Annex I to the CLH report

Proposal for Harmonised Classification and Labelling

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

International Chemical Identification:

Talc ($Mg_3H_2(SiO_3)_4$)

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

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

Index Number: **-**

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1 HEALTH HAZARDS

1.1 Carcinogenicity

1.1.1 Animal data

1.1.1.1 NTP, 1993 - rat

Study reference:

Toxicology and Carcinogenesis Studies of Talc (CASRN 14807-96-6) in F344/N Rats and B6C3F1 Mice (Inhalation Studies). National Toxicology Program (NTP)Technical Report (TR) 421[1]

RL 1

Detailed study summary and results:

Test type

NTP toxicology and carcinogenesis study, similar to OECD test guideline study 453 . The study is GLP compliant.

Test substance

- Talc (MP 10-52 grade) from two different lots: W101882 (used beginning of the 2-year studies through January 1986) and B541 (used from 27 January 1986 to the end of the studies on 31 October 1986). Both lots were free of asbestos and virtually free of silica (1 particle of silica in 1,466 particles examined). More than 75% of the particles were in to 1.0 to 3.0 µm range. More than 90% of the talc particles had aspect ratios between 1 and 1.4, and less than 1% had ratios greater than 3:1.
- Degree of purity: ≥96%
- Impurities (Karl Fischer water analysis and spark source mass spectrometry)
    - Elemental analyses values and moister content of both lots were similar.
    - W101882: 1.0% iron, 0.7% aluminium, 0.2% absorbed water, 0.5% fluorine, 0.1% phosphorus, 0.05% calcium, other elemental impurities <0.01%
    - B5415: 1.2% absorbed water, 1% iron, 0.5% aluminium, 0.35% fluorine, 0.1% calcium, 0.04% phosphorus, 0.03% sodium, other impurities <0.03%

Test animals

- Rat F344/N
- 50 males and females per group
- Age and weight at the study initiation: 6-7 weeks; male: 118-121 g, female: 97-101 g

Administration/exposure

[1] https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr421.pdf

- Inhalation (talc aerosol)
- Life-time study: rats were exposed to talc aerosols until mortality in any exposure group reached 80% (113 weeks for males and 122 weeks for females). Study conducted July 1984 until October 1986.
- 0, 6 or 18 mg/m^3 (overall mean concentrations were 6.1 and 18.6 mg/m^3) equivalent to 0, 2.8 or 8.4 mg/kg/d in males and 0, 3.2 or 9.6 mg/kg/d in females. These exposures were selected based on 4-week inhalation studies of the terminal lung talc burden in F344/N rats (see 1.2.1.1); concentrations greater than 18 mg/m^3 were expected to overwhelm lung clearance mechanisms to impair lung function.
- Whole body exposure, 6 hours per day, 5 days per week
- Satellite group: additional study groups of 22 male and female rats, similarly exposed to 0, 6 or 18 mg/m^3, were designated for interim pathology evaluations; lung burden measurements; serial pulmonary function measurements (rats only); and lung biochemistry, cytology, and phagocytosis measurements. Rats were evaluated at 6, 11, 18 and 24 months.
- Aerosol size distribution was determined once a month for each chamber. Particle size
    - Mass median aerodynamic diameter at 6 and 18 mg/m^3: 2.7 ± 0.4 and 3.2 ± 0.4 µm (respectively)
    - Geometric standard deviation at 6 and 18 mg/m^3: 1.9 ± 0.4 and 1.9 ± 0.2 µm (respectively) (respectively)
- Talc was mixed with stainless steel powder at approximately 1 to 2.5 g per 500 g bed material. Talc aerosols were generated in a single fluidized-bed generator by injecting compressed air into the bed. The aerosolized talc particles were then mixed with diluting air before being delivered to the exposure chambers. A second fluidized-bed generator for the control chamber contained only the stainless steel bed material. At week 11, the chamber concentrations for the 18 mg/m^3 rat group varied from 30 to 40 mg/m^3 for a period of 7 weeks due to difficulties with the aerosol monitoring system (September through November, 1984). In addition, at approximately week 70 there were problems experienced in maintaining control of chamber concentrations during a 12-week period (November 5, 1985 through January 27, 1986). Concentrations of aerosolized talc were significantly below target. The talc-laden stainless steel bed material fed into the generator less freely than in the beginning of the study. Higher loadings were used in an effort to maintain target concentrations. There were no observable chemical changes in either the talc or the stainless steel bed material and no malfunctions in the generation system which could be pinpointed as the underlying cause of the poor flow characteristics of the bed material. On January 27, 1986, the generator was restarted with a new batch of talc. After a stabilization period of 3 weeks, the flow properties of the bed material showed significant improvement. It was also observed during February 1986, that when the ratio of talc to bed material was increased above 1.6 g talc per 500 g bed materials, the bed began to show

the poor flow properties characteristics of the previous batch of talc. When the bed loading was reduced below this amount (set as maximum loading limit), the flow properties stabilized. By March 1986, the generator had stabilized and chamber target concentrations were achieved. The exact cause of these generations problems was never resolved.

Results and discussion

- mortality and time to death
    - Survival and number of deaths of exposed male and female rats were similar to that of the controls (Table 1).

Table 1: Survival of rats in the lifetime inhalation study of talc

	0 mg/m^3	6 mg/m^3	18 mg/m^3
Male			
Lifetime Study Groups			
Animals initially in study	49	50	50
Moribund	23	19	20
Natural deaths	17	17	14
Animals surviving to study termination[a]	9	14	16
Percent probability of survival at end of study[b]	18	28	32
Mean survival (days)[c]	696	707	711
Survival analysis[d]	P=0.217N	P=0.422N	P=0.192N
Special Study Groups[e]			
Animals initially in study	22	22	22
Moribund	9	5	6
Natural deaths	2	2	6
Scheduled evaluation	11	15	10
Females			
Lifetime Study Groups			
Animals initially in study	50	50	50
Missing[f]	0	1	0
Moribund	28	17	27
Natural deaths	11	19	14
Animals surviving to study termination	11	13	9
Percent probability of survival at end of study	22	28	18
Mean survival (days)	743	753	758
Survival analysis	P=0.846	P=0.805N	P=0.977
Special Study Groups			
Animals initially in study	22	22	22
Moribund	5	3	8
Natural deaths	2	1	2
Scheduled evaluation	15	18	12

[a] Includes animals that died during the last week of the study
[b] Kaplan-Meier determinations
[c] Mean of all deaths (uncensored, censored, and terminal sacrifice).
[d] The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the exposed columns. A negative trend or lower mortality in a group is indicated by N.
[e] Not included in survival analyses
[f] Censored from survival analyses

- clinical signs
    - No clinical findings were attributed to talc exposure.
- body weight
    - Mean body weights of rats exposed to 6 mg/m^3 were similar to control (male/female: 9/-3%)). At 18 mg/m^3, body weights were lower than those of controls (final mean body weight male/female: -4/-14%), particularly after 65 weeks in females.
- food/water consumption
    - Not specified

- ophthalmoscopic examination
    - Not specified
- clinical chemistry
    - For lung, see below
- haematology
    - Not specified
- urinalysis
    - Not specified
- lung burden, function, lavage and biochemistry
    - Lung burden in the 6 mg/m^3 exposure group were similar and increased progressively from 6 to 24 months in both sexes (Table 2). At 18 mg/m^3, lung burden increased progressively from 6 to 24 months in females, but in males lung burden remained about the same after 18 months. Lung burdens were generally proportional to exposure concentration at each interim evaluation (Table 3). The exposure-normalized lung burdens of rats exposed to 6 or 18 mg/m^3 were generally similar at each of the interim evaluations except for statistically significantly increases at 18 mg/m^3 (compared to 6 mg/m^3) for males at 6 and 12 months and females at 6 months. This 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.

Table 2: Lung talc burden (normalized to control lung weight) of rats[a]

	6 months	12 months	18 months	24 months
Male				
0 mg/m^3	–[b]	–	–	–
6 mg/m^3	2.63 ± 0.24	4.38 ± 0.59°	7.31 ± 0.71°°	10.45 ± 1.26°°
18 mg/m^3	10.83 ± 0.23	20.96 ± 2.04°	27.57 ± 0.91°	24.15 ± 3.41°
Female				
0 mg/m^3	–	–	–	–
6 mg/m^3	2.43 ± 0.19	4.71 ± 0.26°	7.66 ± 0.34°°	9.10 ± 0.88°°
18 mg/m^3	8.34 ± 0.12	14.16 ± 3.36	24.33 ± 0.63°	29.40 ± 2.40°°

° Significantly different (P≤0.05) from the 6 month group by Dunn's or Shirley's test
°° P≤0.01
[a] Mean ± standard error; units are presented as mg talc/g control lung.
[b] No measurements taken

Table 3: Lung talc burden (normalized to exposure concentration) of rats[a]

Lung Talc Burden (Normalized to Exposure Concentration) of Rats[a]

	Male		Female	
	6 mg/m^3	18 mg/m^3	6 mg/m^3	18 mg/m^3
6-Month Interim	0.439 ± 0.040	0.602 ± 0.013*	0.406 ± 0.032	0.464 ± 0.007*
12-Month Interim	0.731 ± 0.098	1.165 ± 0.113*	0.785 ± 0.043	0.787 ± 0.187
18-Month Interim	1.22 ± 0.12	1.53 ± 0.05	1.28 ± 0.06	1.35 ± 0.04
24-Month Interim	1.74 ± 0.21	1.34 ± 0.19	1.52 ± 0.15	1.63 ± 0.13

* Significantly different ($P \leq 0.05$) from the 6 mg/m^3 group by Dunn's or Shirley's test
[a] Mean ± standard error; units are presented as mg talc/g control lung per mg talc/m^3.

- A concentration-related impairment in respiratory function, which increased in severity with increasing exposure duration and mostly observed from 11-month interim evaluation onwards at 18 mg/m^3 in male and female rats (Figure 1). Impaired respiratory function was characterized by: statistically significantly reduced lung volume (total lung capacity [Table 4], vital capacity [Table 5], and forced vital capacity [Table 6] at ≥ 6 mg/m^3), quasistatic chord (measured as the slope of the curve over the chord between the apneic lung volume and the volume at 10 cm H_2O pressure) and dynamic lung compliance at ≥ 6 mg/m^3 (Table 7 and Table 8), gas exchange efficiency (carbon monoxide diffusing capacity; Table 9) at 18 mg/m^3, and statistically significantly increased nonuniform intrapulmonary gas distribution (slope III of nitrogen washout; Table 10) at 18 mg/m^3.

Figure 1: Effects of 18 mg talc/m^3 exposure on respiratory function of male and female rats surviving to 104 weeks

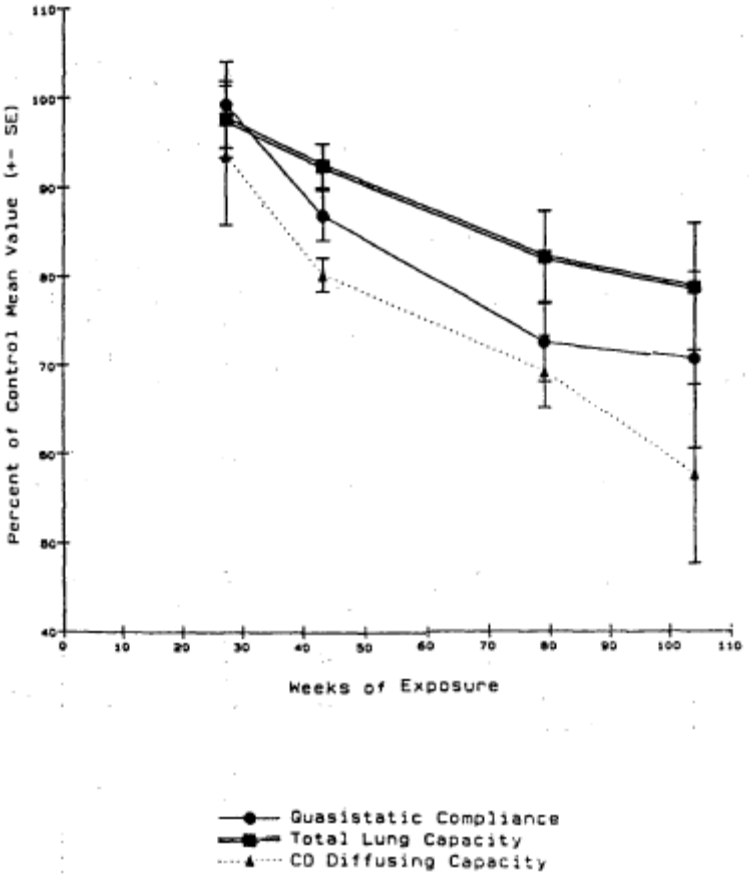


Table 4: Total lung capacity of rats[a]

	0 mg/m^3	6 mg/m^3	18 mg/m^3
Male			
6-Month Interim	19.86 ± 0.54	19.48 ± 0.46	19.25 ± 0.39
11-Month Interim	20.06 ± 0.32	18.44 ± 0.39**	17.67 ± 0.45**
18-Month Interim	20.30 ± 0.45	18.87 ± 0.41*	16.34 ± 0.52**
24-Month Interim	20.50 ± 0.83	20.20 ± 0.28	16.47 ± 1.53
Female			
6-Month Interim	14.20 ± 0.25	14.56 ± 0.27	13.80 ± 0.27
11-Month Interim	13.29 ± 0.21	12.91 ± 0.17	12.06 ± 0.26**
18-Month Interim	13.94 ± 0.26	12.68 ± 0.28**	11.43 ± 0.31**
24-Month Interim	14.85 ± 0.31	13.73 ± 0.34*	11.50 ± 1.07**

* Significantly different (P≤0.05) from the control by Dunn's or Shirley's test
** P=≤.01
[a] Mean ± standard error; units are presented as mL.

Table 5: Vital capacity of rats[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
6-Month Interim	16.96 ± 0.49	16.49 ± 0.44	16.61 ± 0.32
11-Month Interim	18.01 ± 0.27	16.82 ± 0.37°	15.97 ± 0.42°°
18-Month Interim	18.35 ± 0.45	17.15 ± 0.38	14.36 ± 0.51°°
24-Month Interim	17.27 ± 0.48	17.35 ± 0.34	14.27 ± 1.26
Female			
6-Month Interim	12.02 ± 0.22	12.17 ± 0.20	11.33 ± 0.28
11-Month Interim	12.06 ± 0.20	11.68 ± 0.18	10.40 ± 0.25°°
18-Month Interim	12.66 ± 0.21	11.14 ± 0.31°°	9.61 ± 0.26°°
24-Month Interim	13.15 ± 0.27	11.99 ± 0.32°	9.77 ± 0.90°°

° Significantly different (P≤0.05) from the control by Dunn's or Shirley's test
°° P≤0.01
[a] Mean ± standard error; units are presented as mL.

Table 6: Forced vital capacity of rats[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
6-Month Interim	17.88 ± 0.40	17.15 ± 0.45	17.38 ± 0.41
11-Month Interim	19.03 ± 0.38	18.07 ± 0.43*	17.25 ± 0.45*
18-Month Interim	19.45 ± 0.45	17.92 ± 0.34*	15.28 ± 0.56**
24-Month Interim	17.27 ± 0.61	17.53 ± 0.46	14.90 ± 1.08
Female			
6-Month Interim	12.53 ± 0.33	12.38 ± 0.26	11.27 ± 0.33*
11-Month Interim	12.86 ± 0.25	12.44 ± 0.26	11.22 ± 0.25**
18-Month Interim	13.39 ± 0.24	11.91 ± 0.28**	10.24 ± 0.27**
24-Month Interim	13.08 ± 0.30	12.33 ± 0.33	10.03 ± 0.93**

* Significantly different (P≤0.05) from the control by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error; units are presented as mL.

Table 7: Quasistatic chord compliance of rats[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
6-Month Interim	1.18 ± 0.05	1.16 ± 0.04	1.17 ± 0.03
11-Month Interim	1.34 ± 0.02	1.20 ± 0.04°	1.15 ± 0.04°°
18-Month Interim	1.343 ± 0.037	1.205 ± 0.040°	0.982 ± 0.037°°
24-Month Interim	1.167 ± 0.104	1.220 ± 0.035	0.890 ± 0.124
Female			
6-Month Interim	0.824 ± 0.030	0.895 ± 0.091	0.802 ± 0.024
11-Month Interim	0.841 ± 0.020	0.809 ± 0.016	0.684 ± 0.025°°
18-Month Interim	0.879 ± 0.019	0.749 ± 0.027°°	0.607 ± 0.030°°
24-Month Interim	0.883 ± 0.035	0.764 ± 0.024°	0.573 ± 0.084°°

° Significantly different (P≤0.05) from the control by Dunn's or Shirley's test
°° P≤0.01
[a] Mean ± standard error; units are presented as mL/cm H_2O.

Table 8: Dynamic compliance of rats[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
6-Month Interim	0.546 ± 0.053	0.575 ± 0.043	0.536 ± 0.058
11-Month Interim	0.748 ± 0.041	0.647 ± 0.048	0.687 ± 0.046
18-Month Interim	0.990 ± 0.080	0.741 ± 0.043°	0.685 ± 0.050°°
24-Month Interim	0.930 ± 0.173	0.987 ± 0.130	1.173 ± 0.186
Female			
6-Month Interim	0.399 ± 0.029	0.445 ± 0.032	0.380 ± 0.034
11-Month Interim	0.492 ± 0.024	0.426 ± 0.027°	0.393 ± 0.020°°
18-Month Interim	0.618 ± 0.053	0.527 ± 0.027	0.372 ± 0.025°°
24-Month Interim	0.650 ± 0.065	0.618 ± 0.045	0.377 ± 0.077°

° Significantly different (P≤0.05) from the control by Dunn's or Shirley's test
°° P≤0.01
[a] Mean ± standard error; units are presented as mL/cm H_2O.

Table 9: Carbon monoxide diffusing capacity of rats[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
6-Month Interim	0.364 ± 0.014	0.347 ± 0.008	0.336 ± 0.010
11-Month Interim	0.400 ± 0.010	0.373 ± 0.010	0.331 ± 0.020°°
18-Month Interim	0.338 ± 0.022	0.301 ± 0.015	0.235 ± 0.009°°
24-Month Interim	0.303 ± 0.027	0.288 ± 0.011	0.177 ± 0.035°
Female			
6-Month Interim	0.238 ± 0.012	0.241 ± 0.008	0.213 ± 0.010
11-Month Interim	0.233 ± 0.008	0.231 ± 0.005	0.190 ± 0.003°°
18-Month Interim	0.233 ± 0.010	0.207 ± 0.009	0.137 ± 0.011°°
24-Month Interim	0.198 ± 0.007	0.183 ± 0.006	0.113 ± 0.017°°

° Significantly different (P≤0.05) from the control by Dunn's or Shirley's test
°° P≤0.01
[a] Mean ± standard error; units are presented as mL/minute per mm Hg.

Table 10: Slope III of nitrogen washout of rats[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
6-Month Interim	0.400 ± 0.023	0.431 ± 0.037	0.481 ± 0.049
11-Month Interim	0.449 ± 0.019	0.446 ± 0.037	0.437 ± 0.040
18-Month Interim	0.393 ± 0.037	0.361 ± 0.035	0.555 ± 0.041°
24-Month Interim	0.627 ± 0.077	0.438 ± 0.045	0.597 ± 0.083
Female			
6-Month Interim	0.587 ± 0.059	0.528 ± 0.049	0.596 ± 0.042
11-Month Interim	0.704 ± 0.027	0.735 ± 0.029	0.813 ± 0.076
18-Month Interim	0.601 ± 0.053	0.699 ± 0.074	1.008 ± 0.087°°
24-Month Interim	0.535 ± 0.040	0.580 ± 0.071	1.520 ± 0.409°

° Significantly different (P≤0.05) from the control by Dunn's or Shirley's test
°° P≤0.01
[a] Mean ± standard error; units are presented as percent N_2/mL.

- Increases in cytoplasmic (lactate dehydrogenase and glutathione reductase) and lysosomal (B-glucuronidase) enzymes were observed in bronchoalveolar lavage fluid, indicative of cellular injury at the 24-month interim evaluation (Table 11 ; enzyme levels not assessed for other time points). Viability and phagocytic activity of macrophages recovered from lavage fluid were not statistically significantly affected at the 24-month interim evaluation (Table 12).

Table 11: Bronchoalveolar lavage fluid enzymes of rats at the 24-month interim evaluation[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
ß-Glucuronidase	1.09 ± 0.40	18.86 ± 3.20*	89.24 ± 14.24**
Lactate Dehydrogenase	1,634 ± 545	3,193 ± 606	8,262 ± 380*
Alkaline Phosphatase	364.7 ± 147	572.8 ± 86.8	1,604.7 ± 143*
Glutathione Reductase	103.03 ± 16.43	99.35 ± 19.79	110.99 ± 51.27
Total Protein[b]	1.78 ± 0.40	3.12 ± 0.64	5.79 ± 0.55*
Female			
ß-Glucuronidase	3.33 ± 0.97	41.05 ± 4.39**	154.16 ± 17.21**
Lactate Dehydrogenase	1,655 ± 266	3,906 ± 444*	14,436 ± 1,218**
Alkaline Phosphatase	427.8 ± 30.9	853.6 ± 79.7**	2,504.7 ± 221**
Glutathione Reductase	100.6 ± 1.7	135.2 ± 22.4	460.0 ± 44.8*
Total Protein	1.20 ± 0.22	4.30 ± 0.36**	12.96 ± 0.28**

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error; units presented as mIU/g control lung.
[b] Mean ± standard error; units presented as mg/g control lung.

Table 12: Viability and phagocytic activity of macrophages in bronchoalveolar fluid of rats at the 24-month interim evaluation

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
Viability[a]	63.67 ± 5.91	66.73 ± 1.59	57.70 ± 5.00
Phagocytic Activity[b]	83.13 ± 4.54	63.12 ± 8.14	65.30[c]
Female			
Viability	82.65 ± 9.65	74.64 ± 3.24	61.00 ± 4.42
Phagocytic Activity	75.60 ± 5.14	66.51 ± 8.09	70.15 ± 2.85

[a] Mean ± standard error; units are presented as percent viable cells.
[b] Mean ± standard error; units are presented as percent cells phagocytizing sheep erythrocytes.
[c] n=1; no standard error calculated

- Increases in total protein (Table 11) and neutrophils (Table 13) in lavage fluid were observed at the 24-month interim evaluation (levels not assessed for other time points). These findings were consistent with the inflammation observed histologically in the lungs.

Table 13: Bronchoalveolar lavage fluid cell populations of rats at the 24-month interim evaluation[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
Polymorphonuclear Cells	0.333 ± 0.167	24.417 ± 2.557*	32.500 ± 3.000*
Lymphocytes	0.000 ± 0.000	0.500 ± 0.258	0.500 ± 0.500
Macrophages	93.67 ± 3.72	70.25 ± 2.53*	62.75 ± 1.75*
Epithelial Cells	6.00 ± 3.61	4.83 ± 1.41	4.25 ± 1.75
Female			
Polymophonuclear Cells	0.625 ± 0.315	25.778 ± 2.673**	37.000 ± 1.528**
Lymphocytes	0.000 ± 0.000	0.722 ± 0.188*	1.333 ± 0.667*
Macrophages	91.38 ± 1.75	71.22 ± 2.95**	57.33 ± 4.67**
Epithelial Cells	8.00 ± 2.01	2.28 ± 0.50*	4.33 ± 2.60

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error; units presented as percent of total cells.

- Total lung collagen was statistically significantly increased in exposed male and female rats compared to control at the 24-month interim evaluation (Table 14; levels not assessed for other time points). In females, collagenous peptides and collagen production (% newly synthesized protein) was statistically significantly increased upon exposure compared to control (Table 14). Non-collagenous protein synthesis was statistically significantly increased in treated males (at 6 and 18 mg/m^3) and females (at 18 mg/m^3) compared to controls (Table 14).

Table 14: Lung collagen metabolism and protein synthesis in rats at the 24-month interim evaluation

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
Lavage Fluid Collagenous Peptides[a]	39.79 ± 5.07	46.99 ± 6.51	79.21 ± 13.73
Total Lung Collagen[b]	13.87 ± 0.60	15.98 ± 0.39*	18.88 ± 3.35*
Collagen Production[c]	1.58 ± 0.17	1.60 ± 0.17	1.63 ± 0.22
Collagen Degradation[d]	31.67 ± 1.72	27.74 ± 1.42	9.18 ± 2.38*
Non-Collagenous Protein Synthesis[e]	142.1 ± 14.5	199.8 ± 22.1*	312.2 ± 10.6**
Female			
Lavage Fluid Collagenous Peptides	78.27 ± 11.64	115.36 ± 8.61*	174.71 ± 13.56**
Total Lung Collagen	14.32 ± 0.66	19.95 ± 1.58*	36.47 ± 3.39**
Collagen Production	0.982 ± 0.185	1.804 ± 0.144*	2.264 ± 0.347**
Collagen Degradation	14.41 ± 2.44	21.59 ± 4.99	9.38 ± 1.63
Non-Collagenous Protein Synthesis	173.9 ± 34.5	325.8 ± 90.9	554.3 ± 107*

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error; units are presented as μg/g control lung.
[b] Mean ± standard error; units are presented as mg/g control lung.
[c] Mean ± standard error; units are presented as percent new protein.
[d] Mean ± standard error; units are presented as percent new collagen.
[e] Mean ± standard error; units are presented as disintegrations per minute x 10^{-3}/g control lung.

- In lavage fluid, acid proteinase (primarily cathepsin D) was statistically significantly increased (compared to control) at ≥6 mg/m^3 in females and at 18 mg/m^3 in males (Table 15). In homogenate supernatant fluid, acid (primarily cathepsin D) and neutral proteinase activity was increased (compared to control) at 6 and 18 mg/m^3 in both sexes (Table 15).

