>observed in this cohort. A non-significantly increased NMRD risk was observed at high dust exposures. There were no deaths from pneumoconiosis.

<u>NMRDs:</u>
<table>
<tr><th>Exposure category</th><th>No. of cases/deaths</th><th>SMR (95% CI)</th></tr>
<tr><td>Total cohort</td><td>10</td><td>0.4 (0.2-0.7)</td></tr>
<tr><td>Miners</td><td>3</td><td>0.5 (0.1-1.6)</td></tr>
<tr><td>Millers</td><td>7</td><td>0.3 (0.1-0.7)</td></tr>
<tr><td colspan="3">Years employed and years since first employment <20</td></tr>
<tr><td><10</td><td>0</td><td>-</td></tr>
<tr><td>≥10</td><td>0</td><td>-</td></tr>
<tr><td colspan="3">Years employed and years since first employment >20</td></tr>
<tr><td><10</td><td>4</td><td>1.0 (0.3-2.5)</td></tr>
<tr><td>≥10</td><td>6</td><td>0.4 (0.1-0.8)</td></tr>
</table>
<table>
<tr><th>Exposure category</th><th>No. of cases</th><th>RR (95% CI)</th></tr>
<tr><td>0+1</td><td>1</td><td>1</td></tr>
<tr><td>2</td><td>5</td><td>2.3 (0.3-19.7)</td></tr>
<tr><td>3</td><td>4</td><td>3.6 (0.4-32.5)</td></tr>
</table>
p-trend: 0.24

<u>NMRDs (excl. pneumonia and influenza):</u>
<table>
<tr><th>Exposure category</th><th>No. of cases/deaths</th><th>SMR (95% CI)</th></tr>
<tr><td>Total cohort</td><td>7</td><td>0.5 (0.2-1.1)</td></tr>
<tr><td>Miners</td><td>2</td><td>0.8 (0.1-2.7)</td></tr>
<tr><td>Millers</td><td>5</td><td>0.5 (0.2-1.1)</td></tr>
</table>
</td>
<td>al. (2017)</td>
</tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td>employment. Employment time and exposure intensity category were available for 80 miners and 264 millers, who were included in these exposure-based analyses.</td><td></td><td></td></tr>
<tr><td>Retrospective cohort study

Limitations: small cohort, lack of quantitative exposure data, lack of information on other employment and other potential occupational exposures, and the lack of information on other potential confounding or interactive factors, such as tobacco smoking

427 male talc workers (200 miners, 196 millers, 30 worked in mine and mill, and occupation for 1 unknown) from Vermont, USA.</td><td>Follow-up of Selevan et al. (1979)</td><td>Employed >1 year from 1930-1940 and from 1970-1983; mortality follow-up: through 2012; 80% of cohort was deceased; loss to follow-up, 5%; analysis based employees who worked exclusively as miners or millers.

In the publication of this study, US population mortality rates were used as reference.</td><td>This study provides evidence that excess deaths among Vermont talc workers (miners and millers) are largely due to excess mortality from NMRDs.

<u>All NMRDs:</u>
<table>
<tr><td>Exposure category</td><td>No. of cases/deaths</td><td>SMR (95% CI)</td></tr>
<tr><td>Total cohort</td><td>64</td><td>2.7 (2.1-3.5)**</td></tr>
<tr><td>Millers</td><td>24</td><td>2.4 (1.5-3.5)**</td></tr>
<tr><td>Miners</td><td>33</td><td>2.8 (1.9-3.9)**</td></tr>
<tr><td colspan="3">Latency period (years)</td></tr>
<tr><td>0-14</td><td>3</td><td>7.1 (1.5-20.6)*</td></tr>
<tr><td>15-29</td><td>7</td><td>2.7 (1.1-5.6)*</td></tr>
<tr><td>≥30</td><td>54</td><td>2.6 (2.0-3.4)**</td></tr>
</table>
*$p < 0.05$, **$p < 0.01$

All NMRDs included influenza, pneumonia, bronchitis, emphysema and other NMRDs.

<u>Other NMRDs:</u>
<table>
<tr><td>Exposure category</td><td>No. of cases/deaths</td><td>SMR (95% CI)</td></tr>
<tr><td>Total cohort</td><td>35</td><td>4.1 (2.9-5.7)**</td></tr>
<tr><td>Millers</td><td>14</td><td>3.9 (2.1-6.5)**</td></tr>
<tr><td>Miners</td><td>18</td><td>4.1 (2.5-6.7)**</td></tr>
<tr><td colspan="3">Latency period (years)</td></tr>
<tr><td>0-14</td><td>1</td><td>9.1 (0.0-50.5)</td></tr>
</table></td><td>Fordyce et al. (2019)</td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>15-29</td><td>4</td><td>4.7 (1.3-12.0)*</td></tr>
<tr><td>≥30</td><td>30</td><td>4.0 (2.7-5.7)**</td></tr>
</table>
*$p < 0.05$, **$p < 0.01$

Other NMRDs included acute upper/lower respiratory infections, bronchiectasis, lung disease due to external agents (pneumoconiosis, silicosis).
</td><td></td></tr>
<tr><td>Retrospective cohort study

Limitations: limited data on smoking and lack of information on potential confounders (e.g. alcohol consumption).

1822 talc workers from Val Chisone (Piedmont), Italy</td><td>Follow-up of Rubino et al. (1976 and 1979), Coggiola et al. (2003) and Pira et al. (2017).

Talc was directly sampled from the mine before any cleaning and processing in the period 2017-2020. No detectable level of asbestos was measured using electron microscopy.</td><td>Employed ≥1 month in mine or mill during 1946–1995; mortality follow- up, 1946–2020; loss to follow-up, 5%; analysis based on 1184 miners and 565 millers. The analyses was restricted to male workers. Number of subjects included in this analysis higher compared to previous analysis (n = 1722) as missing information on few subjects were retrieved.

Detailed job histories from plant records; workers classified on basis of job held (miner versus miller), duration of exposure (years) and time since first exposure (years).

Adjusted for age, calendar period; study population overlaps with that of Rubino et al. (1976, 1979), Coggiola et al. (2003) and Pira et al. (2017); national death rates used for pre-1970 period; national death rates for early 1950s used for 1946–1949;</td><td>Excess mortality from pneumoconiosis, in particular in miners. A high number of deaths from silicosis (69 observed vs. 2.6 expected) in the absence of an excess risk for lung cancer was found. Deaths from pneumoconiosis observed among miners from this cohort and, to a lesser extent, among millers are therefore attributable to high silica exposure in the past, when rock drilling activities were frequent and technical prevention means had not yet been introduced.

A trend with duration of employment was not observed for non-neoplastic respiratory diseases ($p = 0.23$); pneumoconiosis was positively associated with duration of employment ($p < 0.0001$).

According to the study authors, no deaths from pneumoconiosis were observed among workers first employed after 1969, and no new cases of silicosis were observed during medical surveillance since 1991.