Table 15: Proteinase activity in lavage fluid and lung homogenate supernatant fluid of rats at the 24-month interim evaluation[a]

	0 mg/m^3	6 mg/m^3	18 mg/m^3
Male			
Lavage Fluid			
Acid Proteinase	0.994 ± 0.329	1.866 ± 0.174	4.307 ± 0.218*
Cathepsin D	0.147 ± 0.147	0.599 ± 0.150	2.420 ± 0.147**
Cathepsin B	0.924 ± 0.415	1.267 ± 0.094	1.887 ± 0.365
Homogenate Supernatant Fluid			
Acid Proteinase	10.92 ± 0.64	17.51 ± 0.90*	25.13 ± 1.50**
Cathepsin D	8.53 ± 0.91	14.04 ± 0.62*	21.03 ± 1.56**
Cathepsin B	2.39 ± 0.41	3.48 ± 0.37	4.10 ± 0.06*
Neutral Proteinase	0.715 ± 0.168	2.417 ± 0.304*	4.505[b]
PMN Elastase Cathepsin G	0.490 ± 0.218	1.936 ± 0.242*	4.457 ± 0.377**
Macrophage Elastase Collagenase	0.225 ± 0.099	0.482 ± 0.077	0.000[b]
Female			
Lavage Fluid			
Acid Proteinase	1.52 ± 0.12	3.46 ± 0.33*	6.05 ± 0.73**
Cathepsin D	0.015 ± 0.015	1.310 ± 0.292*	4.043 ± 0.578**
Cathepsin B	1.61 ± 0.26	2.15 ± 0.22	2.01 ± 0.17
Homogenate Supernatant Fluid			
Acid Proteinase	14.04 ± 0.95	29.43 ± 1.18**	38.61 ± 1.81**
Cathepsin D	10.05 ± 0.68	22.97 ± 1.07**	30.25 ± 1.60**
Cathepsin B	3.99 ± 0.58	6.46 ± 0.60*	8.37 ± 0.42**
Neutral Proteinase	0.648 ± 0.087	5.040 ± 0.418**	12.293 ± 1.598**
PMN Elastase Cathepsin G	0.785 ± 0.142	4.351 ± 0.261**	10.313 ± 2.694**
Macrophage Elastase Collagenase	0.054 ± 0.037	0.683 ± 0.175*	2.012 ± 1.126*

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error; units are presented as mg/hour per gram control lung.
[b] n=1; no standard error calculated

- organ weights
  - Absolute and relative lung weights of male rats exposed to 18 mg/m^3 were statistically significantly greater than those of controls at the 6-, 11-, and 18-month interim evaluations and at the end of the lifetime study, while those of female rats exposed to 18 mg/m^3 were significantly greater at the 11-, 18-, and 24-month interim evaluations and at the end of the lifetime study (Table 16). No other exposure related effects on absolute and relative organ weights were noted.

Table 16: Absolute and relative lung weights in rats in the lifetime inhalation study of talc

	Male			**Female**		
6-Months (mg/m^3)	*0*	*6*	*18*	*0*	*6*	*18*

Absolute (g)	1.196 (100%)	1.201 (100%)	1.6** (134%)	1.006 (100%)	0.986 (98%)	1.09 (108%)
Relative (mg organ weight/g body weight)	3.15 (100%)	3.29 (104%)	4.55** (144%)	4.71 (100%)	4.69 (100%)	5.17 (110%)
11-months (mg/m^3)	*0*	*6*	*18*	*0*	*6*	*18*
Absolute (g)	1.228 (100%)	1.152 (94%)	1.979** (161%)	0.959 (100%)	1.039 (108%)	1.551** (162)
Relative (mg organ weight/g body weight)	2.9 (100%)	2.85 (98%)	5.02** (173%)	3.79 (100%)	4.18 (110%)	6.27** (165%)
18-months (mg/m^3)	*0*	*6*	*18*	*0*	*6*	*18*
Absolute (g)	1.691 (100%)	1.852 (110%)	3.169** (187%)	1.13 (100%)	1.395** (123%)	2.6** (230%)
Relative (mg organ weight/g body weight)	3.78 (100%)	4.34 (115%)	7.36** (195%)	3.71 (100%)	5.07** (137%)	9.31** (251%)
24-months (mg/m^3)	*0*	*6*	*18*	*0*	*6*	*18*
Absolute (g)	1.766 (100%)	2.15 (122%)	2.473 (144%)	1.014 (100%)	1.447 (143%)	3.261** (322%)
Relative (mg organ weight/g body weight)	4.4 (100%)	5.18 (118%)	6.48 (147%)	3.4 (100%)	4.88 (144%)	12.73** (374%)
End of study (mg/m^3)	*0*	*6*	*18*	*0*	*6*	*18*
Absolute (g)	2.154 (100%)	2.509 (116%)	4.026** (187%)	1.575 (100%)	2.673** (170%)	4.05** (257%)
Relative (mg organ weight/g body weight)	5.76 (100%)	6.34 (110%)	12.65** (220%)	6.11 (100%)	11.77* (193%)	17.83** (292%)

*Absolute/relative weight in corresponding control group set as 100%. Statistically significantly different from the control group (Williams' or Dunnett's test): *P≤0.05, ** P≤0.01*

- histopathological findings
    - Lung: Inhalation exposure of rats to talc produced a spectrum of inflammatory, reparative, and proliferative processes in the lungs (Table 17). Granulomatous inflammation occurred in nearly all exposed rats and the severity increased with exposure duration and concentrations. Hyperplasia of the alveolar epithelium and interstitial fibrosis occurred in or near foci of inflammation in many exposed rats, while squamous metaplasia of the alveolar epithelium and squamous cysts were also occasionally seen. Accumulations of macrophages (histiocytes), most containing talc particles, were found in the peribronchial lymphoid tissue of the lung and in the bronchial and mediastinal lymph nodes. Minor alterations attributed to talc exposure were also observed in the upper respiratory tract.

Table 17: Incidences of selected lung lesions in rats in the lifetime inhalation study of talc

	Male			Female		
	0 mg/m³	6 mg/m³	18 mg/m³	0 mg/m³	6 mg/m³	18 mg/m³
6-Month Interim Evaluation						
Lung[a]	3	3	3	3	3	3
Inflammation, Granulomatous[b]	0	3* (1.3)[c]	3* (2.3)	0	3* (1.3)	3* (3.0)
Peribronchial Hyperplasia, Histiocytic	0	1 (1.0)	2 (2.0)	0	1 (1.0)	2 (1.0)
Hyperplasia, Alveolar Epithelium	0	0	0	0	1 (1.0)	1 (1.0)
11-Month Interim Evaluation						
Lung	2	3	3	3	3	3
Inflammation, Granulomatous	0	3* (1.7)	3* (3.0)	0	3* (1.7)	3* (2.7)
Peribronchial Hyperplasia, Histiocytic	0	0	0	0	1 (1.0)	2 (1.5)
Hyperplasia, Alveolar Epithelium	0	3* (2.0)	3* (1.7)	0	3* (1.0)	3* (2.3)
Interstitium, Fibrosis, Focal	0	2 (1.0)	3* (1.0)	0	2 (1.0)	3* (1.0)
18-Month Interim Evaluation						
Lung	3	3	2	3	3	3
Inflammation, Granulomatous	1 (1.0)	3 (1.3)	2 (2.0)	0	3* (1.7)	3* (2.0)
Peribronchial Hyperplasia, Histiocytic	0	2 (1.0)	2 (1.0)	0	1 (1.0)	2 (1.0)
Hyperplasia, Alveolar Epithelium	1 (1.0)	3 (1.0)	2 (1.0)	1 (1.0)	3 (1.0)	3 (1.3)
Interstitium, Fibrosis, Focal	0	3* (1.0)	2 (1.5)	0	3* (1.3)	3* (1.7)
Alveolar/bronchiolar Adenoma	0	0	0	0	1	0
24-Month Interim Evaluation						
Lung	3	6	2	5	9	3
Inflammation, Granulomatous	0	6* (1.5)	2 (2.0)	1 (1.0)	9**(1.4)	3 (1.7)
Peribronchial Hyperplasia, Histiocytic	0	1 (1.0)	1 (2.0)	0	2 (1.0)	0
Hyperplasia, Alveolar Epithelium	0	6* (1.0)	2 (1.5)	1 (1.0)	9**(1.4)	3 (2.3)
Interstitium, Fibrosis, Focal	0	5* (1.0)	2 (1.5)	0	8**(1.4)	3* (3.0)
Core Study						
Lung	49	50	50	50	48	50
Inflammation, Granulomatous	2 (1.0)	50**(1.6)	49**(2.3)	2 (1.5)	47**(1.5)	50**(2.8)
Peribronchial Hyperplasia, Histiocytic	0	12**(1.3)	8** (1.9)	0	8** (1.3)	9**(1.3)
Alveolar Epithelium, Hyperplasia	5 (2.0)	26**(1.3)	38**(1.7)	2 (1.0)	27**(1.2)	47**(2.1)
Alveolus, Metaplasia, Squamous	0	0	2 (1.0)	0	0	8** (1.1)
Interstitium, Fibrosis, Focal	1 (1.0)	16**(1.2)	33**(1.8)	1 (1.0)	24**(1.5)	45**(2.1)
Cyst (Squamous)	0	0	3	0	1	7**

* Significantly different (P≤0.05) from the control by Fisher's exact test (interim evaluation) or logistic regression (lifetime study)
** P≤0.01
[a] Number of animals with lung examined microscopically.
[b] Number of animals with lesion.
[c] Average severity grades of lesions in affected animals: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked

- Nose: Hyperplasia of the respiratory epithelium of the nasal mucosa was noted in males (0, 6, 18 mg/m³: 0/49, 3/48, 14/47) and in some females (1/48, 1/45, 2/48). The lesion consisted of an increase in the number of goblet cells primarily in the mucosa of the nasal septum. Accumulation of cytoplasmic eosinophilic droplets in the nasal mucosal epithelium (mucosa, inflammation, suppurative) in male (3/49, 18/48, 40/47) and female rats (5/48, 23/45, 46/48) occurred with a concentration-related increased incidence in the exposed groups.
- Lymph node: Histiocytic hyperplasia, consisting of accumulations of macrophages in the subscapular and medullary sinuses, occurred in the bronchial lymph nodes (male: 0/41,

44/48, 46/49; female: 0/46, 40/47, 45/47) and in the mediastinal lymph nodes of rats exposed to talc (male: 0/48, 40/49, 43/47; female: 0/47, 33/44, 40/47). The macrophages had foamy cytoplasm filled with birefringent particles of talc.

- Adrenal medulla: Focal adrenal medulla hyperplasia or pheochromocytoma were observed in rats at the various interim evaluations, but the number, of affected rats was too small to draw definitive conclusions (Table 20). Although adrenal medulla hyperplasia occurred with similar frequency among exposed and control females (22/48, 20/47, 16/49), the incidences of hyperplasia in exposed males (20/49, 8/48**, 9/47*) were significantly lower than controls. The lower incidences in exposed males are possibly due, in part, to the reduced amount of normal medullary tissue (e.g. medullary tissue without a pheochromocytoma) in which to observe hyperplasia. Focal hyperplasia consisted of irregular, small foci of small to normal sized medullary cells arranged in packets or solid clusters slightly larger than normal; compression of the surrounding tissue was minimal or absent.

- tumour data
  - The incidences of **alveolar/bronchiolar adenoma, carcinoma, and adenoma or carcinoma (combined)** in the 18 mg/m^3 group were significantly greater than those of controls (Table 18) and historical control data (Table 19) in female rats. The incidences of pulmonary neoplasms in exposed male rats were similar to those in controls (Table 18) or historical control data (Table 19). The adenomas were irregular, circumscribed masses consisting of cuboidal to columnar epithelium arranged in alveolar, tubular, or papillary formations and separated by varying amounts of collagenous connective tissue. The neoplastic epithelium generally formed a single layer and was relatively uniform with minimal cellular atypia. The carcinomas were distinguished from the adenomas on the basis of having greater cellular pleomorphism and atypia, but they exhibited little evidence of invasion and non-metastasized. In several benign and malignant neoplasms, the central portion of the mass was composed primarily of dense collagen and the epithelial component was located at the periphery. The extent of fibrosis in these neoplasms is not typical of spontaneous alveolar/bronchiolar neoplasms in control F344/N rats. The fibrous connective tissue was not interpreted as being a primary scirrhous response to the neoplastic epithelium, but rather a component of the prolonged inflammatory reaction to talc.

Table 18: Incidences of lung neoplasms in rats in the lifetime inhalation study of talc

	Male			Female		
	0 mg/m³	6 mg/m³	18 mg/m³	0 mg/m³	6 mg/m³	18 mg/m³
Core Study						
Alveolar/bronchiolar Adenoma						
Overall rates[a]	0/49 (0%)	1/50 (2%)	1/50 (2%)	1/50 (2%)	0/48 (0%)	9/50 (18%)
Terminal rates[b]	0/9 (0%)	0/14 (0%)	1/16 (6%)	0/11 (0%)	0/13 (0%)	1/9 (11%)
First incidence (days)	–[d]	781	799 (T)	805	–	716
Logistic regression test[c]	P=0.494	P=0.527	P=0.615	P<0.001	P=0.503N	P=0.010
Alveolar/bronchiolar Carcinoma						
Overall rates	0/49 (0%)	0/50 (0%)	1/50 (2%)	0/50 (0%)	0/48 (0%)	5/50 (10%)
Terminal rates	0/9 (0%)	0/14 (0%)	1/16 (6%)	0/11 (0%)	0/13 (0%)	3/9 (33%)
First incidence (days)	–	–	799 (T)	–	–	828
Logistic regression test	P=0.370	–	P=0.615	P=0.003	–	P=0.028
Alveolar/bronchiolar Adenoma or Carcinoma						
Overall rates	0/49 (0%)	1/50 (2%)	1/50 (2%)	1/50 (2%)	0/48 (0%)	13/50 (26%)
Terminal rates	0/9 (0%)	0/14 (0%)	1/16 (6%)	0/11 (0%)	0/13 (0%)	4/9 (44%)
First incidence (days)	–	781	799 (T)	805	–	716
Logistic regression test	P=0.494	P=0.527	P=0.615	P<0.001	P=0.503N	P<0.001
Squamous Cell Carcinoma						
Overall rates	0/49 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)	0/48 (0%)	1/50 (2%)

(T) Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined microscopically.
[b] Observed incidence at terminal kill
[c] Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The logistic regression test regards these lesions as nonfatal. A lower incidence in an exposure group is indicated by N.
[d] Not applicable; no neoplasms in animal group

Table 19: Historical control data of alveolar/bronchiolar adenoma, carcinoma or combined; in F344/N rats

	Male[a]	Female[a]
Adenoma	18/1054 [range: 0/53 – 5/50] (1.7 ± 2.4%)[b]	12/1050 [range: 0/52 – 2/50] (1.1 ± 1.3%)
Carcinoma	8/1054 [range: 0/53-2/50] (0.8 ± 1.2%)	12/1050 [range: 0/52-2/50] (1.1 ± 1.3%)
Carcinoma or adenoma	26/1054 [range: 0/53-5/50] (2.5 ± 2.6%)	14/1050 [range: 0/52-2/49] (1.3 ± 1.5%)
Squamous cell carcinoma	4/1054 [range: 0/53-1/50] (0.4 ± 0.8%)	1/1050 [range: 0/53-1/50] (0.1 ± 0.4%)

[a] Historical control data (HCD) 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. [b] percentage mean ± standard deviation.

- **Adrenal medulla pheochromocytomas** (benign, malignant, or complex [combined]) occurred with a significant positive trend in male and female rats, and the incidences in the 18 mg/m^3 groups were significantly greater than those of controls (Table 20). The incidences at the highest dose level were also greater than incidences based on historical control data in

F344/N rats from other NTP studies (Table 21). Pheochromocytomas were generally larger than focal hyperplasia and caused variable compression of the surrounding parenchyma; many obscured much or all of any remaining normal medullary tissue. The neoplastic cells were arranged in variably sized aggregates, large solid clusters, and/or trabecular cords several layers thick separated by a delicate fibrovascular stroma. The larger neoplasms usually exhibited greater cellular pleomorphism and atypia than smaller neoplasms. Because the only morphological criterion that unambiguously distinguishes malignant from benign pheochromocytomas is frank invasion or metastasis, a diagnosis of malignant pheochromocytomas was made only when there was invasion of the capsule. Complex pheochromocytomas consisted of an admixture of neoplastic pheochromocytes and neuroblasts, ganglion cells, and/or Schwann cells.

- **Table 20: Incidences of neoplasms and nonneoplastic lesions of the adrenal medulla in rats in the lifetime inhalation study of talc**

	Male			Female		
	0 mg/m³	6 mg/m³	18 mg/m³	0 mg/m³	6 mg/m³	18 mg/m³
11-Month Interim Evaluation						
Adrenal Medulla[a]	2	3	3	3	3	3
Hyperplasia[b]	0	0	0	0	0	0
Pheochromocytoma, Benign	1	0	0	0	0	0
18-Month Interim Evaluation						
Adrenal Medulla	3	3	2	2	3	3
Hyperplasia	0	1	0	0	1	1
Pheochromocytoma, Benign	0	0	1	0	0	0
24-Month Interim Evaluation						
Adrenal Medulla	3	6	2	5	9	3
Hyperplasia	2	2	0	3	0	0
Pheochromocytoma, Benign	0	2	0	0	4	0
Pheochromocytoma, Benign, Bilateral	1	1	2	0	1	3
Core Study						
Adrenal Medulla	49	48	47	48	47	49
Hyperplasia	20	8°°	9°	22	20	16
Pheochromocytoma, Benign						
Overall rates[c]	25/49 (51%)	30/48 (63%)	36/47 (77%)	13/48 (27%)	14/47 (30%)	18/49 (37%)
Terminal rates[d]	6/9 (67%)	11/14 (79%)	16/16 (100%)	5/11 (45%)	5/13 (38%)	6/9 (67%)
First incidence (days)	429	558	614	678	705	697
Logistic regression test[e]	P=0.007	P=0.213	P=0.009	P=0.185	P=0.541	P=0.225
Pheochromocytoma, Malignant						
Overall rates	3/49 (6%)	3/48 (6%)	7/47 (15%)	0/48 (0%)	1/47 (2%)	10/49 (20%)
Terminal rates	1/9 (11%)	1/14 (7%)	3/16 (19%)	0/11 (0%)	0/13 (0%)	3/9 (33%)
First incidence (days)	670	544	645	–[f]	849	784
Logistic regression test	P=0.096	P=0.662	P=0.178	P<0.001	P=0.509	P=0.001
Pheochromocytoma, Complex						
Overall rates	0/49 (0%)	2/48 (4%)	1/47 (2%)	0/48 (0%)	0/47 (0%)	0/49 (0%)
Terminal rates	0/9 (0%)	1/14 (7%)	0/16 (0%)	0/11 (0%)	0/13 (0%)	0/9 (0%)
First incidence (days)	–	558	743	–	–	–
Logistic regression test	P=0.486	P=0.230	P=0.503	–	–	–
Pheochromocytoma, Benign, Malignant, or Complex						
Overall rates	26/49 (53%)	32/48 (67%)	37/47 (79%)	13/48 (27%)	14/47 (30%)	23/49 (47%)
Terminal rates	7/9 (78%)	12/14 (86%)	16/16 (100%)	5/11 (45%)	5/13 (38%)	8/9 (89%)
First incidence (days)	429	544	614	678	705	697
Logistic regression test	P=0.007	P=0.147	P=0.006	P=0.014	P=0.541	P=0.024

° Significantly different (P≤0.05) from the control by logistic regression
°° P≤0.01
[a] Number of animals with adrenal medulla examined microscopically.
[b] Number of animals with lesion.
[c] Number of animals with neoplasm per number of animals with adrenal medulla examined microscopically.
[d] Observed incidence at terminal kill
[e] Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The logistic regression test regards these lesions as nonfatal.
[f] Not applicable; no neoplasms in animal group

- **Table 21: Historical control data of pheochromocytoma (benign, malignant, complex or combined) in F344/N rats.**

	Male[a]	Female[a]
Benign	320/1051 [range: 4/50 – 27/54]	54/1039 [range: 0/50 – 6/47]

	(30.4 ± 10.4%)[b]	(5.2 ± 3.8%)
Malignant	20/1051 [range: 0/53-3/49] (1.9 ± 2.1%)	5/1039 [range: 0/47-2/50] (0.5 ± 1.1%)
Complex	3/1051 [range: 0/50-1/50] (0.3 ± 0.7%)	 5/1039 [range: 0/53-2/45] (0.5 ± 1.1%)
Benign, Malignant or Complex	332/1051 [range: 4/48-27/54] (31.6 ± 10.0%)	64/1039 [range: 0/50-6/47] (6.2 ± 3.5%)

[a] Historical control data (HCD) 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. [b] percentage mean ± standard deviation

- No statistically significantly increased tumour incidence were reported at other sites in exposed groups compared to control.

1.1.1.2 NTP, 1993 - mouse

Study reference:

Toxicology and Carcinogenesis Studies of Talc (CASRN 14807-96-6) in F344/N Rats and B6C3F1 Mice (Inhalation Studies). National Toxicology Program (NTP)Technical Report (TR) 421[1]

RL 1

Detailed study summary and results:

Test type

NTP toxicology and carcinogenesis study, similar to OECD test guideline study 453. The study is GLP compliant.

Test substance

- Same as for the rat study, see 1.1.1.1.

Test animals

- Mouse $B6C3F_1$
- 50 males and females per group
- Age and weight at the study initiation: 7 weeks; male: 23.3-23.8 g, female: 19.3-19.6 g

Administration/exposure

- Inhalation (talc aerosol)
- 2-year study: mice were exposed to talc aerosols for 2 years. Study conducted June 1984 until April 1986.
- 0, 6 or 18 mg/m^3 (overall mean concentrations were 6.1 and 18.6 mg/m^3) equivalent to 0, 2 or 6 mg/kg/d in males and 0, 1.3 or 3.9 mg/kg/d in females. These exposures were selected based on 4-week inhalation studies of the terminal lung talc burden in $B6C3F_1$ (see 1.2.1.3); concentrations greater than 18 mg/m^3 were expected to overwhelm lung clearance mechanisms to impair lung function.

- Whole body exposure, 6 hours per day, 5 days per week
- Satellite group: additional study groups of 40 male and female mice, similarly exposed to 0, 6 or 18 mg/m^3, were designated for interim pathology evaluations; lung burden measurement; and lung biochemistry, cytology, and phagocytosis measurements. Mice were evaluated at 6, 12 and 18 months.
- Aerosol size distribution was determined once a month for each chamber. Particle size
    - Mass median aerodynamic diameter at 6 and 18 mg/m^3: 3.3 ± 0.4 and 3.6 ± 0.4 µm (respectively)
    - Geometric standard deviation at 6 and 18 mg/m^3: 1.9 ± 0.6 and 2.0 ± 0.2 µm (respectively)
- Talc was mixed with stainless steel powder at approximately 1 to 2.5 g per 500 g bed material, and . aerosols were then generated in a single fluidized-bed generator by injecting compressed air into the bed. At approximately week 70 there were problems experienced in maintaining control of chamber concentrations during a 12-week period (November 5, 1985 through January 27, 1986). For more details see 1.1.1.1.

Results and discussion

Describe the relevant findings. If no effects occurred, explicitly note "No effects".

- Mortality
    - Survival and number of deaths of exposed male and female mice were similar to that in the control group (Table 22). One female mouse exposed to 18 mg/m^3 died on day 20 and six female mice died of undetermined causes on day 28.

Table 22: Survival of mice in the 2-year inhalation study of talc

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
Core Study Groups			
Animals initially in study	50	50	50
Missexed[a]	1	1	0
Missing[a]	2	1	1
Moribund	1	2	3
Natural deaths	16	18	14
Animals surviving to study termination	30	28	32
Percent probability of survival at end of study[b]	65	58	66
Mean survival (days)[c]	648	648	645
Survival analysis[d]	P=0.886N	P=0.771	P=1.000N
Special Study Groups[e]			
Animals initially in study	39	40	40
Missing	0	1	1
Moribund	0	1	1
Natural deaths	4	5	7
Scheduled evaluation	35	33	31
Females			
Core Study Groups			
Animals initially in study	50	50	50
Culled[a]	0	1	0
Missing[a]	1	1	0
Moribund	2	4	4
Natural deaths	17	21	21
Animals surviving to study termination	30	23	25
Percent probability of survival at end of study	62	48	50
Mean survival (days)	663	648	590
Survival analysis	P=0.321	P=0.322	P=0.286
Special Study Groups			
Animals initially in study	39	40	40
Moribund	2	5	1
Natural deaths	7	5	10
Scheduled evaluation	30	30	29

[a] Censored from survival analyses
[b] Kaplan-Meier determinations
[c] Mean of all deaths (uncensored, censored, and terminal sacrifice).
[d] The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the exposed columns. A negative trend or lower mortality in an exposure group is indicated by N.
[e] Not included in survival analyses

- clinical signs
    - There were no clinical findings in exposed mice that could be attributed to exposure to talc.
- body weight
    - Mean body weights of male and female mice exposed to talc were similar to controls throughout the study.
- food/water consumption

    - Not specified
- ophthalmoscopic examination
    - Not specified
- clinical chemistry
    - Not specified
- Haematology
    - Not specified
- Urinalysis
    - Not specified
- lung burden, lavage and biochemistry
    - The data, normalized to control lung weight, show that talc burdens of mice exposed to 6 mg/m^3 were similar between males and females and increased progressively from 6 to 24 months, except for males at 18 months (Table 23). However, because of the small sample size of males at 18 months (two animals), the lung talc burden of this sample may not be representative of the group as a whole. The lung talc burdens of mice exposed to 18 mg/m^3 were also similar between sexes at each interim evaluation. Although the talc burdens of males and females increased substantially from 6 to 24 months, the values at 12 and 18 months were similar. The exposure-normalized data show that lung talc burdens of mice exposed to 18 mg/m^3 were disproportionately greater at 12 and 24 months than those of mice exposed to 6 mg/m^3 (Table 24). The slight increases in exposure-normalized lung talc burden were statistically significant in males and females at 12 and 24 months, but not at 6 or 18 months. The lack of statistical significance at 18 months might be explained, in part, by the small sample size. 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.

Table 23: Lung talc burden (normalized to control lung weight) of mice[a]

	6 months	12 months	18 months	24 months
Male				
0 mg/m^3	–[b]	–	–	–
6 mg/m^3	0.415 ± 0.114	1.084 ± 0.130	0.426 ± 0.040	2.973 ± 0.762*
18 mg/m^3	1.41 ± 0.29	9.00 ± 1.45*	8.36[c]	19.73 ± 4.03**
Female				
0 mg/m^3	–	–	–	–
6 mg/m^3	0.524 ± 0.056	0.707 ± 0.170	1.387 ± 0.178**	2.667 ± 0.720**
18 mg/m^3	1.35 ± 0.24	6.17 ± 1.39*	7.83 ± 1.36*	20.05 ± 0.98**

* Significantly different (P≤0.05) from the 6 month group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error; units are presented as mg talc/g control lung.
[b] Not examined
[c] n=1; no standard error calculated

Table 24: lung talc burden (normalized to exposure concentration) of mice[a]

	Male		Female	
	6 mg/m^3	18 mg/m^3	6 mg/m^3	18 mg/m^3
6-Month Interim	0.069 ± 0.019	0.078 ± 0.016	0.087 ± 0.009	0.075 ± 0.013
12-Month Interim	0.181 ± 0.022	0.500 ± 0.081*	0.118 ± 0.028	0.343 ± 0.077*
18-Month Interim	0.071 ± 0.007	0.464[b]	0.231 ± 0.030	0.435 ± 0.075
24-Month Interim	0.496 ± 0.127	1.096 ± 0.224*	0.445 ± 0.120	1.114 ± 0.055*

* Significantly different (P≤0.05) from the 6 mg/m^3 group by Dunn's or Shirley's test
[a] Mean ± standard error; units are presented as mg talc/g control lung per mg talc/m^3
[b] n=1; no standard error calculated

- Increases in total protein, β-glucuronidase, lactate dehydrogenase, glutathione reductase in bronchoalveolar lavage fluid were observed primarily in mice exposed to 18 mg/m^3 at 12, 18 and 24 months (Table 25, Table 26 and Table 27). At 6 mg/m^3 increased total protein (at 18 months in males) and β-glucuronidase (at 24 months in both sexes) were measured. Significant differences in total and differential cell counts were observed at 18 mg/m^3 compared to control at ≥18 months (Table 28 and Table 29). A concentration-related decrease in phagocytic activity of macrophages derived from lavage fluid was noted at ≥12 months (Table 30). Furthermore, increased collagenous peptides (male: 12, 18 and 24 months; female: 24 months) and total lung collagen (male: 18 and 24 months; female: 24 months) were noted at 18 mg/m^3 (Table 30). No statistically significant changes on viability of macrophages were noted at the 24-month interim evaluation (Table 30). No consistent exposure-related changes in lavage fluid acid and neutral proteinase activity were observed.

Table 25: Bronchoalveolar lavage fluid enzymes of mice at the 12-month interim evaluation[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
ß-Glucuronidase	0.188 ± 0.114	0.486 ± 0.346	12.787 ± 3.604*
Lactate Dehydrogenase	1,107.6 ± 545	540.2 ± 59.0	1,487.1 ± 456
Glutathione Reductase	89.50 ± 11.65	91.67 ± 6.60	302.40 ± 65.15*
Total Protein[b]	2.21 ± 0.74	1.56 ± 0.33	6.19 ± 2.63
Female			
ß-Glucuronidase	0.073 ± 0.073	0.413 ± 0.251	9.786 ± 2.271**
Lactate Dehyrogenase	1,209.7 ± 305	447.5 ± 76.1	1,805.3 ± 285
Glutathione Reductase	113.57 ± 19.78	97.93 ± 14.93	198.65 ± 23.44
Total Protein[b]	3.54 ± 1.27	3.61 ± 1.38	4.82 ± 2.88

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error; units are presented as mIU/g control lung.
[b] Mean ± standard error; units are presented as mg/g control lung.

Table 26: Bronchoalveolar lavage fluid enzymes of mice at the 18-month interim evaluation[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
ß-Glucuronidase	0.000 ± 0.000	1.344 ± 1.267	9.937 ± 4.196**
Lactate Dehydrogenase	434.0 ± 45.7	642.4 ± 119	1,039.9 ± 168**
Glutathione Reductase	63.93 ± 14.16	106.38 ± 12.15	217.18 ± 45.29*
Total Protein[b]	3.43 ± 0.62	6.23 ± 0.97*	9.45 ± 1.95**
Female			
ß-Glucuronidase	4.243 ± 4.203	0.334 ± 0.334	19.064 ± 9.200
Lactate Dehydrogenase	501.4 ± 46.9	404.2 ± 97.6	1,217.6 ± 255*
Glutathione Reductase	73.19 ± 14.94	71.27 ± 12.11	240.55 ± 44.06*
Total Protein[b]	2.96 ± 0.40	3.41 ± 0.92	9.59 ± 1.23*

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error; units are presented as mIU/g control lung.
[b] Mean ± standard error; units are presented as mg/g control lung.

Table 27: Bronchoalveolar lavage fluid enzymes of mice at the 24-month interim evaluation[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
ß-Glucuronidase	0.000 ± 0.000	1.811 ± 0.878**	16.571 ± 3.932**
Lactate Dehydrogenase	1,769 ± 259	1,439 ± 295	2,965 ± 131*
Glutathione Reductase	73.66 ± 9.75	87.55 ± 25.16	229.53 ± 58.46*
Total Protein[b]	1.69 ± 0.20	2.34 ± 0.22	4.68 ± 0.70**
Female			
ß-Glucuronidase	0.000 ± 0.000	2.624 ± 1.176**	13.778 ± 2.640**
Lactate Dehydrogenase	1,082 ± 155	1,596 ± 197*	2,026 ± 279**
Glutathione Reductase	68.66 ± 7.42	73.37 ± 13.91	163.46 ± 33.43*
Total Protein[b]	1.111 ± 0.310	0.872 ± 0.261	2.228 ± 0.501

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error; units are presented as mIU/g control lung.
[b] Mean ± standard error; units are presented as mg/g control lung.

Table 28: Bronchoalveolar lavage fluid cell populations of mice at the 18-month interim evaluation[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
Polymorphonuclear Cells	0.250 ± 0.250	8.750 ± 4.404	19.000 ± 6.258*
Lymphocytes	0.000 ± 0.000	0.500 ± 0.500	1.000 ± 0.577
Macrophages	89.00 ± 1.22	82.75 ± 5.81	75.75 ± 4.73
Epithelial Cells	10.75 ± 1.44	8.00 ± 4.74	4.25 ± 2.39
Female			
Polymorphonuclear Cells	0.250 ± 0.250	1.000 ± 0.577	16.000 ± 3.606*
Lymphocytes	0.000 ± 0.000	0.000 ± 0.000	1.333 ± 0.882*
Macrophages	84.50 ± 5.52	92.67 ± 0.88	79.00 ± 3.06
Epithelial Cells	15.25 ± 5.54	6.33 ± 0.88	3.67 ± 2.33

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
[a] Mean ± standard error; units are presented as percent of total cells.

Table 29: Bronchoalveolar lavage fluid cell populations of mice at the 24-month interim evaluation[a]

	0 mg/m³	6 mg/m³	18 mg/m³
Male			
Polymorphonuclear Cells	0.200 ± 0.200	13.000 ± 2.345*	16.500 ± 1.803**
Lymphocytes	0.000 ± 0.000	0.375 ± 0.239	0.500 ± 0.289
Macrophages	89.10 ± 2.50	78.25 ± 1.61*	80.33 ± 0.60*
Epithelial Cells	10.70 ± 2.61	8.38 ± 1.01	2.67 ± 1.59
Female			
Polymorphonuclear Cells	0.000 ± 0.000	7.500 ± 1.607*	20.667 ± 5.918**
Lymphocytes	0.000 ± 0.000	0.500 ± 0.500	0.500 ± 0.500
Macrophages	86.38 ± 3.57	87.00 ± 2.08	73.67 ± 8.46
Epithelial Cells	13.63 ± 3.57	5.00 ± 1.00	5.17 ± 3.03

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error; units are presented as percent of total cells.

Table 30: Phagocytic activity and viability of macrophages and lung collagen in bronchoalveolar lavage fluid of mice

	Male			Female		
12-months (mg/m³)	*0*	*6*	*18*	*0*	*6*	*18*
Phagocytic activity[a]	85.50 ± 1.44	56.10 ± 2.23*	16.77 ± 2.98**	77.07 ± 9.88	52.10 ± 9.22	17.37 ± 6.17**
Lavage fluid collagenous peptides[b]	74.23 ± 9.42	68.73 ± 4.11	117.62 ± 11.07*	89.88 ± 12.99	73.66 ± 11.58	108.55 ±: 7.56
Total lung collagen[b]	11.94 ± 0.47	12.44 ± 0.82	13.30 f 1.11	11.64 ± 0.48	11.84 ± 0.45	13.78 ±: 1.09
18-months (mg/m³)	*0*	*6*	*18*	*0*	*6*	*18*
Phagocytic activity	37.43 ± 8.55	14.10 ± 4.54	11.98 ± 2.22*	46.85 ± 11.08	20.03 ± 7.45	6.65 ± 0.35*
Lavage fluid collagenous peptides	42.54 ± 2.15	51.18 ± 5.40	70.67 ± 8.41**	54.09 ± 11.27	37.68 ± 6.01	64.88 ± 6.56
Total lung collagen	6.60 ± 0.49	7.13 ± 0.30	9.70 ± 0.70**	6.16 ± 0.25	6.96 ± 0.31	7.34 ± 0.43
24-months (mg/m³)	*0*	*6*	*18*	*0*	*6*	*18*
Viability of macrophages [c]	79.20 ± 3.44	64.60 ± 4.15	83.23 ± 0.87	60.50 ± 8.80	47.17 ± 2.74	59.77 ± 3.21
Phagocytic activity	37.14 ± 9.80	11.90 ± 4.64	3.56 ± 2.25**.	21.57 ± 6.77	13.60 ± 4.71	4.35 ± 2.65*
Lavage fluid collagenous peptides	54.39 ± 4.42	65.98 ± 5.01	91.92 ± 4.93**	38.09 ± 4.38	39.26 ± 4.01	62.14 ± 9.04*
Total lung collagen	8.53 ± 0.71	8.55 ± 0.59	13.71 ± 2.81*	6.04 ± 0.27	6.41 ± 0.36	7.91 ± 0.35*

[a] Mean ± standard error, units are presented as percent cells phagocytizing sheep erythrocytes; [b] Mean ± standard error, units are presented as µg/g control long; [c] Mean ± standard error, units are presented as percent viable cells. Viability of macrophages was not determined at the 6-, 12- and 18-month sacrifices because the small number of cells recovered from these mice lungs precluded the measurement of cell viability. Viability determination of macrophages was made on macrophages obtained at the final sacrifice because sufficient numbers of cells were generally available at this time; statistically significantly different from control (Dunn's or Shirley's test): *P≤0.05, **P≤0.01

- organ weights
    - Absolute and/or relative lung weights of male and female mice exposed to 18 mg talc/m^3 were statistically significantly greater than those of the controls at the 12- and 18-month interim evaluation and at the end of the study (Table 31). No other exposure related effects on absolute and relative organ weights were noted.

Table 31: Absolute and relative lung weights in mice in the 2-year inhalation study of talc

	Male			**Female**		
6-Months (mg/m^3)	*0*	*6*	*18*	*0*	*6*	*18*
Absolute (g)	0.165 (100%)	0.149 (90%)	0.173 (105%)	0.190 (100%)	0.164 (86%)	0.178 (94%)
Relative (mg organ weight/g body weight)	5.29 (100%)	4.78 (90%)	5.35 (101%)	7.11 (100%)	6.03 (85%)	6.04 (85%)
12-months (mg/m^3)	*0*	*6*	*18*	*0*	*6*	*18*
Absolute (g)	0.157 (100%)	0.216 (138%)	0.243* (155%)	0.151 (100%)	0.191 (126%)	0.207* (137%)
Relative (mg organ weight/g body weight)	4.54 (100%)	5.8 (128%)	7.3** (161%)	4.68 (100%)	5.78 (124%)	7.19** (154%)
18-months (mg/m^3)	*0*	*6*	*18*	*0*	*6*	*18*
Absolute (g)	0.229 (100%)	0.238 (104%)	0.345* (151%)	0.223 (100%)	0.242 (109%)	0.299** (134%)
Relative (mg organ weight/g body weight)	7.45 (100%)	6.42 (86%)	9.79 (131%)	6.96 (100%)	7.65 (110%)	10.9** (157%)
24-months (mg/m^3)	*0*	*6*	*18*	*0*	*6*	*18*
Absolute (g)	0.252 (100%)	0.258 (102%)	0.408** (162%)	0.276 (100%)	0.293 (106%)	0.410** (149%)
Relative (mg organ weight/g body weight)	7.47 (100%)	8.01 (107%)	13.08** (175%)	8.80 (100%)	9.28 (105%)	13.39** (152%)

*Absolute/relative weight in corresponding control group set as 100%. Statistically significantly different from the control group (Williams' or Dunnett's test): *P≤0.05, ** P≤0.01*

- histopathological findings
    - Lung: The principal lung lesion occurring in exposed mice (Table 32) was an accumulation of alveolar macrophages in the alveoli surrounding terminal bronchioles (hyperplasia, macrophage). The macrophages had abundant, slightly foamy to granular, eosinophilic cytoplasm containing birefringent talc particles. Small numbers of neutrophils were sometimes observed in the affected areas, and the interstitium contained infiltrates of mononuclear inflammatory cells (inflammation, chronic active). In contrast to the pulmonary lesions in rats, hyperplasia of type II pneumocytes or fibrosis were not prominent components of the lesions in mice. The incidences of pulmonary neoplasms were similar among exposed groups and controls.

Table 32: Incidences of selected lung lesions in mice in the 2-year inhalation study of talc

	Male			Female		
	0 mg/m³	6 mg/m³	18 mg/m³	0 mg/m³	6 mg/m³	18 mg/m³
6-Month Interim Evaluation						
Lung[a]	4	4	4	4	4	4
Hyperplasia, Macrophage[b]	0	3 (1.0)[c]	4* (1.0)	0	0	4* (1.0)
Inflammation, Chronic Active	0	0	1 (1.0)	0	0	0
12-Month Interim Evaluation						
Lung	4	4	4	3	4	4
Hyperplasia, Macrophage	0	4* (1.0)	4* (1.8)	0	4* (1.0)	4* (2.0)
Inflammation, Chronic Active	0	0	2 (2.0)	0	0	1 (3.0)
18-Month Interim Evaluation						
Lung	4	4	4	4	4	4
Hyperplasia, Macrophage	0	4* (1.3)	4* (2.5)	0	4* (1.3)	4* (2.5)
Inflammation, Chronic Active	0	0	2 (1.5)	0	0	0
Alveolar/bronchiolar Adenoma	0	1	0	1	0	0
Alveolar/bronchiolar Carcinoma	1	0	0	0	0	0
2-Year Study						
Lung	4	47	48	46	48	50
Hyperplasia, Macrophage	3 (2.3)	46**(1.4)	48**(2.8)	2 (2.5)	45**(1.6)	43**(2.8)
Inflammation, Chronic Active	0	16**(1.1)	40**(2.2)	0	25**(1.4)	38**(2.3)
Alveolar Epithelium, Hyperplasia	1 (1.6)	0	0	0	0	1 (1.0)
Alveolar/bronchiolar Adenoma						
Overall rates[d]	6/45 (13%)	4/47 (9%)	9/48 (19%)	3/46 (7%)	2/49 (4%)	2/50 (4%)
Logistic regression test[e]	P=0.251	P=0.411N	P=0.371	P=0.467N	P=0.499N	P=0.515N
Alveolar/bronchiolar Carcinoma						
Overall rates	7/45 (16%)	2/47 (4%)	2/48 (4%)	2/46 (4%)	4/49 (8%)	1/50 (2%)
Logistic regression test	P=0.069N	P=0.073N	P=0.070N	P=0.325N	P=0.356	P=0.500N
Alveolar/bronchiolar Adenoma or Carcinoma						
Overall rates	12/45 (27%)	5/47 (11%)	11/48 (23%)	5/46 (11%)	6/49 (12%)	3/50 (6%)
Logistic regression test	P=0.522N	P=0.043N	P=0.423N	P=0.269N	P=0.519	P=0.367N

* Significantly different (P≤0.05) from the control by Fisher's exact test (interim evaluation) or logistic regression (2-year study)
** P≤0.01
[a] Number of animals with lung examined microscopically.
[b] Number of animals with lesion.
[c] Average severity grades of lesions in affected animals: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked
[d] Number of animals with neoplasm per number of animals examined microscopically.
[e] Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the control and that exposed group. The logistic regression test regards these lesions as nonfatal. A negative trend or a lower incidence in an exposure group is indicated by N.

- Nose: the incidences of focal cytoplasmic alteration were increased in groups of mice exposed to talc (0, 6, 18 mg/m^3 in male: 5/45, 23/46, 40/47; female: 29/46, 37/46, 40/50). Focal cytoplasmic alterations was characterized by the formation of large eosinophilic droplets in the cytoplasm of olfactory and respiratory epithelial cells and was similar to that observed in rats.
- Lymph node: The bronchial lymph nodes of mice exposed to talc contained accumulations of macrophages in the medullary sinuses (hyperplasia, histiocytic; male: 1/32, 32/39, 42/33; female: 0/38, 25/37, 39/43). The macrophages had abundant, slightly foamy to granular, eosinophilic cytoplasm filled with birefringent particles of talc.

- tumour data

- No statistically significantly increased tumour incidence was reported in exposed mice compared to control.

1.1.1.3 Wehner et al., 1977 - hamster

Study reference:

Inhalation of talc baby powder by hamsters

A.P. Wehner, G.M. Zwicker and W.C. Cannon

Food Cosmet Toxicol. 1977 Apr;15(2):121-9

DOI: 10.1016/s0015-6264(77)80317-9.

RL 3 (use of partclies with large MMAD)

Detailed study summary and results:

Test type

Experimental study, predates GLP

Test substance

- Talc-based baby powder from Johnson's© Baby Powder, lot 228p, high-grade cosmetic talc from Vermont
- Degree of purity: ≥95% w/w platey talc
- Impurities: trace quantities of carbonates (magnesite and dolomite) as well as platey chlorite and rutile

Test animals

- Syrian golden hamsters (E1a: ENG strain)
- 50/group/sex in groups 1-5, 25/group/sex in groups 6 and 7 (control groups), see Table 33
- Age and weight at the study initiation: 4 weeks (groups 1, 2 and 3) or 7 weeks (4 and 5), 45-55 gr (groups 1, 2, 3 and 6; see Figure 2) or 75-90 gr (groups 4, 5 and 7; see Figure 3)

Administration/exposure

- Inhalation (talc aerosol)
- duration of test/exposure period, see Table 33

Table 33: Experimental design for exposure of groups of hamsters to a talc aerosol for various lengths of time

Group	Exposure regimen*		Calculated cumulative exposure	
	No. of min/day	No. of days	(hr)	(mg hr/m^3)
1	3	30	1·5	12
2	30	30	15	120
3	150	30	75	600
4	30	300	150†	1200†
5	150	300	750†	6000†
6 (control)	150‡	30	75†	—
7 (control)	150‡	300	750†	—

*Animals (50 males and 50 females in groups 1–5 and 25 males and 25 females in groups 6 and 7) were treated on 5 days/wk. Desired respirable fraction of talc aerosol = 8 μg/litre.
†Most of these animals died before completion of 300 exposures.
‡Sham exposures.

- doses/concentration levels, rationale for dose level selection
    - Group 1, 2 and 3: 37.1 ± 7.4 mg/m^3, mean respirable fraction 9.8 ± 2.4 mg/m^3, MMAD of 4.9 µm; distribution, bimodal with peaks at 0.6 and 2.6 µm
    - Group 4 and 5: 27.4 ± 3.4 mg/m^3, mean respirable fraction 8.1 ± 1.0 mg/m^3, MMAD of 6.0 µm; distribution, bimodal with peaks at 0.6 and 4.0 µm
    - Group 6 and 7 (control groups) were exposed to air
    - It should be noted the MMAD of talc particles used here is larger than recommended by the OECD[2]
- frequency of treatment (see Table 33)
    - Whole body exposure
    - Group 1, 2 and 3: 3, 30 and 150 min/day, respectively
    - Group 4 and 5: 30 and 150 min/day, respectively
    - Group 6 and 7: 150 min/day
    - Aerosol concentrations and exposure times were based partly on results of simulated infant-exposure experiments in which women dusted infant-size dolls with baby powder as they would dust infants. In addition, median infant exposure was estimated based on a study involving 72 babies ranging from 1 to 24 months of age, that mother applied talc from one to nine times each day with a median frequency of twice a day. A time-weighted average exposure for 'one dusting' of 0.1 ± 0.04 mg min/m^3 was determined in individual tests on 48 mother-infant pairs. From the resulting cumulative frequency distribution, a median infant exposure of 0.058 mg hr/m^3/week and an upper 95th percentile of 0.105 mg hr/m^3/week were determined.

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

- post exposure observation period
    - After completion of the exposures the hamsters were maintained for observations for the remainder of their natural lifespan with the qualification that 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%.
- analytical verification of test atmosphere concentrations
    - Total aerosol concentrations was measured daily by means of two probes, inserted into opposite quadrants of the chamber. Two probes were used to monitor and ascertain even aerosol distribution within the chamber. Each probe sampled for 60 min concurrent with the Casella sampler at a rate of 2.3 L/min through a vertically positioned 25-mm-diamter Metricel DM-450 filter paper, which was weighed before and after sampling. Weekly mean aerosol concentrations were computed from the daily data. The mean aerosol concentrations referred to in this paper are the means of the combined weekly means. Particle size and particle-size distribution were determined periodically by collecting aerosol samples in an Andersen Cascade Impactor.
- type or preparation of particles (for studies with aerosols)
    - A Wright Dust Feed Mechanism served as the aerosol generator, the talc powder being packed into the cup at a pressure of 263 kg/cm^2. The mechanism was operated with an air flow of approximately 20 L/min with an upstream air pressure of 5 lb/in^2 (34 kPa) to give a fairly reliable aerosol generation. Air-flow rate through the exposure chamber was 208 L/min. The Casella Type 113A Gravimetric Dust Sampler, which included a horizontal elutriator to remove larger particles from the aerosol prior to collection of the respirable particles on a glass-fibre filter. A sample was taken continuously for the duration of each day’s exposure at a sampling rate of 2.5 L/min. The Whatman GF/A filters from the samples were weighed before and after sampling to determine the quantity of talc deposited, and the sample volume was measured by the sampler. From these data the respirable fraction of the aerosol concentrations was determined.
    - Sham exposures consisted of placing the control animals in an identical exposure chamber for the specified periods of time to simulate the stress of handling. Instead of aerosol, filtered room air was drawn through the chamber.

Results and discussion

Describe the relevant findings. If no effects occurred, explicitly note "No effects".

- mortality and time to death (indicate number died per sex per dose and time to death)
    - There were no significant differences among the survival times of the exposed groups, nor between the exposed groups and the controls (Table 34).

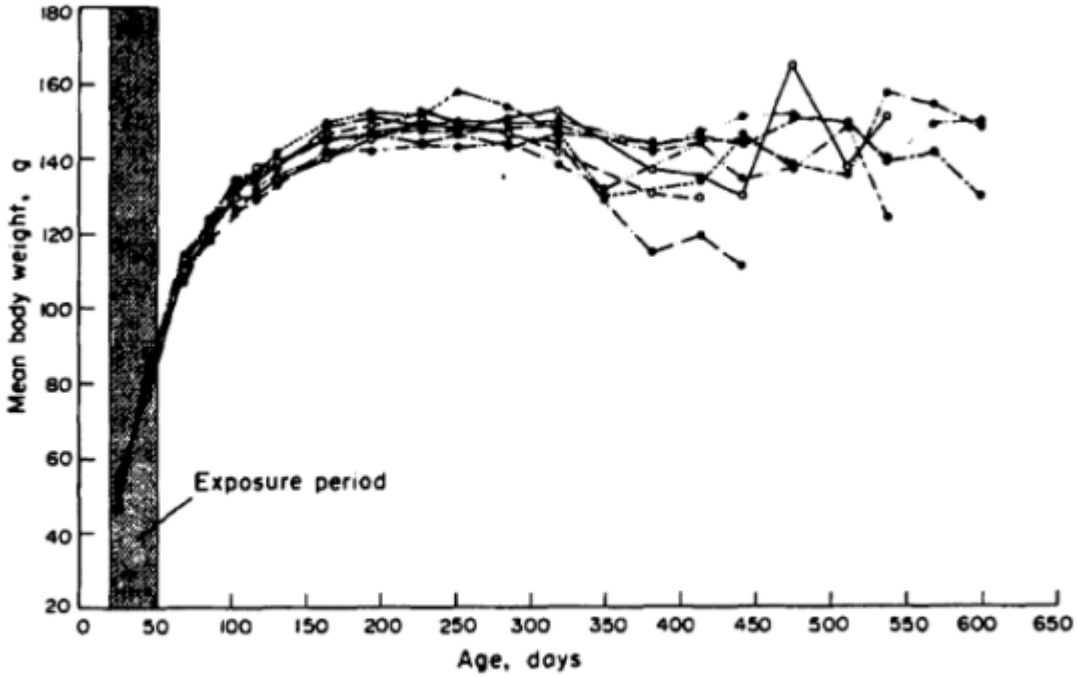
- A high mortality was observed in all groups, especially among females. The study authors noted that the mean survival time of males was statistically significantly ($p < 0.05$) longer than that of females.