<u>Mortality non-neoplastic respiratory diseases:</u>
<table>
<tr><td>Exposure category</td><td>No. of cases/deaths</td><td>SMR (95% CI)</td></tr>
<tr><td>Total cohort</td><td>152</td><td>2.1 (1.8-2.5)</td></tr>
<tr><td>Miners</td><td>124</td><td>2.7 (2.2-3.2)</td></tr>
<tr><td>Millers</td><td>28</td><td>1.1 (0.7-1.5)</td></tr>
<tr><td colspan="3">Duration of employment (years)</td></tr>
<tr><td><15</td><td>42</td><td>1.8 (1.3-2.4)</td></tr>
<tr><td>15-24</td><td>47</td><td>2.2 (1.6-2.9)</td></tr>
<tr><td>≥25</td><td>63</td><td>2.3 (1.8-2.9)</td></tr>
</table>

<u>Mortality pneumoconiosis:</u></td><td>Ciocan et al. (2022)</td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td>regional rates used for 1970–2020; for the period 2015-2020 regional rates for 2015-2017 were used; for cancers of oral cavity, oesophagus and suicide no regional rates were available and national rates were used instead for the whole study period.

Limited data available on smoking, see Pira et al. (2017).</td><td>
<table>
<tr><td>Exposure category</td><td>No. of cases/deaths</td><td>SMR (95% CI)</td></tr>
<tr><td>Total cohort</td><td>69</td><td>9.6 (7.4-12.1)</td></tr>
<tr><td>Miners</td><td>63</td><td>12.8 (9.8-16.3)</td></tr>
<tr><td>Millers</td><td>6</td><td>2.6 (1.0-5.7)</td></tr>
<tr><td colspan="3">Duration of employment (years)</td></tr>
<tr><td><15</td><td>11</td><td>4.2 (2.1-7.5)</td></tr>
<tr><td>15-24</td><td>16</td><td>8.8 (5.0-14.3)</td></tr>
<tr><td>≥25</td><td>42</td><td>15.1 (10.9-20.4)</td></tr>
</table>
</td><td></td></tr>
<tr><td colspan="5">Occupational exposure – user industries</td></tr>
<tr><td>Case series

Limitations: retrospective study and preliminary conclusions were based on findings in small group of patients.

The study included 14 patients with pathologically proved talc pneumoconiosis consecutively admitted in a hospital in Osaka, Japan between 1973-1998.

Eight patients worked in a talc factory. Four patients were exposed to talc dust used in the manufacture of rubber products. One</td><td>Talc, type not specified.</td><td>The diagnosis was based on clinical history, occupational exposure to talc dust, and histologic findings obtained at transbronchial lung biopsy (n = 8) or autopsy (n = 6). 11 patients were men. The mean age was 59 years (range, 40-71 years) at initial evaluation. Mean duration of exposure to talc dust was 19 years (range, 8-35 years).

Eleven patients ceased work after the initial evaluation. Ten patients were smokers, and four never smoked. Smokers had a smoking history ranging from 18 to 69 pack-years (mean, 36.3 pack-years).</td><td>Predominant radiographic abnormalities were small nodular opacities affects all lung zones.

Serial chest radiography showed that in talc pneumoconiosis, large opacities progressed more often than small rounded opacities.

CT scans depicted pleural plaques and lymph node enlargement with high-attenuation material not identified on chest radiography. The distribution of small rounded opacities was diffuse, whereas large opacities were present in all lung zones. Pleural plaques and subpleural lines and small rounded opacities were evident.

One patient had CT findings similar to asbestosis: diffuse linear interstitial pattern predominantly distributed in the lower zones of the lungs.

This study revealed that increased CT densities of lymph nodes and large opacities were caused by large number of talc particles.</td><td>Akira et al. (2007)</td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td>patient was exposed to talc dust used as an additive in a cosmetics factory, and one to talc dust used as an additive in a confectionery.</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Case-control study

Limitations: respirable mass sampling method was limited, relative short average exposure to talc (only 9 years).

80 talc workers and from two rubber plants and 189 nonexposed rubber workers from three rubber plants.

Plant locations not specified.</td><td>Nonfibrous industrial-grade talc from Vermont, containing <2 fibres/cm^3 and <1% free silica.</td><td>Workers were surveyed between 1972-1974.

Basic statistics, smoking habits and ethnicity of talc workers and nonexposed rubber workers were similar.

Exposure to talc was evaluated by respirable mass sampling. Talc workers were exposed to levels of talc below the current TLV of 20 mppcf[13] for nonfibrous talc for 8.9 years on average.

Average dust concentration for all workers ranged from 0.47-3.55 mg/m^3, with most jobs exposed to <1 mg/m^3.

Workers were asked about medical, occupational and respiratory histories.

Pulmonary function tests were performed.

Chest x-rays were taken in most exposed workers.</td><td>Results showed an increase in respiratory morbidity after a relatively short exposure to talc.

Prevalence of symptoms related to chronic bronchitis and obstructive respiratory disease higher in talc workers vs. nonexposed workers. Increase in chronic obstructive lung disease and wheezing only among smokers, suggesting interaction talc and smoking according to study authors.

Talc workers had lower FVC standardised flow rates and a lower FEV_1/FVC ratio compared to nonexposed workers. A talc work suffers a statistically significant loss ($p = 0.015$) 26 ml loss of FEV_1 for each year of exposure to talc in excess of that related to age and cigarette smoking. In the talc workers without exposure to curing fume (‘pure’ talc group) the effects of talc exposure was even larger; 33 ml loss of FEV_1 ($p = 0.008$) per year of talc exposure.

None of the talc workers had chest x-rays consistent with classical talc pneumoconiosis.

<u>Respiratory symptoms by job type:</u>
<table>
<tr><th></th><th>Nonexposed workers (%)</th><th>Talc workers (%)</th></tr>
<tr><td colspan="3">Chronic bronchitis symptoms</td></tr>
<tr><td>Cough for 3 months</td><td>7.4</td><td>20.0 (p = 0.004)</td></tr>
<tr><td>Phlegm for 3 months</td><td>12.7</td><td>31.3 (p = 0.001)</td></tr>
<tr><td colspan="3">Recurrent infectious symptoms</td></tr>
<tr><td>History of bronchitis</td><td>7.4</td><td>6.8 (n.s.)</td></tr>
<tr><td>History of</td><td>16.1</td><td>16.2 (n.s.)</td></tr>
</table></td><td>Fine et al. (1976)</td></tr>
</table>