Table 34: Mean survival times of groups of hamsters exposed to a talc aerosol and of sham-exposed controls

Group	Daily aerosol exposure (min)	Actual cumulative exposure (mg hr/m³ ± SD)	Median survival time (days ± SD)			Mean survival time* (days ± SD)		
			Males	Females	M + F	Males	Females	M + F
			30-day exposures					
1	3	14·6 ± 3·6	430	370	398	442 ± 15	349 ± 15	396 ± 12
2	30	146 ± 36	398	363	382	415 ± 15	360 ± 13	387 ± 10
3	150	732 ± 180	434	367	388	453 ± 18	372 ± 9	412 ± 11
6	0	0	412	381	393	426 ± 17	372 ± 14	399 ± 8
			300-day exposures					
4	30	1210 ± 150†	482	400	428	491‡ ± 13	380 ± 12	436‡ ± 10
5	150	6060 ± 750†	481	396	428	462† ± 11	405 ± 12	433‡ ± 10
7	0	0	488	354	411	485‡ ± 21	361 ± 16	423 ± 16

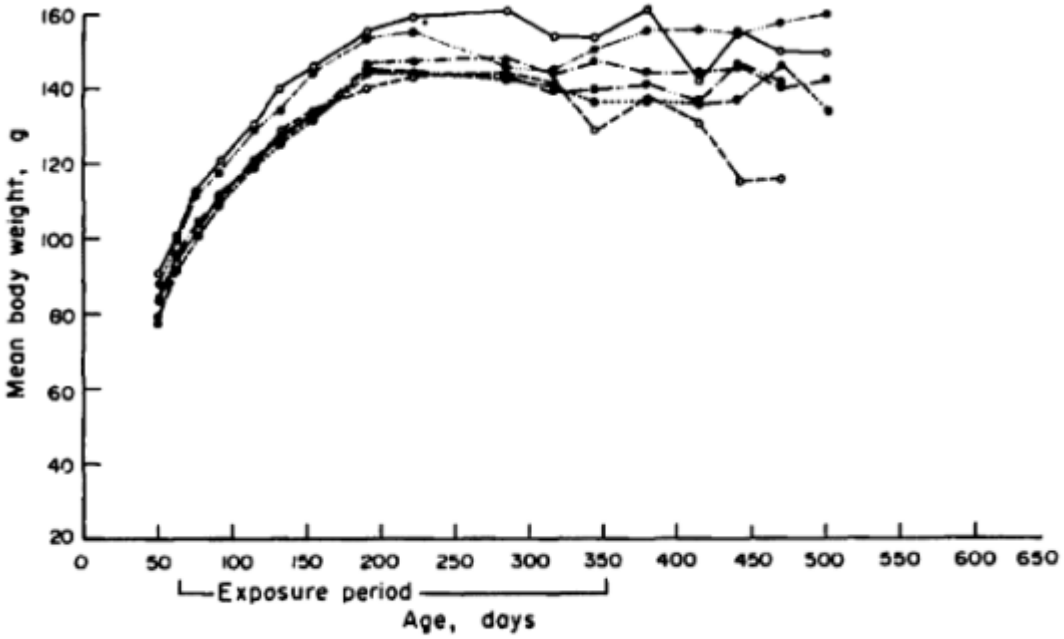
*In all groups, the mean survival time for the males was significantly longer ($P < 0·05$) than that for the females.
†Most of these animals died before completion of the 300 exposures (Fig. 5).
‡The survivors of groups 4, 5 and 7 were killed at the age of 20 months. At that time all females were dead and less than 20% of the males were alive. The male mean survival times and consequently the combined mean survival times are therefore artificially low.

- clinical signs
  - No clinical signs were observed as a results of the talc exposure.
- body weight gain
  - The exposures had no effect in both sexes (see Figure 2 and Figure 3)



Mean body weights of hamsters of groups 1 (———, males; —·—, females), 2 (—··—, males; —···—, females) and 3 (·····), males; -----, females), exposed to talc aerosol for 30 days, and of group 6 (——, males; – – –, females), the sham-exposed control group.

Figure 2: Mean body weights group 1, 2, 3 and 6 (30-day exposure)



Mean body weights of hamsters of groups 4 (—·—, males; —···—, females) and 5 (·····, males; -----, females) exposed to talc aerosol for 300 days, and of group 7 (——, males; – – –, females), the sham-exposed control group.

Figure 3: Mean body weights group 4, 5 and 7 (300-day exposure)

- food/water consumption
    - not described
- clinical chemistry

- not determined

- haematology
  - not determined
- urinalysis
  - not determined
- organ weights
  - not described
- histopathological findings: nature and severity
  - Larynx and trachea (incidence not provided): focal mucosal calcification in the larynx was the most common change, with the highest incidence found in group 3 (150 min/day for 30 days) and the lowest in group 5 (150 min/day for 300 days). Focal calcification of the mucosa was also the most common change in the trachea, with the highest incidence found in group 1 (3 min/day for 30 days) while incidences in the other treatment groups did not differ much from the control groups. The study authors concluded that these incidences were not related to exposure duration.
  - Lungs: focal alveolar emphysema, interstitial pneumonia (most common lesion), focal alveolar histiocytosis, focal alveolar and bronchiolar calcification were noted in all groups (Table 35). No clear dose- or duration of exposure-related effects on incidences were observed for these effects. However, a treatment-related effect was observed for focal alveolar cell hyperplasia, with highest incidences noted in groups with longer duration of exposure (Table 35; group 4 and 5; 300 days). The study authors noted that no significant pattern of incidence of focal alveolar cell hyperplasia was associated with the number of exposure days or number of exposure minutes per day.

Table 35: Summary of incidences of common pulmonary changes observed in hamsters exposed to talc aerosol

Pulmonary change	No. of animals affected in group*														Total affected	Incidence (%)
	1		2		3		4		5		6		7			
	M	F	M	F	M	F	M	F	M	F	M	F	M	F		
No. of hamsters examined	49	47	50	49	48	50	49	50	48	48	25	25	25	25	588	
Alveolar emphysema	16	8	17	5	14	5	4	5	6	8	3	3	3	3	100	17·0
Interstitial pneumonia	23	25	29	24	22	24	18	26	21	30	14	14	12	8	290	49·0
Calcification	21	5	16	5	9	7	3	9	7	12	5	2	3	4	101	17·2
Alveolar hyperplasia	10	5	5	5	11	6	14	11	15	9	7	2	5	0	105	17·9
Alveolar histiocytosis	4	1	5	3	2	4	5	9	6	6	2	2	4	1	54	9·2

  - Other organs: no increased incidences in exposed groups compared to control groups, and/or dose-related increased incidences were noted at other sites.

- tumour incidence data

- Only a few neoplasms were found (Table 36). They were of several different histological types and their incidence was not related to treatment. No primary neoplasms were found in the respiratory system.

Table 36: Summary of incidence of spontaneous neoplasms found in control and talc-exposed hamsters

Site and neoplasm	No. of affected males and females (as specified)* in groups†					Total affected
	1(M)	3(F)	5(F)	6(F)	7(M)	
Adrenal gland						
Adenoma		1			1	2
Phaeochromocytoma		1				1
Uterus						
Leiomyoma			1			1
Unknown site of origin						
Carcinoma					1	1
Lung						
Carcinoma, metastatic	1				1	2
Thorax						
Rhabdomyosarcoma				1		1
Bone						
Osteosarcoma					1	1
Lymph node						
Malignant lymphoma					1	1
Liver						
Osteosarcoma			1			1
Cholangiocarcinoma	1					1
Malignant lymphoma, metastatic					1	1

*No neoplasms occurred in either sex in groups 2 and 4, in the males of groups 3, 5 and 6 or in the females of groups 1 and 7.
†See Table 1 for the identification of groups 1–7.

1.1.1.4 Boorman and Seely, 1995 – rat and mice

Study reference:

The lack of an ovarian effect of lifetime talc exposure in F344/N rats and B6C3F1 mice

G. A. Boorman and J. C. Seely

Regul Toxicol Pharmacol 1995 Vol. 21 Issue 2 Pages 242-3

DOI: 10.1006/rtph.1995.1035

RL 3 (questionable talc particles reached ovaries)

Detailed study summary and results:

Test type

Extension of NTP, 1993. NTP toxicology and carcinogenesis study, similar to OECD test guideline study 453. The study is GLP compliant.

Test substance

- Talc (MP 10-52 grade), see 1.1.1.1 and 1.1.1.2

Test animals

- Rat F344/N and mouse $B6C3F_1$
- 10 females per group
- See 1.1.1.1 and 1.1.1.2

Administration/exposure

- Inhalation (talc aerosol), ample opportunity for perineal exposure as assumed by the study authors, as talc was covering fur and the cage bars.
- Rat: life-time study, rats were exposed to talc aerosols until mortality in any exposure group reached 80% (113 weeks for males and 122 weeks for females)
- Mouse: 2-year study, mice were exposed to talc aerosols for 2 years
- 0, 6 or 18 mg/m^3; whole body exposure, 6 hours per day, 5 days per week
- Rats and mice were selected randomly from the control and exposure groups, and histological slides containing the lungs and ovaries were examined under polarized light for the presence of anisotropic material consistent with talc particles.

Results and discussion

- There were no exposure-related lesions in the ovaries of rats (Table 37) or mice (Table 38).
- The lungs from the controls were negative for anisotropic materials but talc particles were easily identified from the lungs of the exposed rats. The particles were present in the alveolar macrophages and in areas associated with chronic inflammation in the lungs.
- There was no material consistent with talc found in the ovaries or ovarian bursa from any rats from any group.
- Results for mice not further specified.

Table 37: Incidence of ovarian lesions in female rats

Diagnoses	0 mg/m^3	6 mg/m^3	18 mg/m^3
Ovarian cyst	5	0	1
Granulosa cell tumor, malignant	1	0	0
Granulosa cell tumor, benign	0	2	0
Granulosa-theca tumor, benign	0	1	0
Granulosa-theca tumor, malignant	0	0	1

Table 38: Incidence of ovarian lesions in female mice

Diagnoses	0 mg/m^3	6 mg/m^3	18 mg/m^3
Ovarian cyst	6	11	10
Abscess	4	10	7
Thrombosis	1	2	0
Adenoma	1	1	0
Cystadenoma	0	1	0
Luteoma	2	0	0

1.1.1.5 Summary animal studies investigating exposure to talc via routes less relevant to human

An overview of chronic toxicity and carcinogenicity animal studies investigating exposure routes considered less relevant to human can be found in Table 39.

Table 39: Summary table of animal studies on carcinogenicity investigating exposure routes to talc less relevant to human[3]

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
Intraperitoneal			
Intraperitoneal administration Experimental study, no test guideline study Wistar rats (n = 40-80/group, female) Predates GLP RL 3	Four injections of 25 mg granular talc (type unspecified) in saline at weekly intervals Lifetime study	A mesothelioma was observed in 1/36 talc-exposed rats after 587 days compared with none in 72 controls.	Pott et al. (1976a); Pott et al. (1976b); Pott et al. (1974)
Intraperitoneal administration Abstract Evans rats (n = 26-27/group, female) Predates GLP RL 4	Single injection of 100 mg talc (USP grade). Animals were observed for 18-21 months	3/27 tumours (one lymphosarcoma and one reticulum-cell sarcoma in the peritoneal cavity, one cystadenoma of the liver) in talc-treated rats compared to 0/26 in saline-treated controls.	Bischoff and Bryson (1976)
Intraperitoneal administration Experimental study, no test guideline study Swiss albino mice (n = 44-46/group, sex unspecified) GLP not specified	Single injection of 0 or 20 mg talc (type unspecified) in saline Lifetime study	Within 6 months, 16 animals died. In the 24 survivors 3 incidences (12.5%) of mesotheliomas (fibrous sarcomatous and mixed) were noted, compared to 3/46 (8.7%) in saline-treated controls. The IARC working group noted the occurrence of mesotheliomas in saline-treated animals.	Ozesmi et al. (1985)

[3] Adopted from IARC 2010

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
RL 2			
Intraperitoneal administration Experimental study, no test guideline study Mice (n = 12, male) Predates GLP RL 3	As a control group in a study that investigated asbestos, mice were injected with (50%) suspension of talc (USP V, no further analysis) in saline. Animals were sacrificed and investigated at different times after 26-343 days.	Histopathological examination was performed, and no mesotheliomas or other neoplasms were reported	Jagatic et al. (1967)
Intraperitoneal administration Abstract Marsh mice (n = 22-28/group, female) Predates GLP RL 4	Single injection of 0 or 20 mg talc (USP grade) Animals were observed for 18-21 months	Intraperitoneal lymphoid tumours occurred in 5/22 treated animals and in 6/28 saline-treated controls.	Bischoff and Bryson (1976)
Subcutaneous			
Subcutaneous administration Experimental study, no test guideline study R3 mice (n = 50, female) Predates GLP RL 3	Single injection of 8 g talc (type unspecified) and 20 g peanut oil (delivered dose about 80 mg) Lifetime study	Average 50% survival was 596 days, no local tumours were observed.	Neukomm and de Trey (1961)
Subcutaneous administration Abstract Marsh mice (n = 24-26/group, female) Predates GLP	Single injection of 0 or 20 mg talc (USP grade). Animals were observed for 18-21 months	No tumours developed at the injection site in 26 talc-treated and in 24-saline treated animals.	Bischoff and Bryson (1976)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
RL 4			
Intrapleural, intratracheal or intrathoracic			
Intrathoracic instillation Experimental study, no test guideline study Wistar rats (n = 30-38/group, female) GLP not specified RL 2	Single application of 25 mg talc (asbestos-free, not further specified) in saline. Animals were sacrificed at different time points after 1-18 months.	After 1 month, pronounced alveolar proteinosis with type II cell hyperplasia in lungs were noted. Talc particles accumulated in interstitial foreign-body granulomas with multinucleated giant cells, but without fibrosis. A statistically significant ($p < 0.01$) increase in proliferative activity of bronchus epithelium, the number of and area of pneumocytes were induced by talc after 1 month, but this was reversible and no change compared to control was observed ≥ 6 months.	Friemann et al. (1999)
Intrapleural implantation Experimental study, no test guideline study Osborn-Mendel rats (n = 30-50/group, female) GLP not specified RL 2	Implantation of 40 mg talc (one of seven grades, refined commercial talc, each from a separate and diverse source) in hardened gelatine Animals were observed for 2 years.	Fibre distribution of different types of talc used (diameter/length in µm); talc 1: 0.05-4.0/0.01-64; talc 2: 0.5-8.0/0.01-64; talc 3: 0.01-4.0/0.1-4.0; talc 4: 0.05-4.0/0.01-8.0; talc 5: 0.01-4.0/0.01-4.0; talc 6: 0.01-8.0/0.01- >64; talc 7: 0.01-2.5/0.01- >64 The incidence of pleural sarcomas was: talc 1, 1/26; talc 2, 1/30; talc 3, 1/29; talc 4, 1/29; talc 5, 0/30; talc 6, 0/30; talc 7, 0/29; untreated controls, 3/488 (0.6%); and controls that received implants of 'non-fibrous' materials described by the authors as 'non-carcinogenic', 17/598 (2.8%). Other fibrous minerals (e.g. crocidolite, glass, tremolite) were tested as well. Probability of pleural sarcoma correlates best with fibres that measure ≤0.25 µm × >8 µm.	Stanton et al. (1981)
Intrapleural administration Experimental study, no test guideline study Wistar rats (n = 24/sex/group) Predates GLP RL 3	Single application of 20 mg Italian talc (00000 grade, 92% talc; 0.5%-1% quartz, mean particle size 25 µm) in saline Lifetime study	The mean survival rate was 655 days in talc-treated rats compared to 691 days in the control group. No mesotheliomas were observed in either group; one small pulmonary adenoma was found in one treated rat that died 25 months after injection. There was no other relevant pathology of the lungs in these animals.	Wagner et al. (1977)
Intrathoracic administration Abstract Evans rats (n = 28-32/group, female) Predates GLP	Single application of 0 or 50 mg talc (USP grade) Animals were observed for 18-21 months	Intrathoracic reticulum cell sarcomas or lymphomas were observed in 7/30 talc-treated rats, 8/32 saline-treated rats and 7/28 untreated controls.	Bischoff and Bryson (1976)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
RL 4			
Intrathoracic administration No test guideline study Swiss albino mice (n = 80/group/sex) Predates GLP RL 3	Single application of talc (64% silica, 32% magnesium oxide, particle size <5 µm) in saline Animals were sacrificed at different time points after 1-210 days.	After 30 days, increased lymphopoiesis and areas of fibrinous exudate were observed in the peribronchial and perivascular areas. Fibrotic areas showed thickened interalveolar septa at 180 days, but did not progress further by 120 days. The authors concluded that the albino mouse is not a suitable species for experimental pneumoconiosis studies as the histological lesions in mouse do not simulate the human lesions.	Sahu et al. (1978)
Intrathoracic administration Abstract Marsh mice (n = 47-48/group, male) Predates GLP RL 4	Single application of 0 or 10 mg talc (USP grade) Animals were observed for 18-21 months	5/47 talc-treated mice had tumours (two adenocarcinomas and three lymphoid tumours of the lung) compared with none of 48 saline-injected controls	Bischoff and Bryson (1976)
Intratracheal administration Experimental study, no test guideline study Golden Syrian hamsters (n = 3-6/group, male) Predates GLP RL 2	Single application of Vermont talc (53.5% talc, 2.5% MgSi; 78% non-fibrous, 22 fibrous (ratio ≥3:1; MMAD 7.5 µm) 0, 0.15 , 0.75, 3.75 mg/100 g bw Animals were observed for 1-14 days postexposure	One day after exposure, elevated enzyme levels (LDH, β-N-acetylglucosaminidase, peroxidase), pulmonary oedema and increased cell numbers (macrophages and neutrophils) in bronchoalveolar lavage fluid were noted. Macrophage phagocytosis was also inhibited. The elevation in enzyme levels was persistent and the macrophage phagocytosis remained depressed. Phagocytosis of talc fibres by macrophages was observed, and birefringent particles were found in macrophages, neutrophils, and multinucleate giant cells in lavaged cells from talc-exposed animals. This supports the hypothesis that talc fibres induce inflammation and can contributed to lung disease, apart from possible contaminants	Beck et al. (1987); Sato et al. (2020)
Intratracheal administration Experimental study, no test guideline study Golden Syrian hamsters (n =	18 applications of 3 mg talc (USP grade; silica oxide, 61–63%; magnesium oxide, 32–34%; other dusts, 0.85–1.06%;	The animals were allowed to live out their lifespan (average 50% survival, 46–55 weeks). No respiratory tract tumours were observed in the talc-treated, saline-treated or untreated groups. Malignancies were observed in 33/45 animals treated with talc plus benzo[*a*]pyrene. The IARC working group noted the short survival of the animals.	Stenback and Rowlands (1978)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
24/group/sex) Predates GLP RL 3	93.3% < 25 µm in diameter) in saline with/without benzo[*a*]pyrene for 18 weeks Lifetime study		
GSD: geometric standard deviation; MMAD: mass median aerodynamic diameter Statistically significant vs. control, *P≤0.05, **P≤0.01			

1.1.2 Human data

1.1.2.1 Occupational exposure – talc miners and millers [adopted from IARC (2010)]

Rubino et al. (1976) conducted a study of mortality among men who had begun workin the mines and mills of a talc operation in the Germanasca and Chisone valleys (Piedmont), Italy, between 1921 and 1950 and who had been employed for at least 1 year in a job that involved exposure to talc. A total of 1514 miners and 478 millers were identified, of whom 168 miners (11.1%) and 40 millers (8.4%) were lost to follow-up before the end of the study in June 1974, yielding a combined cohort of 1784 men (89.6%) for analysis. The talc from these mines was described as pure and was reported to have been used in the pharmaceutical and cosmetics industries. However, due to the presence of 'footwall contact rocks' and rock-type inclusions in the mines, drilling operations were associated with exposure to dusts that contained high levels of silica; such inclusions were removed before milling and talc products were reported to have acontent of free silica below 2%. [The Working Group understood that the term 'silica' was in fact quartz.] In a few instances, talc samples from the area showed small amounts of tremolite when examined by X-ray diffraction, but no amphibolic asbestos or chrysotile were detected. For each worker, cumulative exposure was estimated from regular measurements of respirable dust content in the air of mines and mills during the period 1948–74 and individual work histories were abstracted from files of the miningcompany. Periods of time during which the dust level was assumed to be uniform were first selected and cumulative exposure was then calculated as the summed product of the number of years in each specific working period (years) and the associated dust levels (million particles per cubic foot; mppcf), resulting in an overall measure of mppcf–years. Once individual cumulative exposures had been assigned, miners and millers were then classified separately into low, medium and high levels of exposure. Ranges of exposure (mppcf–years) for miners were 566–1699, 1700–5665 and 5666–12750, respectively; ranges of exposure for millers were 25–141, 142–424 and 425–906, respectively. For each of

the 1784 workers included (1346 miners and 438 millers), one unexposed control subject was chosen at random from among male inhabitants of a nearby small, rural town. The control was matched to the talc worker on year of birth and vital status at date of entry into the study [date not specified]. Cause of death for 885 (95.1%) of 931 deceased workers and 1067 (94.8%) of 1126 deceased controls was obtained from regional death certificate files supplemented with information from relatives, physicians and medical records. Observed numbers of deaths among talc workers were compared with expected numbers, calculated by the use of age-specific mortality rates experienced by the control cohort. The standardized mortality ratio (SMR) for all causes combined was 0.9 (95% confidence interval (CI), 0.8–1.0) for miners and 0.9 (95% CI, 0.8–1.0) for millers. No relationship was observed with increasing time between first exposure and death or with increasing cumulative exposure. 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. A total of 100 deaths from cancers at all sites combined among miners (SMR, 0.8; 95% CI, 0.6–0.9) and 42 deaths among millers (SMR, 0.9; 95% CI, 0.7–1.2) were below those expected. Nine deaths among miners (SMR, 0.5; 95% CI, 0.2–0.9) and four among millers (SMR, 0.6; 95% CI, 0.2–1.6) were due to lung cancer. No excess risk for lung cancer was found in the highest exposure category among miners (cumulative exposure range, 5666– 12750 mppcf–years; five observed; SMR, 1.1; 95% CI, 0.4–2.7) or millers (cumulative exposure range, 425–906 mppcf–years; no observed deaths versus 1.3 expected). No cases of mesothelioma were found. [The Working Group noted that the lack of comparability between the workers and the comparison groups could influence the mortality ratio estimates of this study.]

In a re-analysis of their 1976 study, Rubino et al. (1979) estimated relative mortality among talc workers using Italian national death rates for men instead of the control cohort. As national rates were available only for the period 1951–74 (end of the study), rates for 1951 were applied for the follow-up period 1946 through to 1950. The number of workers included in this analysis was 1260 miners and 418 millers. In contrast to the previous analysis, the age-standardized mortality for all causes combined was 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). Eight observed cases of lung cancer in miners yielded an SMR of 0.5 (95% CI, 0.2–0.9) and four cases in millers yielded an SMR of 0.7 (95% CI, 0.2–1.7). No trend was observed with increasing cumulative exposure for either group of workers [*p*-value for trend not provided]. Mortality from non-malignant respiratory diseases was significantly increased among miners (109 observed; SMR, 3.3; 95% CI, 2.7–4.0), mainly due to 58 cases of pneumoconiosis and 23 cases of tuberculosis. The number of cases of pneumoconiosis and tuberculosis among millers was three and eight, respectively.

Katsnelson and Mokronosova (1979) conducted a study of mortality among male and female workers [numbers not specified] in a talc mining and processing plant in the former USSR in 1949–75. The talc of the area was reported to contain no tremolite or fibrous materials and levels of quartz ranged from 0.2 to 1.6%. Very high mortality ratios were found for cancer at all sites combined (relative risks, 5.1 for men; 6.4 for women; $p <$

0.001) as well as for lung (relative risks, 4.5 for men; $p < 0.02$; 9.3 for women; $p > 0.05$) and stomach cancer (relative risks, 3.7 for men; $p < 0.02$; 6.3 for women; $p < 0.05$) [observed numbers of deaths not specified]. [The Working Group noted that the deaths observed among exposed workers included current and past workers but that thedenominator comprised only currently employed persons].

Selevan et al. (1979) used radiography records from the annual surveys of workers in dusty trades of the Vermont Health Department to identify all white male workers employed in the Vermont talc industry for at least 1 year between 1940 and 1969. The study covered three areas that had a total of five companies (two of which ceased operations in 1952 and 1960). 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 minerals, when examined by both X-ray diffraction and analytical electron microscopy. Levels of respirable crystalline silica were below 0.25% in nearly all ore and product samples, and free silica was only occasionally detectable in air samples. Insufficient information was available to estimate cumulative lifetime exposures, but the authors stated that historical data were sufficient to demonstrate past exposure levels for miners and millers far exceeded the standard for non-fibrous talc of 20 mppcf that was in force at the time of the investigation. Due to the more continuous nature of the milling operation, it was considered probable that exposures to dust for millers were higher than those for miners. In one mine that had closed by the time of the study, 'cobblestones' of highly tremolitic serpentine rock were present but were avoided or discarded as far as possible before milling. Miners were also exposed to radon daughters at mean levels ranging up to 0.12 working levels (WL), with single peaks of 1.0 WL. The study groups comprised 163 talc miners and 225 millers. Vital status of workers was ascertained through to 1975, and death certificates were obtained for 85 of 90 deceased cohort members. For non- malignant respiratory disease and respiratory cancer, mortality rates for white men from Vermont were used for comparison, because they were considered to be more appropriate than national rates. For other causes of death, rates for the USA were used. Some increase was noted for all malignant neoplasms combined (16 observed [SMR, 1.3; 95% CI, 0.7–2.0]) and specifically for respiratory cancer (six observed [SMR, 1.6; 95% CI, 0.6–3.5]). [The Working Group noted that the results for respiratory cancer were not analysed by latency.] The excess mortality from respiratory cancer was statistically significant among the miners (five observed [SMR, 4.3; 95% CI, 1.4–10.1]), but not among the millers (two observed [SMR, 1.0; 95% CI, 0.1–3.7]). A significant excess of mortality from non- malignant respiratory disease was seen in millers (seven observed [SMR, 4.1; 95% CI, 1.6–8.4]), but not in miners (two observed [SMR, 1.6; 95% CI, 0.2–5.9]). Most workers who died from non-malignant respiratory disease had radiographic evidence of pneumoconiosis (rounded opacities).

In two brief communications, Leophonte et al. (1983) and Leophonte and Didier (1990) reported on the mortality of workers employed in a talc quarry in Luzenac in the South of France and in the associated talc processing plant. The cohort was composed of those who left employment between 1945 and 1981 and who had worked at the plant for more than 1 year. The talc in this region is a mixture of pure talc, chlorite and dolomite with no asbestos; levels of quartz vary from 0.5 to 3%. Of 470 workers available for study, 256 were alive, 209 had died and five were lost to follow-up. Of 204 workers with a known job history and date of death, 192 had

worked exclusively with talc at Luzenac. No significant excess of mortality from cancer in general or specifically from respiratory and digestive cancers was found. [Observed and expected numbers of cause-specific deaths and associated relative risks were not given.] A significant increase in mortalitywas found for non-malignant respiratory disease, especially for pneumoconiosis and obstructive lung disease. No cases of mesothelioma were observed. [The Working Groupnoted the unconventional definition of the cohort and that causes of death were obtaineddifferently for cases (from local doctors, hospitals or families) and controls (from regionalor national records).]

Wergeland et al. (1990) studied 94 male workers at a talc mine in northern Norwaywho had been employed in talc-exposed jobs for at least 1 year during 1944–72 and 295 male workers at a talc mill in western Norway who had been employed for at least2 years during 1935–72. Data on miners were gathered from the company pay rolls, lists of union memberships and the central registry of workers exposed to silica in Norway;data on millers were collected from the company protocol and the local occupational health service. The information included name, date of birth, first and last date of employment and number of periods of employment. According to the authors, Norwegiantalc contains only trace quantities of quartz, tremolite and anthophyllite as determined byoptical microscopy and by electron microscopic analysis. The talc in the region where themine was located is composed mainly of pure talc and magnesite. Approximately 90% ofthe raw material in the mill came from the mine and the rest was imported from India. Inaddition to talc, dolomite and mica were also processed at the mill. Personal air samplescollected in the early 1980s showed that total dust levels varied greatly by job categoryand 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).X-Ray diffractometry indicated that dust samples from both operations contained less than 1% quartz. The mean value for concentrations of radon daughters in the mine was 3.5 pCi/L [0.04 WL], with a range of 1.5–7.5 pCi/L [0.02–0.08 WL]. The majority of the389 workers could be classified into one of three categories according to degree of dustexposure, based on measurements and qualified assessments of dust level by experienced co-workers. Information on tobacco smoking habits, gathered during the study in 1981, was available for 63 of the 94 miners and showed that smoking rates among these workers were above the national average. Follow-up for cancer incidence (through data linkage to the national cancer registry) and cause-specific mortality (through linkage to the national mortality files) was begun at the date of entry into the cohort or 1 January1953, whichever came later, and ended at date of death or 31 December 1987, whichevercame first. National rates were used to calculate expected numbers of cancers and deaths.The SMR for all causes for the total cohort was 0.8 (117 observed; 95% CI, 0.6–0.9), which reflected a decrease among both miners (27 observed [SMR, 0.8; 95% CI, 0.5– 1.2]) and millers (90 observed [SMR, 0.7; 95% CI; 0.6–0.9]). An excess of deaths from all cancers was observed in miners (nine observed [SMR, 1.3; 95% CI, 0.6–2.5]), but notin either the total cohort (26 observed [SMR, 0.8; 95% CI; 0.5–1.1]) or in millers (17 observed; [SMR, 0.6; 95% CI; 0.4–1.0]). Mortality from non-malignant respiratory diseases was decreased, with one observed death among miners [SMR, 0.4; 95% CI, 0–2.2] and two observed deaths among millers [SMR, 0.2; 95% CI, 0–0.9]. No deaths frompneumoconiosis were

reported. The standardized incidence ratio (SIR) for all types of cancer combined was [1.4 (15 observed; 95% CI, 0.8–2.3)] among the miners and [0.8 (31 observed; 95% CI, 0.5–1.1)] among the millers. Two cases of lung cancer were observed among miners [SIR, 1.6; 95% CI, 0.2–5.7] and four cases among millers [SIR, 0.8; 95% CI, 0.2–2.0]. The non-significant excess risk among the miners was confined to cancer of the stomach (three observed [SIR, 2.5; 95% CI, 0.5–7.4]) and cancer of the prostate (four observed [SIR, 2.0; 95% CI, 0.6–5.2]). In the subgroup of 80 workers who belonged to the highest exposure category, a total of six cases of cancer were observed [SIR, 0.4; 95% CI, 0.2–1.0], none of which were cancer of the lung. There were no observed cases of mesothelioma.

Wild (2000) conducted a retrospective cohort mortality study, within a nested case-control study, at the same talc quarry and milling plant at Luzenac as that used by Leophonte et al. (1983) and Leophonte and Didier (1990). The cohort included employees who were active in 1945 or hired in the milling plant during the period 1945–94 and who had been employed continuously for at least 1 year. Employees, who were identified from the company files, comprised a total of 1070 men and 90 women. [The authors did not indicate the extent of overlap of the study population with that investigated by Leophonte *et al.* (1983) and Leophonte and Didier (1990).] Dust levels in the 1960s and 1970s were generally high, ranging from below 5 mg/m^3 to more than 30 mg/m^3. Average dust levels dropped to below 5 mg/m^3 in the 1990s through process changes and installation of engineering controls (e.g. installation of a central vacuum system). Overall 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. Overall, 32 (2.8%) employees were lost to follow-up. Of 106 individuals who died before 1968, cause of death was ascertained for 78 cases. SMRs were calculated using both regional mortality rates (pre- and post-1968) and national mortality rates (pre-1968). When regional mortality rates for 1968 and later were used, the SMR for all causes of death combined was 0.9 (294 observed; 95% CI, 0.8–1.0) for men and 0.8 (11 observed; 95% CI, 0.4–1.4) for women. Eighty men died from cancer at any site (SMR, 1.0; 95% CI, 0.8–1.3) and 21 died from lung cancer specifically (SMR, 1.2; 95% CI, 0.8–1.9). Mortality from lung cancer was non-significantly increased in subgroups of employees who were under 60 years of age (seven observed; SMR, 2.0 [95% CI, 0.8–4.0]), had a latency period of less than 20 years (five observed; SMR, 2.4 [95% CI, 0.8–5.6]) or had a duration of employment of less than 10 years (eight observed; SMR, 2.1 [95% CI, 0.9–4.1]). A slightly increased risk was seen for stomach cancer (five observed; SMR, 1.2; 95% CI, 0.4–2.8). Twenty-six men died from non- malignant respiratory diseases (SMR, 1.1; 95% CI, 0.7–1.6), three of which were pneumoconiosis (SMR, 5.6; 95% CI, 1.1–16.2). When pre-1968 national reference rates were applied, the overall SMR for men was 0.8 (101 observed; 95% CI, 0.6–1.0) and the excess mortality from lung cancer and non-malignant respiratory diseases disappeared. Of the 101 deaths observed during this period, one was caused by lung cancer (SMR, 0.3 [95% CI, 0.7–1.5]) and five were caused by non-malignant respiratory diseases (SMR, 0.7 [95% CI, 0.2–1.6]). A nested case–control study was performed to investigate further the risks for lung cancer, stomach cancer and non-malignant respiratory diseases in the men of the

cohort. For the lung cancer case–control study, 67 controls were individually matched to the 22 cases by age and sex (approximately three controls per case). Information on job history at the plant and tobacco consumption was collected through interviews of subjects who were alive and/or from experienced co-workers. A semiquantitative site-specific job–exposure matrix for talc dust was established using dust levels measured from 1986 onwards and estimates of levels before that year. Information on job history was then converted into estimates of cumulative exposure of the individual employees (expressed as mg/m^3–years). Multiple logistic regression analysis with adjustment for tobacco smoking habits and exposure to quartz estimated the odds ratio for lung cancer to be 0.7 (three cases and 15 controls) and 0.9 (three cases and 10 controls) for employees with a cumulative exposure to talc dust of 400–800 mg/m^3–years and more than 800 mg/m^3–years, respectively, when compared with unexposed employees (six cases and 20 controls). [The Working Group noted that information on smoking habits was available for only 52% of cases and 75% of controls, and that no specific information was given on the proportion of subjects alive among cases and controls at the date of interview.]

Wild et al. (2002) conducted a combined analysis of previously published cohort mortality studies among 1070 male employees at a talc quarry and milling plant in the south of France (Site A) (Wild 2000) and 542 male employees at three talc mines and their respective mills in Austria (Sites B, C and D). The Austrian cohort comprised workers who had been employed for at least 1 year between 1 January 1972 and 31 December 1995. Complete work histories for the Austrian workers were abstracted from company registries and from the regional social insurance. Information on tobacco smoking habits was obtained from earlier unpublished studies of mortality and pneumoconiosis, from colleagues and from records of the compensation claim insurance. Talc from two of the three Austrian plants (Sites B and C) had a content of quartz that was less than 4%, while that of the third plant (Site D) had higher but unspecified levels. Vital status of workers was verified through to 1995, and cause of death for those who had died was obtained from national mortality files. Local mortality rates yielded an overall SMR for the Austrian cohort of 0.8 (67 observed; 95% CI, 0.6–1.0;). A total of 17 deaths were due to cancer at any site (SMR, 0.7; 95% CI, 0.4–1.2), seven of which were from cancer of the lung (SMR, 1.1; 95% CI, 0.4–2.2). One death from stomach cancer (SMR, 0.4; 95% CI, 0–2.3) and no deaths from mesothelioma (0.1 expected) occurred. On the basis of 23 lung cancer deaths observed in the French cohort in 1968–96 and seven in the Austrian cohort in 1972–95, a nested case–control study was conducted. A total of 88 control subjects were selected from the two cohorts, individually matched to cases on age, calendar period and company. All job tasks at the companies were categorized according to measured and estimated levels of talc dust into one of four exposure groups (no exposure, < 5 mg/m^3, 5–30 mg/m^3 and > 30 mg/m^3). Job histories of cases and controls were converted into cumulative exposure to talc dust by summing the products of duration and level of exposure for each of the tasks held by the subject (mg/m^3–years). Subjects were also categorized according to tobacco smoking habits, exposure to quartz or a history of underground work on a yes/no basis. Information on smoking habits was available for approximately 50% of the cases and 75% of the controls in the French cohort and for 100% of the Austrian cohort. When the no-exposure category was

used as the standard (nine cases, 23 controls), the unadjusted odds ratios for lung cancer were as follows: 0.9 (exposure category, 1–100 mg/m^3–years; six cases, 18 controls); 1.1 (exposure category, 101–400 mg/m^3–years; seven cases, 15 controls), 0.6 (exposure category, 401–800 mg/m^3–years; five cases, 21 controls) and 0.7 (exposurecategory, > 801 mg/m^3–years; three cases, 10 controls). Assuming a linear trend, the oddsratio was 1.0 (95% CI, 0.9–1.1) per unit of 100 mg/m^3–years. Adjustment for tobacco smoking, exposure to quartz or underground work or any two of these variables did notchange the results.

Coggiola et al. (2003) updated the cohort of Rubino et al. (Rubino et al. 1979; Rubino et al. 1976) to include 1974 men who had worked for at least 1 year in the mine and/or in the factory during theperiod 1946–95. The mortality analysis included 1795 subjects (90.9% of the total cohort; 1244 miners and 551 millers), after excluding 179 workers who were lost to follow-up. No data on smoking habits were available. Follow-up began on 1 January 1946 or the date of first employment and ended at the date of death or 31 December 1995, during which time a total of 880 deaths occurred. The expected number of deaths was calculated from national rates for 1950–69 and regional mortality rates for 1970 onwards (with theexception of cancers of the oral cavity and oesophagus for which regional rates were unavailable; national rates were therefore used). Rates for the early 1950s were appliedfor the period 1946–49. Total mortality among workers was higher than expected(880 observed; SMR, 1.2; 95% CI, 1.1–1.3), mainly due to excess mortality from non- malignant respiratory tract diseases among the subgroup of miners (105 observed; SMR,3.1; 95% CI, 2.5–3.7). Of the 105 deaths in this category, 58 were from silicosis. In thecombined cohort of workers, there was no excess mortality for all cancers (185 observed; SMR, 1.0; 95% CI, 0.9–1.1) or for lung cancer, in particular (44 observed; SMR, 0.9; 95% CI, 0.7–1.3). No deaths from pleural or peritoneal mesothelioma were found. A significantly elevated risk was seen for cancers of the oral cavity (31 observed; SMR, 5.1; 95% CI, 3.5–7.3) and the oesophagus (10 observed; SMR, 2.1; 95% CI, 1.1–3.9). When the analysis was stratified by job, the SMR for lung cancer was 1.1 (33 observed; 95% CI,0.7–1.5) among miners and 0.7 (11 observed; 95% CI, 0.3–1.2) among millers. The slightexcess found among miners seemed to be due to a slightly elevated risk in workers withless than 20 years since first exposure (latency) (six observed; SMR, 1.1; 95% CI, 0.4–2.3) compared to that of workers with 20–30 years (10 observed; SMR, 1.0; 95% CI, 0.5–1.8) and more than 30 years (28 observed; SMR, 0.9; 95% CI, 0.6–1.3) since first exposure. There was no variation in lung cancer mortality by duration of exposure. Cancer of the oral cavity caused the death of 24 miners (SMR, 6.2; 95% CI, 3.9–9.1) and seven millers (SMR, 3.3; 95% CI, 1.3–6.9) and oesophageal caused the death of sevenminers (SMR, 2.3; 95% CI, 0.9–4.8) and three millers (SMR, 1.8; 95% CI, 0.4–5.2). Excess mortality was seen in miners for non-malignant respiratory tract diseases(105 observed; SMR, 3.1; 95% CI, 2.5–3.7), non-malignant digestive tract diseases (50 observed; SMR, 1.4; 95% CI, 1.0–1.8) and liver cirrhosis (37 observed; SMR, 1.8; 95% CI, 1.3–2.5). An increased risk for liver cirrhosis was also observed in millers (18 observed; SMR, 1.7; 95% CI, 1.0–2.7).

Meta-analysis of risk for lung cancer

Wild (2006) performed a meta-analysis of lung cancer mortality among miners andmillers 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. Previouslyunpublished 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, Frenchand Austrian workers. Data indicated that the prevalence of smoking was higher than thatin the reference populations [figures not specified]. In the estimation of the overall risk formillers, data from all five countries were used, while only data from the USA, Norwayand Italy were included in that for miners. Based on SMRs for lung cancer of 1.0 (USA;two cases; 95% CI, 0.1–3.7), 0.7 (Italy; 11 cases; 95% CI, 0.3–1.2), 1.2 (France; 21 cases; 95% CI, 0.8–1.9), 0.7 (Austria, Site B; three cases; 95% CI, 0.1–2.0) and 1.1 (Austria, Site C; one case; 95% CI, 0–6.2) and an SIR of 0.8 (Norway; four cases; 95% CI, 0.2–2.0) for talc millers, a summary SMR of 0.92 (42 cases; 95% CI, 0.7–1.3) was obtained. No heterogeneity between studies was detected. Similarly, based on mortality ratios forlung cancer of 4.4 (USA; five cases; 95% CI, 1.4–10.2) and 1.1 (Italy; 33 cases; 95% CI, 0.7–1.5) and an incidence ratio of 1.6 (Norway; two cases; 95% CI, 0.2–5.7) for talc miners, a summary SMR of 1.2 (40 cases; 95% CI, 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 (40 cases; SMR, 1.9; 95% CI, 0.7–5.1).

1.1.2.2 Occupational exposure – user industries [adopted from IARC (2010)]

Information on risk for cancer among workers exposed to talc is available from studies that were conducted in user industries. However, they are less informative than those conducted in talc miners and millers because the potential contamination of talc was not addressed. In addition, these studies provided no details about the type of talc used.

Manufacture of ceramic plumbing fixtures

Thomas and Stewart (1987) conducted a cohort mortality study of 2055 white men employed for at least 1 year between 1939 and 1966 at three plants of a single company in the USA that manufactured ceramic plumbing fixtures. Crystalline silica was said to be the major occupational exposure of these workers, but, in some parts of the plant, exposure to fibrous [tremolitic] and non-fibrous [tremolite-free] talc had also occurred. Vital status was ascertained for 96% of the cohort through to 1 January 1981 and observed numbers of deaths were compared with numbers expected from cause-specific mortality rates for white men in the USA. For each job title–department combination, exposure to silica and talc were qualitatively assessed by an experienced industrial hygienist. Silica exposure was categorized as none, low or high; high exposure to silica was further categorized on the basis of no exposure to talc, exposure to fibrous talc and exposure to non-fibrous talc. The SMR for all causes combined was 0.9 (578 observed [95% CI, 0.8–1.0])

and that for lung cancer was 1.4 (52 observed [95% CI, 1.1–1.9]). The excess mortality from lung cancer was seen exclusively among workers who had been exposed to high levels of silica dust (44 observed; SMR, 1.8 [95% CI, 1.3–2.4]) and, to a greater extent, in the subgroup with additional exposure to non-fibrous talc (21 observed; SMR, 2.5 [95% CI, 1.6–3.9]) than in subgroups with additional exposure to fibrous talc (five observed; SMR, 1.7 [95% CI, 0.6–4.0]) or no exposure to talc (18 observed; SMR, 1.4 [95% CI, 0.8–2.2]). [The Working Group noted that all jobs that involved exposure to talc also involved high exposure to respirable silica.]

Manufacture of pulp and paper

Langseth and Andersen (1999) examined cancer incidence among a cohort of 4247 women who had been employed for at least 1 year between 1920 and 1993 in the Norwegian pulp and paper industry. The women had worked mainly in paper sorting and packing departments in 10 paper mills or in administration (85% of the cohort). Production was judged to involve occupational exposures that included paper dusts, microbes, formaldehyde, talc and asbestos (the latter was used as insulation material in boilers and in the breaks of various rolling machines), but no measurement data were available. Women were followed for cancer incidence between 1953 and 1993 and SIRs were calculated by comparing the observed incidence to the 5-year age-specific incidence rates for the female population of Norway. Information on cancer incidence was obtained by linkage with the National Cancer Registry and information on dates of death and emigration was obtained from the Central Bureau of Statistics of Norway. Records of women who died between 1953 and 1960 were identified manually. Between 1953 and 1993, 535 women in the cohort had died, 65 women had emigrated and 380 new cases of cancer had been diagnosed. The SIR for all cancers was 1.2 (380 observed; 95% CI, 1.1– 1.3). An excess of ovarian cancer diagnoses was observed (37 observed; SIR, 1.5; 95% CI, 1.1–2.1). In the analyses, workers were also stratified by exposure into the following categories: short-term (< 3 years) versus long-term (≥ 3 years); period of first exposure (1920–39, 1940–59, 1960–74, 1975–93); and time since first exposure (3–14 years, 15– 29 years, ≥ 30 years). The excess risk was predominantly seen among women who had been employed in the industry for 3 years or more (31 observed; SIR, 1.6; 95% CI, 1.1– 2.3). The excess risk for ovarian cancer was also highest for women under the age of 55 years at diagnosis, with an SIR of 8.0 (six observed; 95% CI, 2.9–17.4) for women aged 25–35 years at diagnosis. Among women who worked in the paper mills, the SIR for ovarian cancer was 2.1 (18 observed; 95% CI, 1.3–3.4). In the discussion, the authors noted that talc is added as a filler in paper mills and may contribute to the excess risk for ovarian cancer observed.

On the basis of an extended follow-up of cohort members for cancer incidence to the end of 1999, Langseth and Kjaerheim (2004) conducted a nested case–control study that included 46 employees who had ovarian cancer and 179 controls individually matched to cases by incidence density sampling. An experienced oncologist reviewed the pathology for all cases. Work histories were obtained from personnel records at each mill. Exposure to asbestos, talc and total dust was assessed on the basis of the work histories, questionnaires on production processes completed by industrial hygienists and senior employees, as well as

semiquantitative exposure assessments for the 10 mills extracted from an international database of exposure in the pulp and paper industry. Information on possible confounders (including use of talc on sanitary napkins, underwear or diapers) was obtained for 76% of cases and 57% of controls through a personal interview with the study subject or next of kin. Odds ratios for ovarian cancer were derived by conditional logistic regression. Ever exposure to asbestos was associated with a non-significantly increased odds ratio for ovarian cancer of 2.0 (95% CI, 0.7–5.7), while ever exposure to talc (odds ratio, 1.1; 95% CI, 0.6–2.2) or to total dust (odds ratio, 0.8; 95% CI, 0.4–1.7) was associated with risks that were close to unity. Among women who were interviewed, the odds ratio for exposure to asbestos was 2.2 (95% CI, 0.5–9.1). 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.

Rubber manufacturing industries

Following the finding of an excess risk for stomach cancer in a cohort of rubber workers in the USA, Blum et al. (1979) carried out a nested case–control study of stomach cancer. Cases were defined as deaths from stomach cancer in two of the rubber companies from 1 January 1964 to 31 December 1973 (100 deaths in total). Four controls were matched to each case on age, race, sex and company. Using the recorded job history of each worker, the investigators and a group of environmental scientists assessed the potential for exposure (high, moderate, low or none) in each job to the following substances: polycyclic hydrocarbons, nitrosamines, carbon black and detackifiers (anti- sticking agents which were mainly talc). No information was available on the purity or composition of the talc (i.e. whether it contained asbestiform materials or other fibrous or non-fibrous carcinogens). While no clear elevation of odds ratio was reported in Company B, a significantly increased relative risk of 2.4 (27 observed; 90% CI, 1.4–4.1) was found in Company A when workers with moderate and high exposure to talc were pooled into one group. High exposure in the latter company was associated with a modest increase in relative risk of 1.3 (13 observed; 90% CI, 0.7–2.5).

Based on the employment files of five rubber production plants in Germany, Straif et al. (1999) conducted a mortality cohort study of 8933 male blue-collar workers who were hired after 1 January 1950 and who were alive on 1 January 1981. Follow-up was started on the date of completion of 1 year of employment or 1 January 1981, whichever came last, and ended on at death, at 85 years of age, at the date of loss to follow-up or 31 December 1991, whichever came first. Cause of death was obtained for 97% of 1521 deceased workers. Work histories were reconstructed from cost centre codes and were classified into six work areas. SMRs were calculated from national death rates and were estimated at 1.2 (154 observed; 95% CI, 1.0–1.4) for lung cancer and 1.2 (44 observed; 95% CI, 0.8–1.6) for stomach cancer. In a subsequent analysis (Straif et al., 2000), information on work history was combined with semiquantitative levels of exposure to asbestos, talc, nitrosamines and carbon black that were estimated by industrial hygienists to yield overall estimates of cumulative exposure (low, medium, high) for approximately 95% of the cohort. Talc is widely used in rubber production and, according to the authors, asbestos was used in all five plants at least until the

early 1980s. In risk analyses that were unadjusted for exposure to asbestos or other potential workplace confounders, high and medium occupational exposure to talc were associated with relative risks for lung cancer of 1.9 (21 observed; 95% CI, 1.1–3.1) and 1.1 (41 observed; 95% CI, 0.8–1.6), respectively, when workers with low exposure were used as the reference group. Equivalent risk estimates were 4.3 (11 observed; 95% CI, 2.1–9.0) and 1.2 (12 observed; 95% CI, 0.6–2.4) for stomach cancer and 5.4 (three observed; 95% CI, 1.1–27.0) and 2.8 (two observed; 95% CI, 0.5–16.7) for laryngeal cancer. Separate risk analyses with adjustment for potential confounders were not performed. [The Working Group noted that risk analyses that adjusted for estimates of exposure to asbestos were not presented.]

1.1.2.3 Community-based studies [adopted from IARC (2010)]

Chen et al. (1992) conducted a case–control study in Beijing, China, of several risk factors for ovarian cancer that included occupational exposure to talc. A total of 220 cases of newly diagnosed epithelial ovarian cancer were identified between 1984 and 1986 through the Beijing Cancer Registry. Of these, 67 [30.5%] were excluded due to death, 37 [16.8%] due to unavailability of current contact information and four [1.8%] due to patient refusal. The analysis was carried out on 112 cases and 224 community controls, with two age-matched controls per case. Potential controls were excluded if they had a history of serious illness, although the percentage of those excluded for this reason was not specified. In addition, 15 of the 224 eligible controls initially selected [6.7%] refused to participate in the study and were therefore replaced by other eligible controls. No information was provided on the age range of the cases and controls, although the mean age at the time of interview was similar for cases (48.5 years) and controls (49.0 years).

All cases were confirmed by laparotomy and pathological review. Data were collected in- person by trained interviewers. Odds ratios were estimated using conditional logistic regression adjusted for education and parity. Occupational exposure to talc was associated with an odds ratio for ovarian cancer of 0.9 (95% CI, 0.3–2.9). [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 who 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.]

Hartge and Stewart (1994) analysed the occupational histories of 296 women aged 20–79 years who were diagnosed with ovarian cancer between 1978 and 1981 in the Washington DC area of the USA and 343 hospital-based controls matched to cases on age and race. Pathology was confirmed for all cases. Trained interviewers used a standardized questionnaire to obtain information from each participant on their lifetime job history and occupational exposure to talc. An industrial hygienist blinded to the case status of each participant evaluated each industry and occupation for potential exposure to talc, ionizing radiation, polycyclic aromatic hydrocarbons and solvents, using a scale of 0 (definitely not exposed) to 4 (definitely exposed). Women were considered to be exposed if they had an exposure rating of 2–4 (possibly, probably or definitely exposed). Logistic regression adjusted for race, age, parity, gynaecological surgery and duration of employment in jobs with the exposure of interest was used for the analyses. Controlling for additional

known and potential risk factors for ovarian cancer, including parity, oral contraceptive use and cigarette smoking, did not change these estimates. Women who were classified as having been occupationally exposed to talc had odds ratios below the null, although the confidence limits were wide due to the small number of exposed women (12 cases, 31 controls). For women with 10 or more years of employment in an occupation with possible, probable or definite exposure to talc, the odds ratio was 0.5 (five exposed cases; 95% CI, 0.2–1.5). The risk for ovarian cancer was not significantly elevated for any exposure or duration of employment assessed. [Limitations of this analysis include the small number of women occupationally exposed to talc.]

'Industrial talc' was one of the substances evaluated by the exposure assessment team in the community-based case–control study carried out in Montréal, Canada (Siemiatycki 1991) and described in detail in the monograph on carbon black. About 5% of the 4263 study subjects was considered to be exposed to industrial talc, mostly in the following occupations: painters, motor vehicle mechanics and farmers. Exposure to talc was analysed in relation to 11 different types of cancer, at two levels of exposure (any or substantial). No statistically significant increases in risk were observed. The odds ratios for lung cancer were 0.9 (35 exposed cases; 90% CI, 0.6–1.4) for 'any exposure' and 0.9 (nine exposed cases; 90% CI, 0.5–1.9) for 'substantial exposure'. Prostate cancer was the only site with a borderline significant increased risk, with an odds ratio of 1.4 (29 exposed cases; 90% CI, 1.0–2.1) for 'any exposure' and 1.1 (seven exposed cases; 90% CI, 0.5–2.3) for 'substantial exposure'. [The main limitation of the study was the reliance on expert opinions of exposure rather than measurements for exposure assessment. Also, exposure levels tend to be lower in such community-based studies than in the workplaces that are selected for cohort studies. The main advantages were the availability of histologically confirmed incident cases and detailed information on tobacco smoking habits and other characteristics of the subjects.]

1.1.2.4 Cosmetic use of talc [adopted from IARC (2010)]

This evaluation was limited to ovarian cancer because the Working Group was unaware of studies of other cancers associated with the cosmetic use of talc.

The content of body powders used by women varies by product and has changed over time, although data that document this are limited. Before the mid-1970s, body powders may have contained varying but usually small quantities of amphiboles. After that time, amphibole was voluntarily reduced to less than detectable levels, at least in western Europe and the USA. Other non-talc minerals that include chlorite, quartz, carbonates and pyrophyllite may also be found in body powders in varying and occasionally not insignificant quantities in the past and currently. Other added ingredients, which depend on the product, could include cornstarch and perfumes.