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>pneumonia</td><td></td><td></td></tr>
<tr><td>Winter colds (3 week cough and phlegm for 3 years)</td><td>3.2</td><td>7.5 (n.s.)</td></tr>
<tr><td colspan="3">Symptoms related to obstructive respiratory disease</td></tr>
<tr><td>Dyspnoea</td><td>-</td><td>-</td></tr>
<tr><td>Wheezing (most days and nights)</td><td>5.3</td><td>16.3 (p = 0.005)</td></tr>
<tr><td>Chronic obstructive lung disease criteria[25]</td><td>10.1</td><td>17.5 (n.s.)</td></tr>
<tr><td colspan="3">Other respiratory diseases</td></tr>
<tr><td>History of asthma</td><td>2.1</td><td>2.7 (n.s.)</td></tr>
</table>
<u>Lung function:</u>
<table>
<tr><td colspan="3">Standardised flow rates (flow rate/FVC) in white male workers >24 years old</td></tr>
<tr><td></td><td>Nonexposed workers (n = 141)</td><td>Talc workers (n = 69)</td></tr>
<tr><td>At 50% of FVC</td><td>0.85 ± 0.23</td><td>0.81 ± 0.27</td></tr>
<tr><td>At 25% of FVC</td><td>0.32 ± 0.11</td><td>0.30 ± 0.11</td></tr>
<tr><td>At 12.5% of FVC</td><td>0.14 ± 0.08</td><td>0.11 ± 0.06 (p = 0.023)</td></tr>
<tr><td colspan="3">≥10 years duration</td></tr>
<tr><td></td><td>Nonexposed workers (n = 100)</td><td>Talc workers (n = 27)</td></tr>
<tr><td>FEV_1 (ml)</td><td>3578</td><td>3389 (n.s.)</td></tr>
<tr><td>Residual FEV_1 (ml)</td><td>+64</td><td>-211 (p = 0.02)</td></tr>
<tr><td>FEV_1/FVC</td><td>78.2</td><td>75.5 (n.s.)</td></tr>
</table>
</td><td></td></tr>
<tr><td>Retrospective cohort study
Limitations: no</td><td>Talc (type not specified) but crystalline</td><td>Workers employed >1 year in period 1936-1966; mortality</td><td>In the preliminary study an increased frequency of NMRDs and tuberculosis were found in workers.</td><td>Thomas and Stewart (1987);</td></tr>
</table>

[25] Wheezing most days and nights; grade 3 dyspnoea; $FEV_1/FVC \times 100\% \leq 6.0\%$

<table>
<tr><th>Type of study/data</th><th>Test substance (composition and particle size)</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Reference</th></tr>
<tr><td>information available on smoking patterns in the cohort of pottery workers

2055 male workers in 5 ceramic plumbing fixture plants from 1 company in the USA</td><td>silica was the major exposure; also exposure to non-fibrous and fibrous talc</td><td>follow-up 1936-1981; vital status 96%.

Exposure to silica and talc assessed qualitatively by job title–department by industrial hygienist</td><td>In the follow-up study, the risk of NMRD rose with the number of years exposed, was not further enhanced by talc exposure, and appeared to be appreciably lower among those exposed in more recent time periods. Nonmalignant respiratory disease was elevated among persons with exposure to high levels of silica dust regardless of nonfibrous talc exposure.

<u>Mortality NMRDs:</u>
<table>
<tr><td>Exposure category</td><td>No. of cases/deaths</td><td>SMR (95% CI)</td></tr>
<tr><td>All NMRDs</td><td>64</td><td>1.7*</td></tr>
<tr><td>Pneumonia</td><td>16</td><td>1.1</td></tr>
<tr><td>Emphysema</td><td>7</td><td>0.8</td></tr>
<tr><td>Other</td><td>41</td><td>2.9*</td></tr>
<tr><td colspan="3">Duration (years) of exposure to nonfibrous talc in pottery workers 1940-1980</td></tr>
<tr><td><5</td><td>9</td><td>4.1*</td></tr>
<tr><td>5-14</td><td>6</td><td>1.6</td></tr>
<tr><td>>15</td><td>1</td><td>0.8</td></tr>
<tr><td colspan="3">Years since first exposure (latency) to nonfibrous talc in pottery workers 1940-1980</td></tr>
<tr><td><5</td><td>0</td><td>-</td></tr>
<tr><td>5-14</td><td>9</td><td>3.4*</td></tr>
<tr><td>>15</td><td>7</td><td>1.8</td></tr>
</table>
*$p < 0.05$

<u>Mortality NMRD per exposure category:</u>
<table>
<tr><td>Exposure category</td><td>No. of cases/deaths</td><td>SMR (95% CI)</td></tr>
<tr><td>High silica</td><td>54</td><td>2.3*</td></tr>
<tr><td>High silica+non-fibrous talc</td><td>16</td><td>2.2*</td></tr>
<tr><td>High silica+non-fibrous talc+fibrous talc</td><td>2</td><td>0.7</td></tr>
<tr><td>High silica+no talc</td><td>36</td><td>2.6*</td></tr>
</table>
*$p < 0.05$</td><td>Thomas (1982)</td></tr>
</table>

Type of study/data	Test substance (composition and particle size)	Relevant information about the study (as applicable)	Observations	Reference

COPD: chronic obstructive pulmonary disease; ECSC: European Coal and Steel Community; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; GSD: geometric standard deviation; mppcf: million particles per cubic foot; MMEF: maximum midexpiratory flow; NMRD: non-malignant respiratory disease; OR: odds ratio; RR: relative risk; SD: standard deviation; SEM: standard error of the mean; SIR: standardised incidence ratio; SMR: standardised mortality ratio; TLC: total lung capacity; TLV: threshold limit value; VC: vital capacity; WL: working levels

10.12.1 Short summary and overall relevance of the provided information on specific target organ toxicity – repeated exposure

In vitro studies

As discussed in 10.9.1, a general cytotoxic response upon exposure to talc was observed in multiple cell types and talc triggered pro-inflammatory changes and oxidative stress in human mesothelial cells and in murine macrophages (Mandarino et al. 2020; Mierzejewski et al. 2021; Nasreen et al. 1998; Shukla et al. 2009; Toledano-Magana et al. 2021). Development of an inflammatory response can result in fibrotic and proliferative lesions.

Animal studies

Multiple subacute and chronic toxicity animal studies are available for talc (not containing asbestos or asbestiform fibres) via inhalation or oral exposure in rats, mice and hamsters (Table 18). For the inhalation route, five studies similar to guidelines (OECD TG 412 and 453) and according to GLP and two non-guideline studies are available. Two non-guideline studies are available for the oral route. In addition, prenatal developmental toxicity studies investigating oral repeated exposure to talc in rats, mice, rabbits and hamsters are summarised in Annex I. No dermal toxicity animal studies are available for talc.

F344 rats (n = 50/group/sex) were exposed to talc (≥96% pure) via inhalation (aerosols; 0, 6 and 18 mg/m^3; MP10-52 grade; MMAD 6/18 mg/m^3: 2.7/3.2 µm), 6 h per day, 5 days per week (whole body) until mortality in any exposure group reached 80% (113 weeks for males and 122 weeks for females) in a lifetime follow-up study (NTP 1993), see also 10.9.1 and Annex I. In addition, satellite groups (n = 22/group/sex) were included for control and exposure groups for interim evaluation (6, 11, 18 and 24 months) of pathology, lung burden measurements, serial pulmonary function measurements, lung biochemistry, cytology, and phagocytosis measurements. No clinical signs and exposure-related mortality were noted in male and female rats. In female rats, body weight was reduced (-14% compared to control group), no body weight changes were noted in male rats. Lung burdens were in general proportional to exposure concentration at each interim timepoint (6 to 24 months; normalised to exposure concentration) in all exposed female rats and at 6 mg/m^3 in male rats. In males at 18 mg/m^3, lung burdens remained similar at 18- and 24- month interim evaluations. Clearance of talc from the lungs was either not substantially impaired at increased exposure concentrations or impaired similarly at both dose levels. However, it is not likely lung clearance was impaired as viability and phagocytic activity of macrophages recovered from lavage fluid were not statistically significantly affected in any dose group compared to controls.