Cohort studies

Gertig et al. (2000) carried out the only 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, a 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. 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 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. 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 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. 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). Overall, no association between 'ever use' of talcum powder and total risk for epithelial ovarian cancer (relative risk, 1.1; 95% CI, 0.9–1.4) and no trend of increased risk for ovarian cancer with increasing frequency of talc use were observed. However, a modest increase in risk for serous invasive cancers was associated with any history of talc use (relative risk, 1.4; 95% CI, 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 (relative risk, 1.0; 95% CI, 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. [Limitations of this analysis include the 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, 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.]

Case-control studies

Cramer et al. (1982) reported the first epidemiological study of genital talc use and the risk for ovarian cancer. The analysis included 215 cases of epithelial ovarian cancer and 215 population-based controls matched to cases by age (within 2 years), race and residence. All cases were Caucasian, English-speaking residents of Massachusetts, USA, aged 18–80 years, who had been diagnosed with epithelial ovarian cancer between November 1978 and September 1981. Cases were identified through pathology logs or tumour boards of 12 participating Boston hospitals. Among 297 eligible cases identified during the time period of interest, 41 were excluded from the study due to: physician refusal (13), patient refusal (14) or death/change of address (14). An additional 41 cases were excluded because they had a non-ovarian primary (18) or a non-epithelial ovarian tumour based on a review of pathology specimens by the authors. Controls were identified though annual listings of the names, addresses and ages of all Massachusetts residents. Among 475 women identified as potential controls, 11.8% (56) could not be reached, 6.1% (29) were ineligible due to previous bilateral oophorectomy, 4.2% (20) were the wrong age, not Caucasian or did not speak English and 32.6% (155) refused to participate. All cases and controls were interviewed in person to obtain information on their medical history, menstrual and reproductive histories, as well as potential for exposure to talc by way of contraceptives, perineal hygiene or surgery. Ninety-two cases (42.8%) and 61 controls (28.4%) reported a history of regular use of talc as a dusting powder to the perineum, on sanitary napkins or on both. After adjustment for parity (yes/no) and menopausal status (pre-/post-), a significant association was found between 'any perineal use' of talcum powder and the risk for ovarian cancer (odds ratio, 1.9; 95% CI, 1.3–2.9). This association was attenuated but still significant after adjustment for additional potential confounders, including religion, marital status, level of education, weight, age at menarche, parity (number of children), oral contraceptive use, menopausal use of hormones and tobacco smoking (adjusted odds ratio, 1.6; 95% CI, 1.0–2.5). A single type of perineal exposure to talc (either as a dusting powder to the perineum or on sanitary napkins) was associated with a borderline significantly increased risk for ovarian cancer (odds ratio, 1.6; 95% CI, 1.0–2.5) after adjustment for parity and menopausal status, while a history of both types of perineal exposure was associated with a significant increase in risk (adjusted odds ratio, 3.3; 95% CI, 1.7–6.4). No association was seen between other potential sources of exposure to talc (pelvic surgery, use of condoms, use of diaphragm or using talc for diaphragm storage) and the risk for ovarian cancer. In addition, the results were essentially unchanged after excluding women who had had a tubal ligation or hysterectomy (odds ratio, 2.8; $p < 0.003$), although the authors noted that these surgical procedures are usually performed at mid-life when substantial exposure to talc may already have occurred. The distribution of tumour histologies was similar for exposed and unexposed cases; 53.7% of tumours were classified as serous among the unexposed cases and 48.9% among the exposed cases with 'any' perineal use of talc. [Limitations of this report include the lack of information on duration and frequency of talc use. In addition, 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 also found (odds ratio, 2.44; $p < 0.05$).]

Hartge et al. (1983) published a brief report of a study conducted between 1974 and 1977 in the Washington DC (USA) area. The study included 197 cases treated for pathologically confirmed epithelial ovarian cancer at participating hospitals and 197 controls treated at the same hospitals for conditions other than pregnancy, malignancies and gynaecological or psychiatric diseases. Controls were frequency- matched to cases by age, race and hospital. Interviews were conducted in the hospital for controls and at home for most cases to collect information on reproductive and sexual history, medical history, drug use and other exposures. Questions on exposure to talc were added after the study began. As a result, the analysis included only 135 cases and 171 controls with information on exposure to talc. Sixty-seven cases [49.6%] and 100 controls [58.5%] reported 'any' use of talc (including non-genital uses), while seven cases [5.2%] and three controls [1.8%] reported genital use of talc (including use on genitals, on sanitary napkins or on underwear). No association was observed between 'any' use of talc and the risk for ovarian cancer (odds ratio, 0.7; 95% CI, 0.4–1.1). This estimate was unchanged after adjustment for race, age and pregnancy. A non-significant positive association was found between genital use of talc and the risk for ovarian cancer (odds ratio, 2.5; 95% CI, 0.7–10.0). [Limitations of this study included its 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. In addition, no information was given in this brief report on the methods used in the analysis to control for confounding.]

Whittemore et al. (1988) analysed the association between perineal use of talc and the risk for invasive epithelial ovarian cancer among 188 cases and 539 controls in the San Francisco Bay area (CA, USA). Cases were residents of northern California, aged 18– 74 years, who had been diagnosed with an invasive ovarian tumour between January 1983 and December 1985 at one of eight hospitals. Controls were either selected from among women who had been hospitalized for a non-cancerous condition at one of these eight hospitals or were identified from the population using random-digit dialling. Women in each control group were matched to each case by age (within 5 years) and race (white, black, other), plus hospital and date of admission (within 3 months) for the hospital controls (n = 280) and telephone area code and prefix for the population-based controls (n = 259). Structured interviews were conducted in the homes of participants to obtain information on the history, frequency and duration of perineal use of talc, medical history and additional covariates of interest (menstrual and reproductive histories, family history and environmental exposures, such as consumption of alcohol, coffee and tobacco). Of 317 eligible cases, eight (2.5%) were excluded due to physician refusal, 30 (9.5%) due to patient refusal, 44 (13.9%) due to death or incapacitating illness and 47 (14.8%) due to non-invasive tumours, which left 188 (59.3%) for inclusion in the analysis. Among the controls, 68% of the women identified as eligible hospital controls (n = 354) and 71% of the women identified by telephone as eligible population-based controls (n = 329) agreed to participate. After excluding controls matched to cases with bordeline tumours, 280 hospital controls and 259 population controls were included in the analysis (Wu et al. 1988). Exposure to talc was categorized by type of application (perineum only, sanitary pads only, diaphragm only, any two types of application or all three

types of application), duration of use before tubal ligation (none, 1–9 years, ≥ 10 years, unknown) and frequency of use (none, 1–20 applications per month, > 20 applications per month, unknown). Conditional logistic regression was used to calculate the odds ratio for each exposure and to test for trend. Ninety-seven cases (51.6%) and 247 controls (45.8%) reported previous use of talcum powder on the perineum to yield an odds ratio of 1.40 (p = 0.06) after adjustment for parity. Since the odds ratios were similar when hospital-based and population-based controls were analysed separately, analyses using the combined group of controls were reported. After adjustment for parity and oral contraceptive use, the odds ratio for use of talc on the perineum only was 1.5 (95% CI, 0.8–2.6). No significant associations were observed with either individual or multiple types of perineal talc use, including the combination of use on the perineum, sanitary napkins and a diaphragm (odds ratio, 1.4; 95% CI, 0.9–2.0 for any two types of use versus 0.4; 95% CI, 0.0–2.9 for all three types combined). No significant trend was observed with duration of talc use on the perineum before tubal ligation or hysterectomy. Odds ratios were 1.6 (95% CI, 1.0–2.6) for 1–9 years of exposure and 1.1 (95% CI, 0.7–1.7) for more than 10 years of exposure. A non-significant trend of increased risk with increasing frequency of perineal use of talc was observed, with an overall odds ratio of 1.3 (95% CI, 0.9–1.9; p = 0.19) for 30 applications per month. When stratified by history of perineal use of talc (yes/no) and history of tubal ligation or hysterectomy (yes/no), women who had used talc perineally and but had not undergone surgery for sterilization had the highest risk for ovarian cancer (odds ratio, 1.3; 95% CI, 0.9–2.0). [Limitations of this study included the lack of information on talc use.]

Booth et al. (1989) reported results of a hospital-based case–control study of the risk for ovarian cancer conducted in 15 hospitals in London and Oxford (United Kingdom) from October 1978 to February 1983. Women aged 65 years or under at diagnosis and who were diagnosed within 2 years of the study interview were eligible for inclusion. A total of 280 potential cases were identified, interviewed and classified with respect to tumour histology. After excluding 45 women, 235 cases were included in the analysis. A total of 451 controls with the same age distribution as the cases were selected from the same 15 hospitals. Controls had a range of admission diagnoses; gastrointestinal disease (n = 105) and bone or joint disease (n = 70) were the most common. Women were excluded as controls if they had a history of bilateral oophorectomy or if they had a condition related to oral contraceptive use or other reproductive factors. Participation rates were not provided. Interviewers used a standard questionnaire to obtain information on reproductive and menstrual history, as well as exposure to exogenous estrogens, cigarettes and talc. Talc exposure was categorized according to the frequency of perineal use (never, rarely, monthly, weekly or daily) and whether it was used for storage of a diaphragm. Multiple logistic regression adjusted for age and socioeconomic status was conducted. Fifty-seven cases [24.3%] and 77 controls [17.1%] reported a history of weekly use of talc in the genital area, while 71 cases [30.2%] and 139 controls [30.8%] reported daily use. Weekly genital use of talc was associated with a significantly increased risk for ovarian cancer (odds ratio, 2.0; 95% CI, 1.3–3.4), while daily use was associated with a non-significant increase in risk (odds ratio, 1.3; 95% CI, 0.8–1.9), after adjustment for age and socioeconomic status. The p-value for trend with increasing frequency of use was of borderline significance (p = 0.05). The percentage of diaphragm users who reported storing their

diaphragm in talc was not significantly different between the cases (86%) and controls (81%). [Limitations of this hospital-based study included the 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.]

Harlow and Weiss (1989) conducted a study of perineal use of powder and the risk for borderline ovarian cancer in western Washington State, USA. Cases were 116 Caucasian women aged 20–79 years who had been diagnosed with borderline serous or mucinous epithelial ovarian cancer between 1980 and 1985, and who were identified by International Classification of Diseases-0 codes obtained from a population-based cancer-reporting system. Controls were identified from the same counties of residence by random-digit dialling. A total of 158 women with a similar age distribution to the cases and who had not undergone a bilateral oophorectomy were included in the analysis. Cases and controls were interviewed in-person to obtain information on reproductive, sexual and medical histories, as well as on perineal exposure to talc (through multiple open- ended questions about the history of powder use of the participant). Among all eligible cases and controls identified for the study, 68% of the cases and 74% of the controls were interviewed. The authors controlled for age (20–39, 40–59 or 60–79 years), parity (nulliparous or parous) and oral contraceptive use (ever/never). Exposure to talc was broadly categorized as 'any perineal use of dusting powders' (after bathing, on sanitary napkins or for diaphragm storage) and further subcategorized according to method of use (diaphragm storage only, after bathing only, sanitary napkins only, after bathing and on sanitary napkins and specific combinations of the various methods) and type of powder used (cornstarch only, baby powder only, talc unspecified (no combined use), deodorizing powder only or combinations of powders). Forty-nine cases [42.2%] and 64 controls [40.5%] reported a history of 'any perineal exposure to powder' to yield an odds ratio of 1.1 (95% CI, 0.7–2.1). When analysed by the type of powder used, the risk for borderline ovarian cancer was elevated only for perineal use of deodorizing powder alone (odds ratio, 3.5; 95% CI, 1.2–28.7) or in combination with other powders (odds ratio, 2.8; 95% CI, 1.1–11.7). No association was noted for the use of baby powder alone (odds ratio, 0.8; 95% CI, 0.4–1.9) or for combined use (odds ratio, 0.9; 95% CI, 0.5–2.0) or for other unspecified use of talc (odds ratio, 1.0; 95% CI, 0.4–2.4). No significant association was found between risk for borderline tumours and any individual method of powder use, including use after bathing, on sanitary napkins or for diaphragm storage. The authors reported no increase in risk with increasing number of days of powder use, although the data were not provided in the paper. [Limitations of this study included the incomplete information on powder use and its small size.]

Chen et al. (1992) (described in detail in 1.1.2.2) conducted a case–control study in Beijing, China, of several risk factors for epithelial ovarian cancer that included perineal exposure to talc (yes/no use of dusting powder to the lower abdomen or perineum for 3 or more months). The analysis was carried out on 112 newly diagnosed cases identified between 1984 and 1986 through the Beijing Cancer Registry and 224 age-matched community controls (two controls per case). Seven cases [6.3%] and five controls [2.2%] reported use of talc-containing powders which resulted in an odds ratio of 3.9 (95% CI, 0.9–10.6) after adjustment for

education and parity. [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), the limited 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.]

Harlow et al. (1992) analysed perineal exposure to talc and the risk for ovarian cancer among 235 cases and 239 controls in the Boston, MA metropolitan area (USA). Cases were diagnosed with ovarian cancer between June 1984 and September 1987 at one of 10 Boston hospitals and controls were identified from town registers listing the name, age and address of all residents in Massachusetts. All cases were Caucasian women aged 18– 76 years at diagnosis and were similar to the controls with respect to race, age and area of residence. Of 397 cases identified during the study period, 31% were not interviewed due to physician and/or patient refusal, death or change of address. After excluding women whose cancer diagnosis was not confirmed by an independent pathology review [9.4% of eligible cases], 235 women were included in the analysis. A total of 526 women were contacted as potential controls. Of these, 239 [45.4%] were interviewed, 25% could not be reached, 10% reported a previous bilateral oophorectomy and 19% did not wish to participate in the study. In-person interviews were conducted with cases and controls to obtain information on occupational history, medical and reproductive histories, dietary history, cigarette smoking and hygienic practices (use of douches, types of sanitary protection used, perineal exposure to talc). Exposure to talc was categorized on the basis of 'any' exposure, the method of application (dusting on sanitary napkins and/or underwear, via partner or application to diaphragm, dusting on perineum), the brand used, age at first use, duration and frequency of use. Total lifetime exposure to talc was estimated by cumulating the frequency of exposure and years of use to arrive at a summary measure of the total number of applications (< 1000, 1000–10 000, > 10 000). Covariates evaluated as potential confounders included age, education, marital status, religion, weight, use of oral contraceptives and parity; of these, age, education (< 12 years, > 12 years), marital status (never/ever), religion (Jewish, non-Jewish), weight (< 140 lb, ≥ 140 lb) and parity (0, 1–2, > 2) were included in all multivariable models. A history of 'any' perineal exposure to talc-containing powders was reported by 48.5% of cases and 39.3% of controls to yield an odds ratio of 1.5 (95% CI, 1.0–2.1). When the method of application was examined, only direct application to the perineum as a dusting powder was associated with a significant increase in risk (odds ratio, 1.7; 95% CI, 1.1– 2.7). Women who reported at least 30 applications of talcum powder per month had a significant increase in risk (odds ratio, 1.8; 95% CI, 1.1–3.0), while women with fewer applications per month did not. A significant positive trend was seen with number of monthly applications ($p = 0.046$). Women with at least 10 years of perineal exposure had a borderline significant increase in risk (odds ratio, 1.6; 95% CI, 1.0–2.7) and the p-value for trend was also of borderline significance ($p = 0.07$). Analyses stratified by age at first use indicated that women who first used talc genitally before the age of 20 years had the highest risk (odds ratio, 1.7; 95% CI, 1.1–2.7); those stratified by years since last use suggested that women with the most recent perineal use of talc (within the previous 6 months) had the highest risk (odds ratio, 2.3; 95% CI, 1.3–4.0). In an analysis

stratified by use before versus after 1960, women who reported some perineal use of talc before 1960 had a significantly elevated risk for ovarian cancer (odds ratio, 1.7; 95% CI, 1.1– 2.7), while women with exclusive genital use of talc after 1960 did not (odds ratio, 1.1; 95% CI, 0.6–2.1). Women who had used more than 10 000 lifetime applications had a borderline significant increase in risk (odds ratio, 1.8; 95% CI, 1.0–3.0). This was unchanged after excluding applications that occurred after tubal ligation or hysterectomy (odds ratio, 1.7; 95% CI, 1.0–3.0). However, when use of talc during non-ovulatory periods and after surgical sterilization was excluded, the increase in risk associated with more than 10 000 lifetime applications was significant (odds ratio, 2.8; 95% CI, 1.4–5.4). In analyses of each histological type and grade, the strongest associations were seen for endometrioid tumours (odds ratio, 2.8; 95% CI, 1.2–6.4) and tumours of borderline invasiveness (odds ratio, 2.4; 95% CI, 1.2–4.5) (Table 40).

Rosenblatt et al. (1992) conducted a hospital-based case–control study among 77 women who were hospitalized at Johns Hopkins Hospital in Baltimore, MD (USA) for ovarian cancer (cases) and 46 who were hospitalized for non-gynaecological, non- malignant conditions (controls). The cases were newly diagnosed with pathologically confirmed epithelial ovarian cancer between 1981 and 1985, the majority of whom were aged 40–69 years. Of 140 eligible cases, 108 (77.1%) were interviewed. Thirteen were subsequently excluded because no control was identified and 18 were excluded for an unspecified reason. Controls were matched to cases by age, race and date of diagnostic admission. Information on genital and respiratory exposure to fibre-containing substances (talc, asbestos and fibreglass), as well as potential confounders, was collected using a structured questionnaire which was administered in the hospital and by telephone. Covariates that were considered to be potential confounders included tobacco use, ‘ovulatory time period’, parity, family history of cancer, obesity, education, education of husband, previous history of cancer, marital status, religion and the use of oral contraceptives and other methods of contraception. Sources of genital fibre exposure (yes/no) included diaphragm use and dusting of either the perineum or sanitary napkins with talcum powder. Potential sources of respiratory fibre exposure (yes/no) included use of face or body powders containing talc, insulation installed at residence and living in the vicinity of or employment in a fibre-emitting industry (such as shipyard, asbestos or talc mine, asbestos/talc/fibreglass processing plant). A large percentage of both the cases (87%) and controls (88%) reported exposure to genital fibre, with an odds ratio of 1.0 (95% CI, 0.2–4.0) after adjustment for parity. 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. Odds ratios were also calculated for genital use of bath talc (odds ratio, 1.7; 95% CI, 0.7–3.9), use of talc on sanitary napkins (odds ratio, 4.8; 95% CI, 1.3–17.8) and use of talc on a diaphragm (odds ratio, 3.0; 95% CI, 0.8–10.8). No association was observed between risk for ovarian cancer and history of previous gynaecological or abdominal surgery that may have resulted in peritoneal exposure to talc. [Limitations of this study included the 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.]

Table 40: Perineal talc use and ovarian cancer risk: by tumour histology

References	No. of cases	Histology	Relative risk[a] (95% CI)
Harlow et al. (1992)	60	Serous[b]	1.4 (0.9–2.2)
	17	Mucinous	1.2 (0.6–2.5)
	18	Endometrioid	2.8 (1.2–6.4)
Chang and Risch (1997)	254	Serous[b]	1.3 (1.0–1.9)
	80	Mucinous	1.6 (1.0–2.6)
	74	Endometrioid	1.7 (1.0–2.8)
Cook et al. (1997)	131	Serous	1.7 (1.1–2.5)
	43	Mucinous	0.7 (0.4–1.4)
	36	Endometrioid	1.2 (0.6–2.3)
Cramer et al. (1999)	229	Serous invasive	1.7 (1.2–2.4)
	83	Mucinous	0.8 (0.4–1.4)
	130	Endometrioid/clear cell	1.0 (0.7–1.6)
Wong et al. (1999)	136	Serous	1.2 (0.7–2.1)
	11	Mucinous	1.5 (0.6–4.0)
	21	Endometrioid	1.4 (0.7–2.7)
Gertig et al. (2000)	76	Serous invasive	1.4 (1.0–1.9)
Mills et al. (2004)	42	Serous invasive	1.8 (1.1–2.8)
	10	Mucinous invasive	2.6 (0.9–7.4)
	14	Endometrioid	1.3 (0.6–2.6)

CI, confidence interval

[a] Any or ever use of talc

[b] Includes borderline and invasive serous tumours

Tzonou et al. (1993) conducted a hospital-based case–control study of risk factors for epithelial ovarian cancer in the Greater Athens region of Greece. The cases were 189 women under 75 years of age who underwent surgery for ovarian cancer at one of two cancer hospitals in Athens between June 1989 and March 1991. The controls were 200 women under 75 years of age who were residents of Greater Athens and who visited patients hospitalized in the same wards as the cases during the study period. Ninety per cent of the eligible cases and 94% of the eligible controls agreed to participate. In-hospital interviews were conducted to collect information on a range of demographic, socioeconomic and reproductive factors, as well as information on exposure to hair dyes, analgesics, tranquilizers and talc. Exposure to talc was assessed qualitatively as 'yes/no' application of talc in the perineal region. In multivariable analyses, models were adjusted for age in 5-year groups, education, weight, age at menarche, menopausal status, age at menopause, parity, age at first birth, tobacco smoking status, alcohol use, coffee consumption and the other exposures of interest (use of analgesics, tranquilizers and hair dyes). Application of talc to the perineal region was reported by six cases [3.2%] and seven controls [3.5%] to yield an odds ratio of 1.1 (95% CI, 0.3–4.0) after adjustment for the potential confounders. [Limitations of this hospital-based case–control study included the very low prevalence of perineal use of talc.]

Purdie et al. (1995) conducted a case–control study among women in the three most populous Australian states—Queensland, New South Wales and Victoria. Cases were women, aged 18–79 years, who had been

diagnosed with epithelial ovarian cancer between August 1990 and December 1993 at gynaecological oncology treatment centres in one of these three regions. Women were excluded if they had a metastatic tumour, were outside the eligible age range, could not be contacted, were too ill or were incapable of completing the questionnaire in conjunction with a trained interviewer (because of language difficulties or psychiatric conditions). Each case was confirmed by an independent pathological review of tissue specimens. Of 1116 cases identified during the study period, 201 (18%) were ineligible (e.g. due to a non-ovarian primary cancer or age at diagnosis). Among the 915 eligible cases, 824 (90%) agreed to participate and were interviewed. Reasons for non-participation included death before interview (50 cases), patient refusal (34 cases) and physician refusal (seven cases). Controls were identified from the electoral roll and were similar to the cases in age distribution and area of residence. Women were excluded as a control if they had a history of ovarian cancer or bilateral oophorectomy, could not be reached or could not complete the questionnaire. Among 1527 potential controls identified from the electoral roll, 1178 were located and found to be eligible (77%). Of these, 860 agreed to participate in the study (73% of the eligible controls). Reasons for ineligibility among the controls included failure to locate the individual (192), inability to complete the questionnaire due to language difficulties, a psychiatric condition, illness or death (105), previous bilateral oophorectomy (48) and age (four). Trained interviewers used a standardized questionnaire to collect information on medical, reproductive, family and occupational histories, as well as data on dietary factors and history of talc use. Questionnaires were administered face-to-face either in the clinic (for cases) or in the home of participant (for some cases and all controls). Covariates evaluated as potential confounders included parity, hysterectomy, tubal ligation, duration of oral contraceptive use, age, education, body mass index, tobacco smoking status, family history of cancer and multiple menstrual and reproductive factors. Talc use around the abdomen or perineum was reported by 56.7% of cases and 52% of controls to yield an odds ratio of 1.3 (95% CI, 1.0–1.5) after adjustment for parity. Although enrolment in the electoral roll is mandatory in Australia, the authors determined that 28 cases [3.4%] had never enrolled and the enrolment status could not be confirmed for 46 cases [5.6%]. The results did not change when the analyses were limited to cases with confirmed enrolment in the electoral role.

Green et al. (1997) evaluated the association between tubal ligation or hysterectomy and the risk for ovarian cancer using the Australian study population described by Purdie et al. (1995). [The analysis by Green et al. (1997) used the same number of cases but five fewer controls than Purdie et al. (1995).] Duration of talc use was calculated as age at first reported use until age at occurrence of the earliest of any of the following events: surgical sterilization, reported last use of talc, diagnosis or interview. A modest increase in risk for ovarian cancer was observed with peritoneal use of talc (odds ratio, 1.3; 95% CI, 1.1–1.6). Neither duration of talc use nor age at first use were associated with risk for ovarian cancer, although the relative risks (95% CI) were not provided and the duration categories evaluated were not specified. When compared with women with no history of genital exposure to talc and patent fallopian tubes, women with a history of talc use and no history of surgical sterilization had the highest risk for ovarian cancer (odds ratio, 1.3; 95% CI, 1.0–1.7), while women with a history of tubal ligation or hysterectomy and no talc use had the lowest risk

(odds ratio, 0.6; 95% CI, 0.5–0.8). [The primary limitation of this study was the restricted information on perineal use of talc.]

Shushan et al. (1996) examined the association between exposure to fertility drugs and the risk for ovarian cancer among 200 cases of epithelial ovarian cancer (164 invasive and 36 borderline) and 408 controls. All participants were living in Israel and were 36– 64 years of age at enrolment into the study. Cases were identified through the Israel Cancer Registry from January 1990 to September 1993. Among 287 women who met the eligibility criteria (histologically confirmed diagnosis, cancer diagnosed and reported during study period, born between 1929 and 1957 and alive at time of interview), 87 (30.3%) were excluded because of inability to locate the patient or physician (25%), illness (1%), refusal by the physician (1%) or refusal by the patient (3%). Controls were identified by random-digit dialling and were matched to the cases by geographical area. Women were eligible to be included as a control if they were born in the same period as the cases. Potential controls were excluded if they had a history of bilateral oophorectomy (1%). Of 2072 telephone calls that successfully reached a household member, approximately half of the households [47.8%] contacted had a potentially eligible woman who was at home. Of these, 16.2% refused to participate and 10.7% were excluded because the woman did not speak Hebrew. Trained interviewers administered a standard questionnaire to all cases and controls. The questionnaire collected detailed information on reproductive history, use of oral contraceptives and fertility drugs, as well as exposure to talc (never/seldom, moderate/a lot). Although the main association of interest was use of fertility drugs and the risk for ovarian cancer, the authors reported that 21 cases (10.5%) and 23 controls (5.6%) had a history of moderate or frequent use of talc, which yielded an unadjusted odds ratio of [1.97] (p = 0.04). [Limitations of this study included the 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.]

Chang and Risch (1997) analysed the association between perineal use of powder and the risk for ovarian cancer among 450 cases and 564 population controls from metropolitan Toronto and southern Ontario, Canada. Cases were diagnosed between November 1989 and October 1992 and were between the ages of 35 and 79 years at entry into the study. Of 631 cases identified during the study period, 71.3% (450) were interviewed and included in the analysis. Reasons for non-participation included death (8.7%), physician refusal (4.6%), severe illness (4.8%), loss to follow-up (2.7%) and patient refusal (7.9%). Potential controls were identified through records of the Ontario Ministry of Finance based on their residence and age, were matched to cases within 15-year age groups and were excluded from the study if they had a history of bilateral oophorectomy more than 1 year before entry into the study. Among 873 eligible controls identified, 309 [35.4%] did not participate. Reasons included participant refusal (30.2%), illness (1.9%) or loss to follow-up (3.2%). Interviewers administered a standard questionnaire during an in-home interview to obtain information on the history, frequency and duration of use of talcum and cornstarch powder, as well as multiple medical and reproductive covariates of interest. Talc exposure was categorized on the basis of ‘any’ exposure in the perineal area, on the method of application (directly to the perineum after bathing or showering, dusting on sanitary napkins), on the frequency of application (< 10, 10–25, > 25 applications per

month) and on the duration of exposure (< 30, 30–40, > 40 years of use). Multiple logistic regression was used in the analyses, with adjustment for age, duration of oral contraceptive use, parity (defined as the number of full-term pregnancies), duration of lactation for each pregnancy, history of tubal ligation or hysterectomy and family history of breast or ovarian cancer. Forty-four per cent of cases and 36% of controls reported 'any' talc use in the perineal area to yield an odds ratio of 1.4 (95% CI, 1.1–1.9). Among the specific types of talc exposure, application to the perineum after bathing was associated with a borderline significant increase in risk (odds ratio, 1.3; 95% CI, 1.0–1.7), while application on sanitary napkins (a less common use in this study population) was associated with an elevated but non-significant increase in risk (odds ratio, 1.3; 95% CI, 0.9–2.0). A borderline significant trend was seen with increasing duration of exposure to talc (odds ratio per 10 years of exposure, 1.1; 95% CI, 1.0–1.2), but not with increasing frequency of exposure. An analysis of duration by category (< 30, 30–40, > 40 years) did not suggest a dose–response relationship (odds ratios of 1.0; 1.7; 95% CI, 1.1–2.6; 1.4; 95% CI, 1.0–2.2 and 0.9; 95% CI, 0.5–1.4, respectively). Use of cornstarch in the perineal area, either alone or in conjunction with occasional talc, was not associated with the risk for ovarian cancer, although prevalence of use was low (less than 2% of subjects). To evaluate exposure pre- and post-1970, as well as exposure pre- and post-tubal ligation or hysterectomy, the authors assumed that participants initiated perineal use of after-bath talc at the age of 20 years. A similar, non-significantly elevated, risk for ovarian cancer was seen for use pre- and post-1970. A higher odds ratio was seen for use of after-bath talc before tubal ligation or hysterectomy (odds ratio, 1.1; 95% CI, 1.0–1.2) than for use after these surgical procedures (odds ratio, 1.0; 95% CI, 0.8–1.3). These estimates did not change when different starting ages, between 15 and 24 years, were used in the analysis. The authors also evaluated the association between perineal use of talc and invasive and borderline cancers separately, and found that the risk was elevated for both tumour types but was significant only for invasive tumours. In addition, risk was similar across the major histological subtypes of ovarian cancer (serous, mucinous, endometrioid) (see Table 40). [Limitations of this study included the lack of information on use of talc.]

Cook et al. (1997) evaluated the association between use of genital powders or deodorants and the risk for ovarian cancer in a case–control study conducted in three counties of western Washington State, USA. Cases were aged 20–79 years at diagnosis, were diagnosed with borderline or invasive epithelial ovarian cancer between 1986 and 1988 and were identified using the population-based Cancer Surveillance System of western Washington. Controls were identified using random-digit dialling, were residents of the three counties of interest and were similar in age to the cases. Among 512 eligible cases identified, 329 were interviewed (64.3%) and 313 were included in the analysis [61.1%]. A total of 183 eligible cases were not interviewed due to death (104), physician or patient refusal (73) or loss to follow-up (six). An additional 16 cases who were interviewed were excluded from the analysis because of non-white race (seven) and unknown genital use of powder (nine). Among 721 women identified as potential controls, 521 were interviewed (72.3%) and 422 were included in the analysis [58.5%]. Reasons for excluding interviewed controls from the analysis included: non-white race (28), age greater than 79 years (five), history of bilateral

oophorectomy (58), unknown oophorectomy status (four) and unknown genital use of powder (four). Information on powder use, including the type, method, frequency and duration of use, and the covariates of interest was collected during in-person interviews. Covariates considered to be potential confounders in multivariable analyses included age, education, income, marital status, body mass index, oral contraceptive use and parity. A history of 'any' lifetime genital powder use (perineal dusting, diaphragm storage, use on sanitary napkins or use of deodorant spray) was reported by 50.8% of cases and 39.3% of controls to yield an odds ratio of 1.5 (95% CI, 1.1–2.0) after adjustment for age. Among the individual methods of genital use of powder, risk was significantly elevated only for exclusive perineal dusting (odds ratio, 1.8; 95% CI, 1.2–2.9) after adjustment for age. In analyses adjusted for age and other types of genital use of powder, both perineal dusting (odds ratio, 1.6; 95% CI, 1.1–2.3) and genital deodorant spray (odds ratio, 1.9; 95% CI, 1.1–3.1) were associated with risk for ovarian cancer, while use of powder on a diaphragm or on sanitary napkins was not associated with an increased risk. There was no evidence of an increasing trend in risk with greater duration of perineal dusting, but 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. The effect estimates did not change materially when perineal use of dusting powder after the date of tubal ligation or hysterectomy was excluded. Risk was significantly elevated among women with any history of perineal dusting before 1976 (odds ratio, 1.8; 95% CI, 1.1– 2.9), but the authors were unable to evaluate risk for use exclusively after 1976 due to the small number of women (four cases and 10 controls) who had had this exposure. Among the individual types of powder evaluated (cornstarch, talcum powder, baby powder, deodorant powder, scented body/bath powder), risk for ovarian cancer was non- significantly elevated for 'any' use of talcum powder (odds ratio, 1.6; 95% CI, 0.9–2.8) and bath/body powder use (odds ratio, 1.5; 95% CI, 0.9–2.4) after adjustment for age and other types of powder use (yes/no). The authors also evaluated the association between any genital use of powder and the risk for the major histological subtypes of ovarian cancer (see Table 40). Risk was significantly elevated for serous tumours (odds ratio, 1.7; 95% CI, 1.1–2.5) and all other tumour types (odds ratio, 1.8; 95% CI, 1.1–2.8) but not for mucinous or endometrioid tumours. [Limitations of this study included the relatively low participation rates among the cases and controls.]

Eltabbakh et al. (1998) compared risk factors among 50 cases of primary extra- ovarian peritoneal carcinoma (the 'study' group) and 503 cases of primary epithelial ovarian cancer (the 'control' group) treated at Roswell Park Cancer Institute in Buffalo, NY (USA), between October 1982 and October 1996. No healthy controls were enrolled in this study. Diagnoses were reviewed by staff in the Division of Pathology (study and control groups) and were confirmed by a single pathologist as part of another study (study group only). Information on reproductive history, menstrual history, use of hormones and contraceptives and personal hygiene was collected through a self-administered, 44-item questionnaire which all patients were asked to complete during the hospital admission process. All women who returned a questionnaire were eligible to be included in the study. Among these patients, the overall questionnaire response rate was 60%. Response was

inversely correlated with severity of disease and response rates were similar for the two diagnoses included in this study. Because data on perineal talc use was missing for 37 patients in the 'control' group, only 466 ovarian cancer patients were included in the analysis. 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] $p = 0.003$). Among the other characteristics examined, only age and age at menarche differed significantly in the two groups. [Limitations of this study included the 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 the quality of the responses, and the lack of a 'healthy' comparison group.]

Godard et al. (1998) evaluated risk factors for familial and sporadic ovarian cancer in a population of French Canadian women in Montréal, Quebec (Canada). Of 231 cases who were identified between 1995 and 1996 at two gynaecological oncology clinics in Montréal, 183 (79.2%) were interviewed and 170 (73.6%) were included in the analysis. Reasons for non-inclusion were death (n = 21), refusal/unavailability to participate (n = 12), loss to follow-up (n = 15) and tumours were non-epithelial in origin (n = 13). All cases were between the ages of 20 and 84 years at diagnosis, with a mean age at diagnosis of 53.7 years and a mean age at interview of 55.9 years. Controls were identified using a modified random-digit dialling method and were frequency-matched to cases by age (within 1 year) and French Canadian ethnicity. The mean age at interview for the controls was 56.7 years. Among 750 households contacted regarding participation in the study, 66.7% (n = 500) either did not have an eligible female resident or did not reply to the researchers' inquiries and 10.7% refused to participate. A total of 170 women were interviewed and included in the analysis as controls. A standardized 57-item questionnaire was used to obtain information on the family, medical and reproductive history of each participant. Cases were interviewed either by telephone (30%) or in the study clinics (70%). No information was given on the methods of interview for control subjects. Information on family history of cancer was collected to determine whether risk factors differed for the sporadic and familial cases of ovarian cancer. Familial cases were those patients who had one or more family members (first, second or third degree relatives) with breast cancer diagnosed before 55 years of age or ovarian cancer diagnosed at any age. Sporadic cases were those patients who had no family members with breast cancer diagnosed before 55 years of age or with ovarian cancer diagnosed at any age. Perineal exposure to talc was assessed qualitatively (ever/never, with 'never' as the baseline). Covariates that were considered to be potential confounding variables were 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 and previous breast or abdominal surgery. Talc exposure was more common in cases than controls, with 10.6% of the cases and 4.7% of the controls reported perineal use of talc ($p = 0.06$). No difference between perineal use of talc was reported in the familial and sporadic cases ($p = 0.79$). Multivariate analyses were performed comparing all cases, (all, sporadic, familial) with controls. In these analyses, perineal use of talc was associated with a non-significant increase in the total risk for ovarian cancer (odds ratio, 2.5; 95% CI,

0.9–6.6; $p = 0.07$). Risk was similarly non-significantly elevated for sporadic (odds ratio, 2.5; 95% CI, 0.9–7.1) and familial cases (odds ratio, 3.3; 95% CI, 0.9–12.4) compared with the controls. [Limitations of this study included its 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.]

Cramer et al. (1999) analysed the association between genital exposure to talc and the risk for primary epithelial ovarian cancer among 563 cases and 523 controls residing in eastern Massachusetts and New Hampshire, USA. Cases were identified between May 1992 and March 1997 through hospital tumour boards or statewide cancer registries. Among 1080 cases diagnosed in this period (including borderline tumours), 203 (18.8%) were excluded due to death, change of address, inability to speak English, no telephone in residence or a non-ovarian primary cancer. Of the 877 eligible cases remaining after these exclusions, 563 (64%) were included in the analysis. The remaining 314 cases were excluded because of physician refusal (n = 126) and patient refusal (n = 136). Pathology reports were reviewed to confirm the diagnoses for all cases, and slides were requested and reviewed in the case of discrepancies between the reported histology and the histology assigned based on the pathology report review. Controls were identified by random-digit dialling and town resident books (to identify additional women over the age of 60 years who lived in Massachusetts) and were frequency-matched to cases by age (within 4 years) and location of residence. Of the potentially eligible controls, 72% of those identified by random-digit dialling and 49% of those identified through town books agreed to participate. All study participants were interviewed in-person using a standardized questionnaire to obtain information on their medical and reproductive histories, family history and personal habits. The questionnaire also asked multiple questions on powder use, including route of exposure (application to non-genital areas, application to perineum, sanitary napkins or underwear, husband's use of powders in his genital area), brand of powder used (talc, cornstarch), age at first use, duration and frequency of use (< 30, 30–39, > 40 uses per month). Participants were asked about exposures that occurred at least 1 year before the date of diagnosis (cases) or the date of interview (controls). The results were adjusted for the following potential confounding variables: age, state of residence, body mass index, parity, oral contraceptive use, family history of breast or ovarian cancer and history of tubal ligation. The prevalence of talc use was higher among cases than controls; 44.6% of cases and 36.1% of controls reported 'any' use of talc (included use in both genital and non-genital areas) and 27.0% of cases and 18.2% of controls reported 'genital' use of talc (included dusting of perineum/sanitary napkins/underwear, either exclusively or in combination). Talc use in non-genital areas was not associated with risk when compared with women who did not use personal powder (odds ratio, 1.1; 95% CI, 0.8–1.5). However, genital use of talc was associated with a significant 60% increase in risk (odds ratio, 1.6; 95% CI, 1.2–2.2). Women who reported more than one method of talc use in the genital area had an even greater risk for ovarian cancer (odds ratio, 2.2; 95% CI, 1.3–3.6). No association was observed between genital use of talc and risk for ovarian cancer among women who had undergone tubal ligation after adjustment for age (odds ratio, 1.0; 95% CI, 0.5–2.1). Because of the low prevalence of use (< 1% of the study population) of cornstarch, evaluation of this product

was uninformative. When women who had been exposed to powder only in non-genital areas were excluded from the analysis, no linear trend was observed between risk for ovarian cancer and age at first genital use of talc, duration of use, frequency of use or total number of lifetime applications. However, when non-genitally exposed women were included in the analysis, a significant linear trend was observed with increasing number of lifetime applications, after talc applications that occurred during non-ovulatory years or after tubal ligation or hysterectomy were excluded ($p = 0.02$). Additional findings of interest included: a non-significant increase in risk among married women with no personal talc use whose husbands had used talc for genital hygiene (odds ratio, 1.5; 95% CI, 0.9–2.5); and a stronger association between genital use of talc and risk for ovarian cancer among women who had used talc before their first live birth (odds ratio, 1.6; 95% CI, 1.1–2.3) than for women who had used it exclusively after their first live birth (odds ratio, 1.0; 95% CI, 0.4–2.5). The association with genital use of talc was strongest for serous invasive tumours (odds ratio, 1.7; 95% CI, 1.2–2.4). No association was observed for endometrioid/clear-cell (odds ratio, 1.0; 95% CI, 0.7–1.6) or mucinous tumours (odds ratio, 0.79; 95% CI, 0.4–1.4) (see Table 40).

Wong et al. (1999) reported the results of a case–control study conducted at Roswell Park Cancer Institute, Buffalo, NY (USA) of 499 cases treated between October 1982 and October 1992 (largely those reported by Eltabbakh et al., 1998) and 755 hospital-based controls. The controls were randomly selected from a registry of patients who were being treated for non-gynaecological malignancies and were frequency-matched to cases by age at diagnosis (within 5 years). The most common diagnoses among controls were colorectal (43.3%) and skin cancers (34.5%) and leukaemia (17.7%). All participants completed the self-administered, 44-item questionnaire that all patients were asked to complete during the hospital admission process. All analyses were adjusted for age at diagnosis, parity, oral contraceptive use, tobacco smoking, family history of ovarian cancer, age at menarche, menopausal status, income, education, geographical location and history of tubal ligation or hysterectomy. The analysis was restricted to 462 cases and 693 controls with information on perineal use of talc. ‘Ever’ use of talc (genital or non- genital) was reported by 47.8% of the cases and 44.9% of the controls, while use of talc in the genital or thigh area was reported by 34.0% of the cases and 32.2% of the controls. There was no association between any method of talc use and the risk for ovarian cancer after adjusting for several potentially confounding variables. The adjusted odds ratio for talc use in the genital or thigh area was 1.0 (95% CI, 0.8–1.3). Duration of talc use was similar in the cases and controls, and no association between talc use and the risk for ovarian cancer was found for any duration category. No significant association was observed between talc use and any of the major histological subtypes of ovarian cancer (see Table 40); the odds ratio for serous cystadenocarcinoma was 1.2 (95% CI, 0.7–2.1). No evidence was found of effect modification by history of tubal ligation or hysterectomy. Among women who had not undergone tubal ligation or hysterectomy, the odds ratio for the association between talc use and risk for ovarian cancer was 1.2 (95% CI, 0.8–1.6) while among women who had undergone tubal ligation or hysterectomy, the odds ratio was 0.8 (95% CI, 0.5–1.2). [Limitations of 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.]

Ness et al. (2000) examined whether factors related to an inflammatory response of the ovarian epithelium (such as exposure to talc, endometriosis, cysts and hyperthyroidism) played a role in the risk for ovarian cancer. The study was conducted among 767 recently diagnosed cases of epithelial ovarian cancer and 1367 population- based controls. Cases were aged 20–69 years and were identified between 1994 and 1998 at 39 hospitals in the Delaware Valley region (USA). Of 1253 potentially eligible cases, 61.2% were interviewed and included in the analysis. Reasons for excluding women from the study included: diagnosis more than 6 months before the interview (n = 296), severe illness or death (n = 69), unavailability of contact information (n = 15), physician refusal (n = 14) or patient refusal (n = 92). Controls were identified through random-digit dialling (for controls ≤ 65 years of age) and Health Care Financing Administration lists (for controls 65–69 years of age) and were frequency-matched to cases by age and location of residence. Overall, 72% of the eligible potential controls agreed to participate in the study. A pathological review was conducted for a subset of the cases (n = 120). When compared with the original diagnosis, the central review was 95% concordant for invasiveness and 82% concordant for cell type. The original pathological diagnosis was used in the analysis for all cases. A standardized, 1.5-hour interview was conducted in the homes of the participants to collect information on menstrual and reproductive history, sexual activity, use of contraceptives, history and duration of talc use (genital and non-genital applications and exposure via male sexual partners). Talc use was categorized according to the method of application (never, feet, genital/rectal, sanitary napkins, underwear, diaphragm or cervical cap, or male partner) and duration of exposure (< 1 year, 1–4 years, 5–9 years, > 10 years). Unconditional logistic regression adjusted for age, parity, race, family history of ovarian cancer, oral contraceptive use, tubal ligation, hysterectomy and lactation was used in all analyses. A history of talc use in the genital/rectal area was reported by 161 cases [21.0%] and 219 controls [16.0%] to yield an adjusted odds ratio of 1.5 (95% CI, 1.1–2.0). Significant associations were also observed for the use of talc on sanitary napkins (odds ratio, 1.6; 95% CI, 1.1–2.3) and on underwear (odds ratio, 1.7; 95% CI, 1.2–2.4). The use of talc on the feet, arms or breasts was associated with a significant 40% increase in risk; however, women may also have used talc on more than one area of the body, including the genital and/or rectal area. Use of talc on diaphragms or cervical caps and use by a male sexual partner were not associated with the risk for ovarian cancer. There was no clear trend between risk for ovarian cancer and increasing duration of use of talc on the genital and/or rectal area or feet. Adjusted odds ratios of 2.0 (95% CI, 1.0–4.0), 1.6 (95% CI, 1.1–2.3), 1.2 (95% CI, 0.8–1.9) and 1.2 (95% CI, 1.0–1.5) were observed for < 1 year, 1–4 years, 5–9 years and > 10 years of use, respectively. [Limitations of this analysis included the sparse information on talc use. In analyses of duration, the use of talc on the feet was also included as an exposure. The relatively low participation rates among cases was also a limitation of the study.]

Langseth and Kjaerheim (2004) (described in detail in 1.1.2.2) evaluated the association between employment in the pulp and paper industry in Norway and the risk for ovarian cancer. In addition to the assessment of occupational exposure, information was collected on hygienic use of talc and potential

confounders for a subset of the cases and controls during a personal interview conducted at the mills or by telephone. Exposure to hygienic talc products was categorized as ever/never for personal use on diapers, sanitary napkins, underwear or husband's use in the genital area. Thirty-five cases and 102 of the eligible controls or their next of kin agreed to an interview and an additional 19 women who were not cases were interviewed and included in secondary analyses as supplementary controls. A family member completed the interview (due to the death of the case or control) for 25 of the cases and 31 of the controls. Use of talc on the genital area was reported by 12 cases and 53 controls to yield an odds ratio of 1.2 (95% CI, 0.4– 3.2). [The primary limitations of this analysis were the small number of cases, the small percentage of cases and controls who were interviewed to obtain information on the covariates of interest and use of surrogate respondents to obtain information on covariates for the deceased cases and controls. The Working Group noted that hygienic exposure to talc was assessed retrospectively in the nested case–control study.]

Mills et al. (2004) evaluated the association between perineal exposure to talc and the risk for ovarian cancer in an ethnically diverse population from 22 counties of central California, USA. The study included 256 incident cases diagnosed between 1 January 2000 and 31 December 2001 and identified through two regional cancer registries using rapid case ascertainment procedures and 1122 controls identified by random-digit dialling. Controls were frequency-matched to the cases by age and ethnicity. Pathology reports were reviewed centrally for a subset of the cases to confirm the diagnosis, subtype and invasiveness of each cancer. Potential controls were ineligible for inclusion in the study if they were under 18 years of age, were not a resident of the counties of interest or if they had a history of epithelial ovarian cancer or bilateral oophorectomy. Among 652 cases identified during the study period, 263 (40.3%) were excluded due to: language or hearing difficulties (n = 17), death (n = 76), physician refusal (n = 10), severe illness (n = 41) or unavailability of current contact information (n = 119). Of the 389 eligible cases who were contacted regarding participation in the study, 256 (65.8%) agreed to participate and were interviewed. Of a total of 2327 potential controls, 740 (31.8%) were excluded from the study due to: age (n = 80), location of residence (n = 21), language difficulties (n = 10), previous bilateral oophorectomy (n = 252), severe illness (n = 19) or change of address or telephone number or inability to contact the woman after repeated attempts (n = 358). Of the 1587 potential controls who were contacted and found to be eligible, 1122 (70.7%) agreed to participate and were interviewed. All cases and controls were interviewed by telephone to obtain information on their medical history, covariates of interest and history of perineal exposure to talc, including the frequency, duration and calendar years of use. Information on talc use was unavailable for seven cases and 17 controls; thus, the final study population for this analysis included 249 cases and 1105 controls. For the final models, unconditional logistic regression adjusted for age, race/ethnicity, duration of oral contraceptive use and breastfeeding was used. Additional covariates considered to be potential confounders included family history of breast cancer or ovarian cancer, parity, history of pregnancy, body mass index, hysterectomy, tubal ligation and duration of postmenopausal use of hormones. A history of perineal talc use was reported by 42.6% of the cases and 37.1% of the controls to yield an adjusted odds ratio of 1.4 (95% CI, 1.0–1.9). A significant trend (p = 0.015) with increasing frequency of talc use was observed. The greatest

risk for ovarian cancer was observed among women with the highest frequency of use (odds ratio, 1.7 for use 4–7 times per week; 95% CI, 1.1–2.6). There was a borderline significant trend with increasing duration of use ($p = 0.045$). The highest risk was observed among women with 4–12 years of use (odds ratio, 1.9; 95% CI, 1.2–3.0) and elevated but non-significant risks were seen among women with longer durations of use with odds ratios of 1.5 (95% CI, 0.9–2.3) and 1.2 (95% CI, 0.7–2.1) for 13–30 and > 30 years of use, respectively. A borderline significant trend was noted for cumulative talc use (frequency times duration of use), although this was also not clear-cut ($p = 0.051$). The highest risks were observed in the second and third quartiles of cumulative talc use. When examined according to the time of use, the risk was higher among women who had first used talc after 1975 (odds ratio, 1.9; 95% CI, 1.3–2.9) than among those who had first used talc before or during 1975 (odds ratio, 1.2; 95% CI, 0.8–1.8). Risk was also higher among women who were aged 20 years or more at first talc use than among those who were under 20 years of age and among women who initiated talc use after their first birth than among those who had some use before their first birth. When time since last use was examined, women who had last used talc 1– 2 years previously had the highest risk (odds ratio, 2.4; 95% CI, 1.4–4.1); women who had last used it 3–20 years previously had an elevated but non-significant risk for ovarian cancer (odds ratio, 1.6; 95% CI, 0.9–2.7). Modification of the association between perineal use of talc and risk for ovarian cancer by tubal ligation, hysterectomy, parity, oral contraceptive use, postmenopausal use of hormones and body mass index was also evaluated. Risk was higher among women who had not had tubal ligation (odds ratio, 1.5; 95% CI, 1.1–2.2) than among those who had (odds ratio, 0.9; 95% CI, 0.5–1.7), although the interaction was not statistically significant. Risk was also higher among women who had ever been pregnant (odds ratio, 1.4; 95% CI, 1.1–2.0) than among those who had never been pregnant (odds ratio, 0.9; 95% CI, 0.4–2.3) and among women who had no history of oral contraceptive use (odds ratio, 1.6; 95% CI, 1.0–2.6) than among those who had used oral contraceptives (odds ratio, 1.3; 95% CI, 0.9–1.8). No evidence was found of a modification of effect by hysterectomy status, body mass index or postmenopausal use of hormones. [Limitations of this study included the 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.]

1.1.3 In vitro data (e.g. in vitro germ cell and somatic cell mutagenicity studies, cell transformation assays, gap junction intercellular communication tests)

1.1.3.1 Litton Bionetics, 1974

Study reference:

Mutagenic evaluation of compound FDA 71-43, talc. Report No. FDABF-GRAS-302. NTIS Report PB245458. Prepared for the Food and Drug Administration.

Litton Bionetics, Inc.

RL 2 (predates GLP)

Detailed study summary and results:

Test type: Host-mediated bacterial reverse mutation test and in vitro mammalian chromosomal aberration test

In two host-mediated mutagenicity tests, ICR mice (n = 10, male) were dosed with talc (0, 30, 300, 3000, 5000 mg/kg bw, once or daily for 5 days) via gavage. No significant increase in mutations or recombinant frequencies were noted in Salmonella strains TA-1530 and G-46 or Saccharomyces D3, respectively, at the dose levels tested.

Human embryonic lung cells (WI-38; 5×10^5 cells per condition) were incubated with talc (0, 10, 100, 200, 300, 400, 500, 1000 and 5000 µg/ml; suspended in 0.85% saline) in cytotoxicity assays. It was introduced into tubes containing WI-38 cells in a logarithmic phase of growth. The cells were observed for cytopathic effect and the presence of mitosis at 24 and 48 h. A cytopathic effect and inhibition of mitosis were observed at ≥400 and ≥300 µg/ml, respectively. As a follow-up, cytogenicity of talc was examined in WI-38 cells at 2, 20 and 200 µg/mL and at 24, 48 and 72 h. No chromosomal aberrations were observed.