Impaired lung function was noted in both sexes at the highest dose level from 11 months of exposure onwards and increased in severity with increasing exposure duration. Total lung capacity, vital capacity, forced vital capacity, quasistatic chord (measured as the slope of the curve over the chord between the apnoeic lung volume and the volume at 10 cm H_2O pressure) and dynamic lung compliance were statistically significantly reduced in males and females at ≥6 mg/m^3, although not at every interim time point. At 18 mg/m^3, gas exchange efficiency (carbon monoxide diffusing capacity) was statistically significantly decreased at ≥11 months in both sexes, and nonuniform intrapulmonary gas distribution (slope III of nitrogen

washout) was statistically significantly increased in males (18 month interim evaluation) and in females (≥18 months interim evaluations). Statistically significant increases of total lung collagen, protein, enzyme levels (beta-glucuronidase, alkaline phosphatase, lactase dehydrogenase) in lavage fluid were demonstrated in both sexes at 6 and 18 mg/m^3 after a 24-month exposure.

A spectrum of inflammatory (granulomatous inflammation in all exposed rats), reparative, and proliferative processes (peribronchial and alveolar epithelial hyperplasia, interstitial fibrosis) were noted in the lungs in all exposed male and female rats at interim evaluations, progressing in severity over time, and at final sacrifice (Table 11). Statistically significant increased incidence of alveolar squamous metaplasia and cysts were observed at the highest dose in female rats. At interim timepoints, statistically significantly increased incidences for granulomatous inflammation (≥11 months), alveolar epithelial hyperplasia (11 and 24 months) and interstitial fibrosis (≥11 months) were noted in all exposed animals, but was not statistically significant at every interim timepoint. Absolute and relative lung weights were statistically significantly greater than those of controls in males (6, 11, and 18 months and final sacrifice) and in female rats (≥11 months) at the highest dose. Lung function was thus impaired at 18 mg/m^3 (≥11 months), accompanied with histopathological findings (inflammation and interstitial fibrosis) and changes in lavage fluid. Several methodological limitations regarding this study have been raised which have been discussed in 10.9.1.

In a 4-week study, F344 rats (n = 5-10/group/sex) were exposed to talc (≥96% pure) via inhalation (aerosols; 0, 2, 6 and 18 mg/m^3; MP10-52 grade; MMAD 3.3 µm), 6 h per day, 5 days per week (whole body) and sacrificed within 24 h after the last exposure, to determine dose levels for the NTP lifetime carcinogenicity study (NTP 1993; Pickrell et al. 1989), see Annex I for details. No changes were noted in body weight, organ weights and in mortality. Lung burdens were elevated at ≥6 mg/m^3 in both sexes, and a minimal increase of macrophages (containing talc-particles) were noted in lungs at 18 mg/m^3. No signs of adverse effect were observed and therefore lung tissues of other dose groups were not examined.

Sprague-Dawley rats (n = 6/group/sex) were exposed to talc aerosols (≥96% pure; 0, 5, 50 or 100 mg/m^3; MMAD 3.88 µm), 6 h per day, 5 days per week (whole body) and sacrificed after the last exposure in a 4-week study (Shim et al. 2015), see Annex I for details. No clinical signs, mortality, and changes in body weight or organs weights were noted. Infiltration of macrophages (minimal to moderate) on the alveolar wall and spaces near terminal and respiratory bronchioles were noted and occurred in a dose-dependent manner in both sexes. Furthermore, protein expression of superoxide dismutase 2 (SOD2), an oxidative marker, was elevated in lung tissues. No other exposure-related histopathological changes were noted.

Wistar rats (n = 12/group/sex) were exposed (whole body) to Italian talc (92% pure; 00000 grade) via inhalation (40% as respirable dust [definition of respirable not specified]; 0 or 10.8 mg/m^3; mean particle size 25 µm, upper particle size of 70 µm), 7.5 h per day, 5 days per week for 6 (whole body) or 12 months (Wagner et al. 1977). The mean particle size is large, and the documentation in this study is very limited and therefore not further specified in the Annex of this proposal. Rats were sacrificed ten days after the end of each exposure period or one year after the exposure had discontinued. Per group: 12 rats died, 10 rats were sacrificed, and 2 rats were unaccounted for. Survival of exposed rats (6 and 12 month group combined: 24/48) were similar to the control group (27/48). Minimal fibrosis was noted in exposed rats from 6 months onwards, which progressed to minimal to slight fibrosis 1 year after the exposure had discontinued (incidence not provided).

B6C3F$_1$ mice (n = 50/group/sex) were exposed (whole body) to talc via inhalation (aerosols; 0, 6 and 18 mg/m^3; MP10-52 grade; MMAD 6/18 mg/m^3: 3.3/3.6 µm), 6 h per day, 5 days per week in a 2-year study (103-104 weeks) and then sacrificed (NTP 1993), see Annex I for details. In addition, satellite groups (n = 40/group/sex) were included for control and exposure groups for interim evaluation (6, 12 and 18 months) of pathology, lung burden measurements, lung biochemistry, cytology, and phagocytosis measurements. Aerosol concentrations were not properly controlled throughout the experiment (week 70-82: lower than 6 or 18 mg/m^3 targets). No clinical signs or differences in survival rates were noted in mice (Table 11). The exposure-normalised data show that lung talc burdens of mice exposed to 18 mg/m^3 were disproportionately greater at 12 and 24 months compared to mice exposed to 6 mg/m^3. This was statistically significant at 12 and 24 months in both sexes, but at 6 or 18 months. Clearance of talc from the lungs was either not

substantially impaired by increased exposure concentrations or impaired similarly at both dose levels. These data suggest that clearance of talc from the lung was impaired, or impaired to a greater extent, in mice exposed to 18 mg/m^3 than in mice exposed to 6 mg/m^3. Increased levels of total protein, beta-glucuronidase, lactate dehydrogenase, glutathione reductase, total nucleated cells and polymorphonuclear leukocytes in bronchoalveolar lavage fluid were noted in both sexes at 18 mg/m^3 upon ≥24 month exposure, although some parameters were also increased after 12 months or at 6 mg/m^3. Lung burden was disproportionately greater at 18 mg/m^3 in comparison to 6 mg/m^3 in mice, explained by the statistically significantly reduced phagocytic activity in both sexes at 18 mg/m^3. Absolute and relative lung weights were increased at the highest dose at final sacrifice in both sexes. Chronic active inflammation (minimal to mild) and accumulation of macrophages in the alveoli surrounding terminal bronchioles (hyperplasia, macrophage; minimal to mild) were observed in the lungs at ≥6 mg/m^3 in both sexes at final sacrifice. No other histological findings were noted in the lungs.

In a 4-week study, B6C3F$_1$ mice (n = 5-10/group/sex) were exposed to talc (≥96% pure) via inhalation (aerosols; 0, 2, 6 and 18 mg/m^3; MP10-52 grade; MMAD 2.7 µm), 6 h per day, 5 days per week (whole body) and sacrificed within 24 h after the last exposure, to determine dose levels for the NTP carcinogenicity study (NTP 1993; Pickrell et al. 1989), see Annex I for details. No changes were noted in body weight and organ weights were observed. Two dead male mice were noted (one at 2 mg/m^3 and one at 6 mg/m^3) before the end of the study. Lung burdens increased with increasing talc exposure, but was constant at all exposure levels. The maximum ability of the respiratory tract to clear particles was not exceeded at any dose level. A minimal increase of macrophages (containing talc particles) in lungs (incidence not provided) was noted at 18 mg/m^3. No signs of adverse effects were observed and therefore lung tissues of other dose groups were not examined.

Golden Syrian hamsters (n = 25-50/group/sex) were exposed (whole body, 5 days/week) to talc-based baby powder via inhalation (aerosols, ≥95% w/w platy talc from Vermont) for 30 days (3, 30 or 150 min/day; 37.1 mg/m^3, mean respirable fraction 9.8 mg/m^3, MMAD of 4.9 µm) or 300 days (30 or 150 min/day; 27.4 mg/m^3, mean respirable fraction 8.1 mg/m^3, MMAD of 6.0 µm), see Annex I for details (Wehner et al. 1977c). Corresponding control groups were exposed to air. After completion of the exposures, the hamsters were maintained for observations for the remainder of their natural lifespan. The experiments were concluded by the killing of all surviving animals when the number of deaths in the group with the most survivors exceeded 90%. It should be noted the MMAD of talc particles used here is larger than recommended by the OECD.[14] No statistically significantly differences or dose-response trends in survival rates, clinical toxicity or body weights related to exposure to talc were noted. Mean survival of females was statistically significantly lower compared to males in all groups. An exposure related effect was noted for focal alveolar cell hyperplasia in the groups exposed to talc for 300 days. No clear dose- or exposure duration-related effects on incidences were observed for other histological effects. It should be noted the MMAD of talc particles used here is larger than recommended by the OECD.[14]

Two oral repeated dose studies in rats are available for talc; one 5-day and one 5-month study (Litton Bionetics Inc. 1974; Wagner et al. 1977). In addition, data from oral teratologic studies in rats, hamsters, mice and rabbits are available (see Annex I). No or minimal toxicity and no (gross) histopathological changes upon oral exposure to talc were observed in the oral studies. Studies investigating other routes, including: intrapleural, intratracheal, intrathoracic, subcutaneous or intraperitoneal administration of administration of talc are available (see Annex I for summary table). Hyperplasia and inflammation were noted in the lungs of rats upon intrathoracic instillation after 1 month (Friemann et al. 1999). Inflammatory response in the lungs were also noted in mice and hamsters upon intrathoracic and intratracheal administration, respectively (Beck et al. 1987; Sahu et al. 1978; Sato et al. 2020). No changes in the lungs were reported in other studies.

Animal studies – summary

Upon repeated exposure to talc via inhalation, (chronic) inflammation, fibrosis, oxidative stress, (alveolar) hyperplasia in the lungs and impaired lung function have been described in rats (NTP 1993). This is further supported by evidence of inflammation and fibrosis upon (single) intrathoracic administration of talc in rats,

mice and hamsters (see Annex I). No effects were observed after oral exposure and no data are available for the dermal route.

Human epidemiological studies

No human studies are available for the oral and dermal routes. Development of foreign body granulomas are known upon application of talc to an open skin wound (Lazaro et al. 2006; Tye et al. 1966). Upon inhalation, talc particles can reach the alveoli, depending on the aerodynamic diameter. Therefore the lung is the main target of talc-induced toxicity. Occupational exposure to talc (not containing asbestos or asbestiform fibres) via inhalation has been investigated in multiple epidemiological studies performed in cohorts from multiple regions (Table 19). In most cases, exposure in talc miners and millers has been studied. Studies have been reviewed by the IARC (IARC 1987, 2010), the Cosmetic Ingredient Review Expert Panel (Fiume et al. 2015), and by others (Johnson 2020). These sources were used here as main sources for published epidemiological studies investigating occupational exposure to talc. For a detailed study summary from the IARC, see Annex I. Occupational exposure studies where asbestiform fibres were detected in talc samples are not considered here (Kleinfeld et al. 1967; Kleinfeld et al. 1973; Kleinfeld et al. 1974; Gamble et al. 1979b; Gamble et al. 1979a; Lamm et al. 1988; Brown et al. 1990; Honda et al. 2002; Oestenstad et al. 2002).

Occupational exposure – talc miners and millers –case-control studies

Vallyathan and Craighead (1981) observed x-rays consistent with pneumoconiosis in three male talc workers and fibrosis including accumulated talc in lung tissue of four other workers in the USA in a case-control study. Lifetime exposure ranged from 12 to 5930 mppcf talc (contained traces of chlorite, quartz, mice and feldspar) and a linear correlation was found between talc exposure and accumulation of dusts in the lungs.

Wild et al. (2002) studied cases of NMRD in a nested case-control study including workers from one site in France (1070 male workers) and three sites from Austria (542 male workers) French talc contains various amounts of chlorites, small amounts of dolomite, 0.5-3% quartz and no asbestos. Austrian talc from all sites was a talc-dolomite mixture and contained 1-4% quartz. Workers were categorised in four exposure groups: no exposure (office workers), ambient (<5 mg/m^3; workers with no direct contact to talc dust), medium (5–30 mg/m^3; jobs not entered in other categories) and high (>30 mg/m^3; production jobs before 1985). Increased mortality for NMRDs in the highest exposure groups (OR 2.5) for a cumulative exposure to talc of ≥800 mg/m^3-years. Trends for all cases of NMRDs (OR/100 mg/m^3-years 1.1 (1.0-1.2); statistically significant) and pneumoconiosis (1.2 (1.0-1.2)) with cumulative exposure to talc were noted. Adjustment on potential confounders (smoking and exposure to quartz) did not change the trend for NMRDs to any extent. Most cases (39/40) of NMRDs were from the French cohort. NMRD was thus related to high cumulative exposure to talc dusts.

Occupational exposure – talc miners and millers – cross-sectional studies

In talc workers (average exposure 0.3-2.6 mg/m^3) from three different sites in the USA (Montana, Texas and North Carolina) no significant increases in prevalence of lung symptoms or pneumoconiosis were found compared to blue-collar workers, used as control group (Gamble et al. 1982). Lung function in talc workers was comparable to the control group. However, prevalence of pleural change (7-16%) were increased in talc workers >40 years old compared to the control group. Talc samples contained low levels of silica (<0.8-2.2%) and fibres in the sample from Texas. In addition, talc from Texas contained higher levels (13%) of dolomite as compared to samples from the other states (1-3%).

In contrast, lung function was impaired (decreased forced expiratory volume in 1 second (FEV_1), FEV_1/ forced vital capacity (FVC) and maximum midexpiratory flow (MMEF) compared to predicted) in talc miners and millers from Vermont, USA, exposed to talc (average exposure levels of 0.2-3 mg/m^3 respirable dusts [not further specified]) free from silica and asbestos (Wegman et al. 1982). This was in part due to smoking, but were greater than predicted due to smoking alone. A 43% prevalence of any chest x-ray abnormality was observed, one-third of these abnormalities were parenchymal opacities (small round or irregular) or pleural abnormalities. There was a statistically significant association between x-ray abnormalities and talc years or years of employment.

Leophonte and Didier (1990) conducted a cross-sectional (176 workers) study in French talc workers (sex not specified). French talc contains various amounts of chlorites, small amounts of dolomite, 0.5-3% quartz and no asbestos. Exposure to respirable (not specified) dusts during mining and milling drastically decreased from 1954 to 1988 and ranged from 1 to 30 mg/m^3. Cases of pneumoconiosis (36 had small opacities, 10 had signs of pneumoconiosis with higher profusion or large opacities) were identified in 46/176 workers via chest x-rays. Furthermore, pleural thickenings were observed in three workers. Pulmonary function was tested in 39 workers and was statistically significantly decreased (*p*-value not specified; vital capacity and total lung capacity) compared to reference value. In another study of French talc workers (geometric mean of estimated exposure 1.87 mg/m^3), lung symptoms and lung function were studied (Wild et al. 1995). Prevalence of dyspnoea increased and was associated with increasing cumulative exposure to talc. Lung function decreased (FVC, FEV_1 and MMEF), also when adjusted for smoking. In addition, x-ray abnormalities in the lungs compatible with pneumoconiosis were noted, which were positively linked with smoking.

Occupational exposure – talc miners and millers – cohort studies

The possible association between respiratory diseases and exposure to talc has been studied in numerous epidemiological studies investigating talc miners and millers from several geographical regions. Studies including cohorts from before 1945 are not considered here as conditions in mines greatly improved after this time period.

Rubino et al. studied a cohort of 1678 to 1992 male talc mines and millers in Piedmont, Italy (Rubino et al. 1979; Rubino et al. 1976). IARC (2010) noted that the term silica used by Rubino et al. (1976) was in fact quartz. Talc from this site was reported as pure, containing high levels of respirable quartz and small amounts of tremolite (respirable range 0.5 – 5 µm, as defined by British Medical Research Council criteria). Before milling, rock-type inclusions were removed so that quartz content was <2%. Cumulative exposure levels were estimated from dust content measurements in the period of 1948-1974 for miners and millers were classified in three different levels (miners: 566–1699, 1700–566, 5666–12750 mppcf-years; millers: 25–141, 142–424, 425–906 mppcf-years). Mortality incidences were determined based on the cause of death stated on the death certificate. Mortality due to non-neoplastic respiratory diseases was increased in both groups (SMR miners: 1.4; millers: 1.2; Table 20), predominantly due to silicosis in miners (miners: 62 out of 140 persons; millers: 3 out of 25 persons). This correlated to increasing cumulative exposure. In a follow-up study (1974 male workers), increased mortality due to non-neoplastic respiratory diseases was also observed in both groups and explained by the mixed exposure (including a certain amount of inhalable quartz and/or silica particles) that took place in the past (Coggiola et al. 2003). Dry rock drilling activity was frequent (pre-1950) and technical prevention (forced ventilation system, introduced 1958-1963) means had not yet been introduced. Furthermore, mortality due to non-neoplastic respiratory diseases was higher in miners (high exposure to quartz and/or silica) than in millers (low exposure to quartz and/or silica), predominantly due to past exposure. According to the study authors, the trend of mortality from non-neoplastic respiratory diseases in relation with dose and latency, and the different incidence of silicosis in miners and in millers suggest silica (likely quartz, as noted by IARC (2010)) rather than talc is an inducing factor. Reported mean (range) exposure levels in the mine in later years (method of measurements not further specified) were 1.1 mg/m^3 (0.5-2.5) and 1.0 (0.3-2.0) mg/m^3 for respirable fraction (not specified) and talc alone, respectively. In more recent follow-up studies (1822 workers), mortality incidences, mainly due to pneumoconiosis, and exposure levels reported were similar to earlier studies (Ciocan et al. 2022; Pira et al. 2017). However, pneumoconiosis mortality found by Pira et al. (2017) was much greater in comparison to other studies investigating this same cohort (Table 20).

Table 20: Standardised mortality ratios for non-neoplastic respiratory diseases per cohort and job type. Adopted from Ciocan et al. (2022).

Cause of deaths	Rubino et al. (1976)		Coggiola et al. (2003)		Pira et al. (2017)		Ciocan et al. (2022)	
	Miners	Millers	Miners	Millers	Miners	Millers	Miners	Millers
Non-neoplastic respiratory	1.4[a]	1.2	3.1 (2.5–3.7)	1.0 (0.7–1.6)	2.9 (2.4–3.5)	1.1 (0.7–1.6)	2.7 (2.2–3.2)	1.1

diseases								(0.7–1.5)
Pneumoconiosis	2.0 (1.5–2.6)	1.4 (0.3–4.2)	-	-	38.7 (30.0–50.0)	6.2 (2.3–13.6)	12.7 (9.8–16.3	2.6 (1.0–5.7)

[a] Standardised mortality ratios presented as mean and 95% confidence intervals in parentheses, if available.

Selevan et al. (1979) studied mortality in male talc miners and millers (392 workers) from Vermont, USA. Talc from this site contains chlorite and dolomite but no detectable asbestiform fibres and no significant quantities of free silica (respirable crystalline silica <0.25%, defined as free silica by study authors). No exposure data were available in this cohort, but past exposure levels exceeded levels of 20 mppcf in both miners and millers. An excess mortality from NMRDs was noted for millers (SMR 4.1 (1.6-8.4)) but not for miners. Furthermore, most workers who died from a NMRD had radiographic evidence of pneumoconiosis (rounded opacities). Fordyce et al. (2019) expanded this cohort (427 workers) and showed an excess mortality of NMRDs (SMR 2.7 (2.1-3.5)) and other NMRDs (4.1 (SMR 2.9-5.7)). A linear trend (p = 0.007) for length of employment and mortality from other NMRDs was found. Of all cases of other NMRDs, 26% (9/35) were due to lung disease due to external agents (e.g. pneumoconiosis and silicosis). It was concluded that evidence for excess death due to NMRDs was shown in this cohort.

Leophonte and Didier (1990) conducted a cohort study (97 workers) in French talc workers (sex not specified). French talc contains various amounts of chlorites, small amounts of dolomite, 0.5-3% quartz and no asbestos. Exposure to respirable (not specified) dusts during mining and milling drastically decreased from 1954 to 1988 and ranged from 1 to 30 mg/m^3. An increased mortality (OR 2.4) due to NMRDs was found. This cohort was expanded to include 1070 male talc workers from France and 542 male talc workers from three Austrian sites (Wild 2000; Wild et al. 2002). Austrian talc from all sites was a talc-dolomite mixture and contained 1-4% quartz. Dust levels in the 1990s were <5 mg/m^3. However, exposures before 1985 could be higher; there were cases of exposure to levels higher than 50 mg/m^3 A non-significant excess mortality (SMR 1.1 (0.7-1.6)) due to NMRDs was observed using post-1968 national rates, but not when using pre-1968 national rates. A statistically significant increase in pneumoconiosis mortality was noted (3 cases; SMR 5.6 (1.1-16.3). No increased NMRD mortality or cases of pneumoconiosis were noted in the Austrian cohort. In a subsequent longitudinal study, respiratory health was investigated in 378 French and Austrian talc workers (Wild et al. 2008). Long function, x-rays and respiratory health questionnaire were obtained during compulsory health check-ups between 1987-2004. This study showed no statistically significant changes on lung symptoms based on health questionnaire results. However, the study authors noted that the statistical power was low. Early exposure levels to talc as assessed at inclusion (late 1980s) were associated with decreased lung function (decreased FEV_1 and FVC) and an increased prevalence of small radiological opacities, but no such detrimental effects were observed during the study period. The exposure assessment used to determine cumulative exposure was of a lesser quality at inclusion (expert quantification) versus since inclusion (exposure measurements). The FEV_1 decreased by 66 ml per 100 years.mg/m^3 (corrected for confounding, e.g. smoking) in talc workers.

Wergeland et al. (1990) investigated morbidity and mortality in male 94 miners and 295 millers in Norway. Talc contained magnesite and trace quantities of quartz (<1%) and fibres (tremolite, anthophyllite, talc particles; 0.2-0.9 fibres/ml). Personal air samples collected in the early 1980s showed that total dust levels varied greatly by job category and workplace (mine, 0.9–97 mg/m^3; mill, 1.4–54 mg/m^3). Peak exposures occurred during drilling in the mine (319 mg/m^3) and in the store house in the mill (109 mg/m^3). Deaths due to NMRDs was lower than expected (SMR 0.3 (0.1-0.8) in total cohort), but numbers were too small for further conclusions. In total, three cases of NMRDs were noted; two (one miner, one miller) silicosis and one talcosis (one miller). In a follow-up (1953-2011; 390 male workers), findings were similar; no excess in mortality due to NMRDs was noted (Wergeland et al. 2017). An increased RR of NMRD was associated with high dust exposure, but was not statistically significant. Pneumoconiosis was not classified as underlying cause of death in this cohort. No information about talcosis was found in this update, in contrast to the earlier study conducted. A negative association between NMRD mortality and duration of employment was reported, but this may have been caused by the healthy worker effect. Healthy worker selection effects

in physically demanding work like mining and milling may be particularly pronounced for deaths from respiratory disease. An effect of talc dust on NMRD mortality other than pneumoconiosis was hinted, but was covered by a strong and persistent healthy worker effect.

Occupational exposure – user industries

Several cases of impaired lung function, lung opacities in chest radiographs and pulmonary diseases in patients upon occupational exposure in user industries have been published (Patro et al. 2019; Gysbrechts et al. 1998; Kobayashi et al. 2019; Nath et al. 2014; Tukiainen et al. 1984; Neumann et al. 2011; Van Harlingen et al. 2015).

Akira et al. (2007) published cases of 14 patients with pathologically proved pneumoconiosis (1973-1998) due to exposure to talc (type of talc and exposure unknown) in Japan. Eight patients worked in a talc factory, four patients were exposed to talc in a rubber factory, and one (each) workers was exposed to talc in a cosmetics factory and confectionery factory. Mean duration of exposure was 19 years (range: 8-35 years). Large opacities of talc pneumoconiosis progressed more often compared to small opacities. Pleural plaques and lymph node enlargement, caused by talc particles, were observed in CT scans, but were not observed on chest radiographs. These CT findings were similar to those found for silicosis and asbestosis.

In a case-control study, 80 workers exposed to talc (nonfibrous industrial grade Vermont talc; contains <2 fibres/cm^3 and <1% silica) and 189 nonexposed workers in rubber factories were studied (Fine et al. 1976). Most workers (talc exposed and nonexposed workers) were exposed to <1 mg/m^3 dust (range: 0.47-3.55 mg/m^3), talc exposure was below the threshold limit value (TLV) of 20 mppcf and average duration of talc exposure was 8.9 years. Lung function decreased in workers exposed to talc (statistically significantly decreased FVC standardised flow rate and residual FEV_1) and a 26 ml loss of FEV_1 for each year of talc exposure was observed. This effect was stronger in workers exposed not exposed to curing fume and talc only (33 ml loss of FEV_1 per talc exposed year). In addition, prevalence of lung symptoms (chronic bronchitis, obstructive respiratory disease, cough) were higher in talc exposed workers. In smokers exposed to talc, symptoms related to chronic obstructive respiratory disease and wheezing were more predominant, suggesting an interaction between talc and smoking. Although no cases of talc pneumoconiosis were found in chest radiographs, talc workers had a clear increase in respiratory morbidity.

In workers exposed to silica and talc dusts in ceramic fixture plants increased frequencies of NMRDs and tuberculosis were noted in 3870 male and female workers (Thomas 1982). The preliminary study was expanded in 2055 male workers from 1936-1981 (Thomas and Stewart 1987). Workers were exposed to steatite nonfibrous talc from Montana and to fibrous talc in some glazes prior 1976. All jobs involved high exposure to silica and were further classified to exposure to nonfibrous talc, fibrous talc or no talc. No data on duration or level of exposure were provided. More than 60% of workers were employed for 10 years or more. Mortality of NMRDs increased with years exposed to silica but was not enhanced by exposure to fibrous or nonfibrous talc.

Consumer and medical exposure

Limited information is available regarding respiratory diseases and impairment of lung function in consumers. However, individual cases of impaired lung function and respiratory diseases upon talc exposure by consumers are known (Hollinger 1990; Nam and Gracey 1972; Dekel et al. 2004; Frank and Jorge 2011; Thomeer et al. 1999; Shakoor et al. 2011; Ong and Takano 2012; Tukiainen et al. 1984). In addition, pulmonary talcosis and fibrosis as result of intravenous drug abuse of oral medication have been reported (Padley et al. 1993; Stern et al. 1994; Ward et al. 2000).

Human epidemiological studies – summary

Inhalation is the main route of exposure to talc, as talc particles can reach the alveoli. In multiple epidemiological studies, an increase in mortality due to NMRDs, mainly pneumoconiosis, was noted upon occupational exposure to talc in talc miners and millers from multiple geographical regions (Ciocan et al. 2022; Coggiola et al. 2003; Fordyce et al. 2019; Leophonte and Didier 1990; Pira et al. 2017; Rubino et al. 1976; Selevan et al. 1979; Wild 2000; Wild et al. 2002; Rubino et al. 1979; Wild et al. 1995). In the Italian cohort studies it was suggested pneumoconiosis could be attributed due to (co)exposure (e.g. silica and

quartz) and not talc (Ciocan et al. 2022; Coggiola et al. 2003; Pira et al. 2017; Rubino et al. 1976; Rubino et al. 1979). Mortality due to pneumoconiosis was higher in miners (high exposure to quartz and/or silica) than in millers (low exposure to quartz and/or silica). However, this was not confirmed in other cohort studies (Fordyce et al. 2019; Selevan et al. 1979). In addition, NMRD mortality was not changed upon adjustment of exposure to quartz as confounder in a nested case-control study (Wild et al. 2002). In a Norwegian cohort, mortality of NMRDs was lower than expected in miners and millers, likely due to a strong healthy worker effect (Wergeland et al. 1990; Wergeland et al. 2017). In other studies no association between occupational exposure to talc and NMRDs was observed, likely due to short follow-up time (5 to 10 years) for the development of occupationally related symptoms (Gamble et al. 1982; Wild et al. 2008). Impaired lung function as result of occupational (cumulative) exposure to talc was also demonstrated (Wegman et al. 1982; Wild et al. 1995; Wild et al. 2008; Leophonte and Didier 1990). Prescence of pleural abnormalities on chest radiographs or CT scans due to talc exposure was observed (Vallyathan and Craighead 1981; Wegman et al. 1982; Wild et al. 2008; Leophonte and Didier 1990). These findings are largely supported by occupational exposure studies from user industries (Akira et al. 2007; Fine et al. 1976), although mortality of NMRDs was only found to be enhanced due to silica exposure in one cohort study (Bischoff and Bryson 1976; Thomas 1982; Thomas and Stewart 1987). For consumer use, limited information is available but cases of respiratory diseases and impaired lung function are known (Hollinger 1990; Nam and Gracey 1972; Dekel et al. 2004; Frank and Jorge 2011; Thomeer et al. 1999; Shakoor et al. 2011; Ong and Takano 2012; Tukiainen et al. 1984).

Mode of action

The deposition of talc aerosols in the respiratory tract depends on mass and size; large and dense particles deposit in the upper part of the respiratory tract, while small and less dense particles deposit deeper in the lung (Johnson 2020). Plates will predominantly deposit in the upper airways, but fibres can reach the lower airways and penetrate into the interstitium. Clearance from the upper airways is faster (half-time of ~8 h) as compared in the peripheral lung (half-time of 50 days). The interaction of talc (platy and fibres) with cell surfaces of epithelial cells and macrophages triggers an inflammatory response. This is accompanied by release of cytokines, chemokines, oxidative stress and cytotoxicity. The inflammatory response results in morphologic changes (hyperplasia), fibrotic and proliferative lesions, and subsequently impaired lung function, as noted in animal studies (rat).

10.12.2 Comparison with the CLP criteria

Classification in Category 1 can be based on reliable and good quality evidence from human cases or epidemiological studies. Category 1 is applicable as the evidence available for talc in humans from multiple studies of good quality demonstrates increased mortality, significant lung damage (pneumoconiosis and impaired lung function) and formation of fibrosis and granuloma (pleural abnormalities and) in the lungs. Exposure levels ranging between 0.2 mg/m^3 (0.0002 mg/) and >30 mg/m^3 (0.03 mg/l), mostly as total dust, were reported. Therefore, a classification in Category 1 is warranted based on human data.

Classification in Category 1 can also be based on reliable and good quality evidence from animal studies showing significant and/or severe toxic effects of relevance to human health at generally low exposure concentrations. Severe lung effects were observed in a chronic rat study and included inflammation, granuloma formation, hyperplasia and fibrosis of the lungs. However, no such effects were observed in a chronic study in mice or a 300 day study in guinea pigs. The effects observed in rats resemble the effects observed in humans after exposure to talc (pleural abnormalities, fibrotic lesions and impaired lung function). Therefore, the results from the chronic rat study are considered relevant for humans (Table 21). The conversion of the results from the chronic study towards a 90-day concentration for comparison with the criteria suggests classification in Category 2. However, the incidence of severe effects such as granuloma formation was close to 100% at 6 mg/m^3 (converted value) and no lower concentrations were tested. This value is close to the border between Category 1 and Category 2. Therefore, it is reasonable to assume that concentrations below the border will also induce severe effects like granuloma formation. Therefore, the chronic study in rats also support classification as STOT RE in Category 1.

Classification in Category 2 is based on evidence from animal studies and is not applicable as the evidence available for talc in epidemiological studies is sufficient for classification in Category 1.

Route of exposure

Clear adverse effects fulfilling the criteria for STOT RE were observed in humans and rats after chronic inhalation exposure. No such effects or other adverse effects were observed after oral exposure up to 5 months (Wagner et al. 1977). It is known that talc particles are not absorbed via the oral route (Wehner et al. 1977a; Phillips et al. 1978), and absorption via the dermal route is unlikely. Thus from a toxicokinetic and mechanistic perspective it is unlikely talc induces comparable effects via the oral and dermal route as after inhalation exposure. For the oral route this is supported by the absence of effects outside the lungs after inhalation exposure because a large part of the inhaled particles are moved up the trachea by ciliary movement and then into the gastro-intestinal tract. Overall, it is suggested to limit the STOT RE Category 1 classification to the inhalation route and identify the lung as the target organ.

Particle size

Lung effects after inhalation can only be induced by particles small enough to reach the alveoli. Inclusion of a limitation of the entry in Annex VI of CLP to particles of a certain size has been discussed by RAC and Caracal and applied for several substances with inhalation particle effects such as titanium dioxide (entry 022-006-00-2; in powder form containing 1% or more of particles with aerodynamic diameter ≤ 10 μm). For talc there is no evidence for a clear-cut border, based on animal or human data, and therefore no inclusion of particle size in the entry in Annex VI is suggested.

Asbestiform talc

The presence of low percentages asbestiform talc is not expected to significantly change the potency of talc to induce lung effects (other than carcinogenicity) after inhalation. Therefore, it is also not expected to significantly affect the classification as STOT RE Category 1.

Specific concentration limits

No specific concentration limits are proposed as the available rat data suggest a potency in between Category 1 and 2 and the human data do not provide sufficient information on the potency.

Table 21: Extrapolation of equivalent effective dose for toxicity studies of greater or lesser duration than 90 days

Study reference	Effective dose	Length of exposure	Extrapolated effective dose when extrapolated to 90-day exposure	Classification supported by the study
NTP (1993)	Rat: 18 mg/m^3/6 h/d (5 days/week) = 0.018 mg/l/6 h/d Adverse effects: impaired lung function, inflammation and fibrosis in lung	11 months (335 days)	0.048 mg/l/6 h/d[a]	Category 2 (inhalation dust/mist/fume, 0.02 < C ≤ 0.2 mg/l/6 h/d)
	Rat: 6 mg/m^3/6 h/d (5 days/week) = 0.006 mg/l/6 h/d Adverse effects: histopathological changes in the lungs	m: 113 weeks, f: 122 weeks	0.037 mg/l/6 h/d[b]	Category 2 (inhalation dust/mist/fume, 0.02 < C ≤ 0.2 mg/l/6 h/d)

Study reference	Effective dose	Length of exposure	Extrapolated effective dose when extrapolated to 90-day exposure	Classification supported by the study
	(inflammation, granuloma formation, hyperplasia, fibrosis)			

[a] Conversion factor from 11 months (335 days) to 90 days of 3.7 and conversion factor from 5 days/week to 7 days/week (5/7): 0.018 mg/l/6 h/d * 3.7 * (5/7) = 0.048 mg/l/6 h/d

[b] Conversion factor from 113 weeks (most sensitive) to 90 days (13 weeks) of 8.7 and conversion factor from 5 days/week to 7 days/week (5/7): 0.006 mg/l/6 h/d * 8.7 * (5/7) = 0.037 mg/l/6 h/d

10.12.3 Conclusion on classification and labelling for STOT RE

Classification of talc as **STOT RE 1, H372 (lung)** is proposed, based on adverse effects in the lungs and on lung function as demonstrated in epidemiological studies and supported by animal data.

10.13 Aspiration hazard

Not evaluated in this dossier.

11 EVALUATION OF ENVIRONMENTAL HAZARDS

Not evaluated in this dossier.

12 EVALUATION OF ADDITIONAL HAZARDS

Not evaluated in this dossier.

13 ADDITIONAL LABELLING

Not relevant.

14 REFERENCES

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15 ANNEXES

See Annex I and Confidential Annex