1.1.3.2 Fujita et al., 1988

Study reference:

Mutagenicity test of food additives with Salmonella typhimurium TA97 and TA102 (III)

H. Fujita, M. Nakano, M. Sasaki

Ann. Rep. Tokyo Metr. Res. Lab. P.H. (1988),39, p. 343-350

RL 2

Detailed study summary and results:

Test type: Bacterial reverse mutation test

Original study report in Japanese.

Mutagenicity of talc (purity unknown; 0, 0.1, 0.5, 1, 5 and 10 mg talc per plate; dissolved in DMSO) was investigated in *Salmonella typhimurium* TA97 and TA102, with or without S9 mix. No mutagenic activity was detected for talc.

1.1.3.3 Endo-Capron et al., 1993

Study reference:

In vitro response of rat pleural mesothelial cells to talc samples in genotoxicity assays (sister chromatid exchanges and DNA repair)

S Endo-Capron, A Renier, X Janson, L Kheuang, M C Jaurand

Toxicol. In Vitro. (1993) Jan;7(1):7-14

DOI: 10.1016/0887-2333(93)90107-g.

RL 2 (no GLP)

Detailed study summary and results:

Test type: Unscheduled DNA synthesis (UDS) and sister chromatid exchanges (SCE) assays

The talc samples (French talc (no. 7841), Italian talc (no. 5726) and Spanish talc no. (5725); purity 90-95%) used consisted of particles of respirable size in order to test the effect of particles likely to be deposited in the lung. Genotoxicity was tested in cultures of rat pleural mesothelial cells (RPMC) using genotoxicity assays for unscheduled DNA synthesis (UDS) and sister chromatid exchanges (SCEs). Cells were treated with talc for 24 h for the UDS assay or 48 h for the SCE assay, at 0, 10, 20, 50 µg/m^2 or 0, 2, 5, 10, 15 µg/cm^2, respectively. The effects were compared with those obtained with negative controls (attapulgite and anatase) and positive controls (chrysotile and crocidolite asbestos). In contrast to asbestos, none of the talc samples, nor the negative controls, induced enhancement of UDS or SCEs in treated cultures in comparison with the untreated cultures.

1.1.3.4 Harper et al., 2020

Study reference:

Talcum powder induces malignant transformation of human primary normal ovarian epithelial cells but not human primary normal peritoneal fibroblasts

A.K. Harper, R. Fan, R. Majed, N. King, R.T. Morris, G.M. Saed

Gynecologic Oncology 159 (2020) 79-359

DOI: 10.1016/j.ygyno.2020.05.185

RL 4 (poster abstract)

Detailed study summary and results:

Test type: Cell transformation assay

Talcum baby powder (Johnson & Johnson, NJ, #30027477, Lot#13717RA) or titanium dioxide (TiO_2) were suspended in PBS. Human primary normal ovarian epithelial cells (Cell Biologics) and human primary peritoneal fibroblasts were treated in triplicate with 100 and 500 µg/ml of talcum powder or TiO_2 as a control for 72 hours before assessment with cell transformation assay.

Treatment with talcum powder resulted in formation of colonies, indicating cell malignant transformation in a dose-dependent manner. There were no colonies formed in untreated ovarian cells or control ovarian cells at either dose. Interestingly, there were no colonies formed in normal fibroblasts treated with talcum powder. Treatment with talcum powder significantly increased number of transformed ovarian cells by 11% and 20% in the 100 and 500 µg/ml doses, respectively ($p < 0.05$). There were no detectible transformed cells when treated with TiO_2. Data were analysed with paired *t*-tests.

1.1.4 Other data (e.g. studies on mechanism of action)

1.1.4.1 Chamberlain and Brown, 1978

Study reference:

The cytotoxic effects of asbestos and other mineral dust in tissue culture cell lines

M. Chamberlain, R.C. Brown

Br J Exp Pathol (1978) 59:183–189

PMID:656318

RL 2

Detailed study summary and results:

Test type: Experimental study

Cytotoxicity was determined in V79-4 Chinese hamster lung cells by cloning efficiency from a single cell suspension. 200 cells were seeded into Petri dishes along with talc. Italian talc (purity not stated) was used and was a respirable fraction prepared from a commercial cosmetic grade. The surviving cells were allowed to grow and form colonies for 6-7 days and then fixed and stained. Talc was not toxic at ≤50 µg/ml in V79-4 Chinese hamster lung cells.

1.1.4.2 Woodworth et al, 1982

Study reference:

Comparative effects of fibrous and nonfibrous minerals on cells and liposomes

C.D. Woodworth, B.T. Mossman, J.E. Craighead

Environ Res (1982) 27:190–205

DOI:10.1016/0013- 9351(82)90070-6

RL 2

Detailed study summary and results[4]:

Test type: Experimental study

Effects of talc (99% pure, <1% dolomite, quartz and chlorite, nonfibrous, pseudohexagonal plates; mean size ~1.1-2.0 µm) on cellular and artificial membranes were examined in monolayer cultures of Syrian hamster tracheal epithelial cells, suspensions of sheep erythrocytes (RBC) and preparations of phospholipid cholesterol vesicles. The concentration of talc required to cause 50% haemolysis of red blood cells was 6.5 mg/ml, which is more than 50-fold that of chrysotile. A concentration of 0.1 mg/ml (24 h incubation) talc caused 35% release of ^{51}Cr from Syrian hamster tracheal epithelial cells labelled with radioactive sodium chromate, as measure for cytotoxicity; the concentration was two-fold that required for chrysotile. The epithelial cells phagocytized the particles, as demonstrated by scanning electron microscope (SEM) and phase-contrast microscopy. This process was evident after 4 h, but more pronounced after 24 h. Talc enhanced permeability of liposomes (as measured by release of CrO_4^{2-}) following an 1-h exposure in a dose-dependent manner up to a maximum of ~18% release at 10 mg/ml.

1.1.4.3 Davies et al, 1983

Study reference:

[4] Adopted from IARC (2010)

Cytotoxicity of talc for macrophages in vitro

R. Davies, J.W. Skidmore, D.M. Griffiths, C.B. Moncrieff

Food Chem Toxicol (1983) 21:201–207

DOI: 10.1016/0278-6915(83)90237-5

RL 2

Detailed study summary and results[4]:

Test type: Experimental study

Effects of seven different types of cosmetic-grade talcs (Indian Finex, Italian 00000, micronized Italian 00000, Spanish SS and Australian West Side; purity ≥90%; mean size 0.3-20 µm) and two other talc types (French OXO containing 30-35% w/w chlorite and Chinese No. 1 containing 1.3% w/w amphiboles) were examined on mouse peritoneal macrophages in vitro. Macrophages were exposed to seven specimens of high-purity talcs and the release of lactate dehydrogenase and β-glucuronidase was measured. These enzymes are produced by macrophages after they digest materials that can induce fibrosis and chronic inflammation. Enzyme release after exposure of macrophages to quartz, a known fibrogenic dust, and magnetite, a non-fibrogenic dust, was also measured. Quartz caused the greatest cytotoxic reaction in vitro: the amount of enzyme released increased with the dose. Magnetite had no effect. All seven talc specimens were cytotoxic to the macrophages: the levels of enzymes released were dose-related but were lower than those observed after exposure to quartz. The results show that talc is cytotoxic to macrophages and may be able to induce fibrosis and chronic inflammation in animals. However, the macrophage response to talc appears to be weaker than that for other fibrogenic dusts such as quartz, and the response of macrophages to talc may be different in vivo.

1.1.4.4 Nasreen et al, 1998

Study reference:

Talc-induced expression of C-C and C-X-C chemokines and intercellular adhesion molecule-1 in mesothelial cells

N. Nasreen, D.L. Hartman, K.A. Mohammed, V.B. Antony

Am J Respir Crit Care Med (1998) 158:971–978

DOI: 10.1164/ajrccm.158.3.9801097

RL 2

Detailed study summary and results:

Test type: Experimental study

Confluent primary human pleural mesothelial cells (PMC) were treated with talc (particle size 2.1 µm; purity not stated; 0, 2, 4, 8, 16, 32 and 64 µg/cm^2) for 24 and 72 h. Glass beads similar in size to talc were included as control. A dose-dependent reduction in cell viability (trypan blue dye exclusion) was observed after 72 h (>90% up to 32 µg/cm^2, 75% at 64 µg/cm^2), and after 24 h, a dose-dependent increased production of interleukin-8 (IL-8) was noted up to 4 µg/cm^2 which decreased in a dose-dependent manner at higher

concentrations. On the basis of the dose-response curve, an optimal concentration of 4 µg/cm^2 talc was applied to confluent PMC for 1 to 72 h. IL-8 and monocyte chemotactic protein-1 (MCP-1) levels were increased both at the protein (statistically significantly increased at ≥6 h) and mRNA level (24 h) as compared with control. Talc-stimulated PMC culture supernatant showed chemostatic activity for neutrophils and monocytes. Talc also enhanced intercellular adhesion molecule-1 (ICAM-1) expression in PMC. The data demonstrate that talc stimulates PMC to release chemokines and express adhesion molecules that may play a critical role in pleurodesis.

1.1.4.5 Nasreen et al, 2000

Study reference:

Talc induces apoptosis in human malignant mesothelioma cells in vitro

N. Nasreen, K.A. Mohammed, P.A. Dowling, M.J. Ward, G. Galffy, V.B. Antony

Am J Respir Crit Care Med (2000) 161:595–600

DOI: 10.1164/ajrccm.161.2.9904123

RL 2

Detailed study summary and results:

Test type: Experimental study

The present study was designed to evaluate if talc directly effects cell death of malignant mesothelioma cells (MMC) or normal pleural mesothelial cells (PMC). Three confluent MMC (cell lines; CRL-2081, CRL-5820, CRL-5915) and human primary PMC were exposed to talc (particle size 2.1 µm; purity not stated; 0, 3, 6, 12, 24 µg/cm^2) for 24, 48, and 72 h. In parallel experiments, glass beads similar in size to talc were included as control. Apoptosis was determined by terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick end labelling (TUNEL) and DNA electrophoresis. Talc-induced (6 mg/cm^2) maximum apoptosis in MMC (39.50 ± 2.55%, 31.87 ± 4.69%, and 15.10 ± 3.93% in CRL-2081, CRL-5820, and CRL-5915, respectively) at 48 h, which was significantly ($p < 0.05$) greater than that in control cells. Electrophoresis of DNA isolated from talc-exposed MMC demonstrated the typical ladder pattern of internucleosomal DNA cleavage. Talc did not induce apoptosis in PMC, and glass beads did not cause significant apoptosis in either MMC or PMC. The present study has demonstrated that talc induces apoptosis in MMC without affecting normal mesothelial cells of the pleura.

1.1.4.6 Hamilton et al., 2001

Study reference:

Inflammatory microcrystals induce murine macrophage survival and DNA synthesis

J.A. Hamilton, G. McCarthy, G. Whitty

Arthritis Res (2001) 3:242–246

DOI: 10.1186/ar308

RL 2

Detailed study summary and results:

Test type: Experimental study

Murine bone-marrow-derived macrophages were treated with talc (US Pharmacopeia grade), the cell numbers were monitored over time, and DNA synthesis was measured as the incorporation of [methyl-^{3}H]-thymidine. Talc (≥50 µg/ml, 24 h) promoted DNA synthesis. Enhanced survival of macrophages or proliferation may contribute to talc-induced inflammation and granuloma formation.

1.1.4.7 Shukla et al, 2009

Study reference:

Alterations in gene expression in human mesothelial cells correlate with mineral pathogenicity

A. Shukla, M.B. MacPherson, J. Hillegass, M.E. Ramos-Nino, V. Alexeeva, P.M. Vacek, J.P. Bond, H.I. Pass, C. Steele, B.T. Mossman

Am J Respir Cell Mol Biol. (2009) Jul;41(1):114-23

DOI: 10.1165/rcmb.2008-0146OC

RL 2

Detailed study summary and results:

Test type: Experimental study

Human mesothelial LP9/TERT-1 cells (hTERT-immortalized human mesothelial cell line) and human ovarian epithelial cells (an SV40-immortalized) were treated talc (MP 10-52; purity 95%; chlorite 4.5-5%, dolomite 0.3%; mean size 1.1 µm; nonfibrous)

and asbestos (crocidolite; mean size length × width: 7.4 × 0.25 µm). Negative control groups included cells exposed to fine TiO_2 and glass beads.

Asbestos (75 µm^2/cm^2) caused membrane blebbing and other toxic manifestations in both cell types, while talc, TiO_2 and glass beads were nontoxic. After 24 h, cell viability (trypan blue dye exclusion) of LP9/TERT-1 cells was statistically significantly ($p < 0.05$) decreased upon treatment with asbestos (5 µg/cm^2) and talc (≥15 µg/cm^2) compared to untreated cells. These effects were less striking in ovarian epithelial cells. TiO_2 and glass beads had no effect on cell viability in both cell types. An up-regulation (> 2-fold compared with untreated controls) of mRNA expression of activating transcription factor 3 (*ATF3*; modulates production of inflammatory cytokines and growth factors), superoxide dismutase 2 (*SOD2*; marker of oxidative stress), prostaglandin-endoperoxide synthase 2 (*PTGS2;* a key enzyme in prostanoid biosynthesis associated with modulation of mitogenesis and inflammation) and genes encoding cytokines/chemokines (IL-8 C-terminal variant, *IL1R1, CXCL2, MIP2, CXCL3* and *TFP12*) was noted in LP9/TERT-1 cells upon exposure to talc (75 µm^2/cm^2, 8 h), no significant alterations in gene expression were observed with low concentrations of talc (15 µm^2/cm^2, 24 h) or with TiO_2 or glass beads. At low nontoxic concentrations, asbestos (15 µm^2/cm^2) caused significant changes in mRNA expression of 29 genes at 8 hours and of 205 genes at 24 hours, whereas changes in mRNA levels of 236 genes occurred in cells exposed to high concentrations of asbestos (75 µm^2/cm^2) for 8 hours. Human primary pleural mesothelial cells also showed the same patterns of

increased gene expression by asbestos. No significant mRNA changes were observed with talc in ovarian epithelial cells.

1.1.4.8 Lee et al., 2010

Study reference:

Selective apoptosis of lung cancer cells with talc

P. Lee, L. Sun, C.K. Lim, S.E Aw, H.G. Colt

Eur Respir J. 2010 Feb;35(2):450-2

DOI: 10.1183/09031936.00113109

RL 2

Detailed study summary and results:

Test type: Experimental study

Apoptosis (propidium iodide staining and flow cytometric analysis) was studied in a human lung adenocarcinoma cell line (A549) and in primary human pleural mesothelial cells upon exposure to talc (purity not stated). Talc induced apoptosis in a lung adenocarcinoma cells in a dose- and time-dependent manner (% apoptotic cells at 0, 25, 50, 75 µg/ml for 24 h: 0.2, 1.6, 5.9, 5.9; 48 h: 0.2, 6.2, 9.6, 16.4; 72 h: 0.2, 12.0, 16.0, 26.2). No apoptosis of human pleural mesothelial cells was noted upon exposure to talc (% apoptotic cells 0.1-1.6%).

1.1.4.9 Fletcher et al, 2019

Study reference:

Molecular Basis Supporting the Association of Talcum Powder Use With Increased Risk of Ovarian Cancer

N.M. Fletcher, A.K. Harper, I. Memaj, R. Fan, R.T. Morris, G.M. Saed

Reprod Sci. (2019) Dec;26(12):1603-1612

DOI: 10.1177/1933719119831773

RL 2

Detailed study summary and results:

Test type: Experimental study

Ovarian cancer cells (SKOV-3, A2780 and TOV112D) and normal cells (human macrophages EL-1, primary human ovarian epithelial cells, human ovarian surface epithelial cells (HOSEpiC) and immortalized human fallopian tube secretory epithelial cells FT33) were treated with talcum baby powder (Johnson & Johnson, #30027477, Lot #13717RA; purity not stated). In all talc-treated cells (≥ 5 µg/ml, 72 h), there was a statistically significant ($p < 0.05$) dose-dependent increase in prooxidant (gene expression and protein activity) inducible nitric oxide synthase (iNOS), nitrate/nitrite and myeloperoxidase (MPO) with a concomitant statistically significant ($p < 0.05$) decrease in antioxidant (gene expression and protein activity) catalase, superoxide dismutase (SOD), glutathione reductase (GSR) and glutathione peroxidase (GPX). Upon talc treatment (100 µg/ml, 72 h), point mutations were noted for several oxidant and antioxidant enzymes in

normal and cancer cell types, known to alter enzymatic activity. A statistically significantly ($p < 0.05$) increased protein expression of ovarian cancer biomarker CA-125 was measured upon exposure to talc (100 µg/ml, 72 h) in all cell types. Furthermore, statistically significantly ($p < 0.05$) increased cell proliferation (MTT assay) was reported upon exposure to talc (100 µg/ml, 24 h), which was in general higher in normal cells (45-50% above baseline) than in cancer cells (20-30% above baseline). Caspase-3 activity, as measure of apoptosis, was statistically significantly ($p < 0.05$) reduced in all talc-treated (≥ 5 µg/ml, 72 h) cells in a dose-dependent manner.

1.1.4.10 Mandarino et al, 2020

Study reference:

The effect of talc particles on phagocytes in co-culture with ovarian cancer cells

A. Mandarino, D.J. Gregory, C.C. McGuire, B.W. Leblanc, H. Witt, L.M. Rivera, J.J. Godleski, A.V. Fedulov

Environ Res. (2020) Jan;180:108676

DOI: 10.1016/j.envres.2019.108676

RL 2

Detailed study summary and results:

Test type: Experimental study

Effects of talc (USP grade, particle diameter <10 µm; exposure of 10 µg/well and 24 h, unless stated otherwise) in a co-culture system consisting of a murine ovarian surface epithelial cell line (MOSEC) ID8 and phagocytic murine cell lines J774 and IC21 or RAW264.7 were examined. Talc (4 h) particles were phagocytized and production of reactive oxygen species (ROX) was statistically significantly ($p < 0.05$) enhanced in all macrophagic cell types, with or without oestradiol. Control TiO_2 particles (mean size ~1 µm), tested in parallel, were also phagocytized but the production of ROX was only increased in J774 cells (not statistically significant). Talc treatment, alone and upon co-incubation with oestradiol, produced changes in gene expression that may contribute to tumour growth and metastasis (carbonic anhydrase [*Car9*], heme oxygenase-1 [*Hmox-1*], solute carrier family 2 facilitated glucose transporter member 1 [*Slc2a1*], cellular FLICE-inhibitory protein [*Cflip*], sirtuin2 [*Sirt2*]) and thus promote pro-tumorigenic environment. Furthermore, incubation of talc and oestradiol inhibited gene expression of a cluster of genes responsible for intracellular, internal proteins playing a role in anti-tumour immunosurveillance of the macrophages (Aurora kinase A [*Aurka*], growth arrest and DNA damage-inducible 34 [*Gadd45g*], caspase-7 [*Casp7*], cell division cycle 20 [*Cdc20*], proliferation marker [*Mki67*], stathmin 1 [*Stmn1*], X-linked inhibitor of apoptosis protein [*Xiap*]). Talc was not cytotoxic (with or without oestradiol) in J774 and IC21 cells. Talc-treated J774 and IC21 cells statistically significantly ($p < 0.05$) enhanced survival of ovarian ID8 cells in co-culture and in combination with oestradiol (in some cases also with talc alone). The authors concluded that these data suggest that in vitro exposure to talc particles, particularly in a high-oestrogen environment, may compromise the macrophageal immunosurveillance functions.

1.1.4.11 Mierzejewski et al, 2021

Study reference:

Primary human mesothelial cell culture in the evaluation of the inflammatory response to different sclerosing agents used for pleurodesis

M. Mierzejewski, M.P. Paplinska-Goryca, P. Korczynski, R. Krenke

Physiol Rep. (2021) Apr;9(8):e14846

DOI: 10.14814/phy2.14846

RL 2

Detailed study summary and results:

Test type: Experimental study

Primary human pleural mesothelial cells were treated with talc (purity not stated, 2 and 20 µg/ml) for 6 and 24 h. Exposure of mesothelial cells to the higher talc dose (20 µg/ml) caused a significant decrease in IL-1β Production after 6 h (1.85 pg/ml [1.81–1.90 pg/ml], $p = 0.02$) and insignificant increase as after 24 h (17.14 pg/ml [11.9–33.32 pg/ml]) versus controls. An IL-1β concentration in culture supernatant after 24 h of higher talc dose stimulation was significantly higher compared to 6-h stimulation ($p = 0.02$). Concentrations of IL-6 and IL-8 were similar to those found in the control group after 6- or 24-h treatments with talc. The highest mesothelial response in our study was associated with talc exposure and was expressed as an elevation of IL-1β concentration in culture supernatant. These data suggest talc in vitro induced inflammation in human pleural mesothelial cells.

1.1.4.12 Toledano-Magaña et al, 2021

Study reference:

Toxicological Evaluations in Macrophages and Mice Acutely and Chronically Exposed to Halloysite Clay Nanotubes Functionalized with Polystyrene

Y. Toledano-Magaña, L. Flores-Santos, G. Montes de Oca, A. González-Montiel, J. C. García-Ramos, C. Mora, N. A. Saavedra-Ávila, M. Gudiño-Zayas, L. C. González-Ramírez, J. P. Laclette, and J. C. Carrero*

ACS Omega (2021) 6(44):29882

Physiol Rep. (2021) Apr;9(8):e14846

DOI: 10.1021/acsomega.1c04367

RL 2

Detailed study summary and results:

Test type: Experimental study

Human monocyte-derived macrophages (HMDM), mouse bone marrow-derived macrophages (MMDM) and the RAW 264.7 cell line were treated with talc (purity not stated; 0.01-100 µg/ml) for 12-60 h. Release of cytokine production was assessed upon exposure to 100 µg/ml talc for 24-48 h. Macrophage cultures treated

with talc showed minimal viability decrease (less than 5%) independent of exposure time with concentrations within the range of 0.01–10 μg/ml. When evaluating at the concentration of 100 μg/ml, a time-dependent decrease in viability was observed, but it did not exceed 10% at the maximum exposure time of 60 h for RAW 264.7 and HMDM. The effect was slightly greater in MMDM but did not exceed 15% at 60 h. Overall, the statistical analysis showed no significant differences between groups, independently of the macrophage source or exposure time. Apoptosis (Annexin V staining) was statistically significantly ($p < 0.05$) increased upon exposure to talc (100 μg/ml) in RAW 264.7 after 36-60 h. In addition, necrosis (propidium iodide staining) was slightly increased upon exposure to talc in RAW 264.7, but only statistically significant ($p < 0.05$) after 48 h. At 100 μg/ml talc, cytokine levels were statistically significantly ($p < 0.05$) increased in HMDM (24 h: IFN-γ and IL-17; 36 h: IL-17; 48 h: IL-6 and IL-17) and MMDM cultures (24 h: IFN-γ; 36 and 48 h: IFN-γ and Il-17). Talc did not substantially affect the viability of human and mice macrophages at concentrations as high as 100 μg/ml. Production of inflammatory cytokines was increased upon exposure to talc in human and murine macrophage cultures.

1.2 Specific target organ toxicity – repeated exposure

1.2.1 Animal data

1.2.1.1 NTP, 1993/Pickrell et al., 1989 – rat (4-week)

Study reference:

Toxicology and Carcinogenesis Studies of Talc (CASRN 14807-96-6) in F344/N Rats and B6C3F1 Mice (Inhalation Studies). National Toxicology Program (NTP)Technical Report (TR) 421[5]

RL 1

Detailed study summary and results:

Test type

NTP 4-week inhalation study, similar to OECD test guideline study 412. The study is GLP compliant.

Test substance

- Talc (MP 10-52 grade) lot W101882, for more details see 1.1.1.1
- Degree of purity: ≥96%

Test animals

- Rat F344/N
- 10 males and females per group. Groups of 5 males and females were evaluated for lung talc burden. Animals were sacrificed within 24 h after the last exposure.
- Age and weight at the study initiation: 6-7 weeks; male: 144-150 g, female: 109-110 g

[5] https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr421.pdf and published as 'Talc deposition and effects after 20 days of repeated inhalation exposure of rats and mice to talc'. Pickrell et al. (1989) Environ Res 49: 233–245

Administration/exposure

- Inhalation (talc aerosol)
- 4-week study
- 0, 2, 6 or 18 mg/m^3 (overall mean concentrations were 0, 2.3, 4.3 and 17 mg/m^3)
- Whole body exposure, 6 hours per day, 5 days per week
- Aerosol size distribution
    - Mass median aerodynamic diameter: 3.3 ± 0.1 µm
    - Geometric standard deviation: 1.9
- Aerosol generation, see 1.1.1.1

Results and discussion

- body weight and body weight changes
    - The final mean body weights of exposed male (final weight relative to controls (%) at 2, 6, 18 mg/m^3: 105, 101, 96%) and female (100% at all dose groups) rats were similar to controls.
- food/water consumption
    - Not specified.
- description, severity, time of onset and duration of clinical signs (reversible, irreversible, immediate, delayed)
    - No clinical signs were observed in rats prior to sacrifice 24 hr after the last exposure day.
- sensory activity, grip strength and motor activity assessments (when available)
    - Not studied.
- ophthalmologic findings: incidence and severity
    - Not studied.
- haematological findings: incidence and severity
    - Not studied.
- clinical biochemistry findings: incidence and severity
    - Not studied.
- gross pathology findings: incidence and severity
    - There were no statistically significant increases in any organ-weight-to-body-weight ratios in both sexes. The talc lung burdens increased with talc exposure level (Table 41); however, the ratio of lung burden to exposure concentration was somewhat higher at the 6 and 18 mg/m^3 exposure levels (Table 42). The increase in talc lung burden with exposure concentration may have been because the maximum ability of the respiratory tract to clear particles was exceeded at the 6 and 18 mg/m^3 exposure levels.

Table 41: Lung talc burden of rats in the 4-week inhalation study of talc[a]

	0 mg/m³	2 mg/m³	6 mg/m³	18 mg/m³
Male				
n	5	5	5	5
µg talc	4.28 ± 1.63	81.60 ± 2.06**	186.00 ± 9.27**	846.00 ± 45.45**
µg talc/g lung	4.50 ± 1.86	78.80 ± 2.75**	190.00 ± 7.75**	842.00 ± 69.96**
Female				
n	5	4	5	5
µg talc	0.58 ± 0.24	56.50 ± 1.56*	127.20 ± 9.27**	546.00 ± 35.16**
µg talc/g lung	0.66 ± 0.27	76.00 ± 3.24*	185.00 ± 10.41**[b]	770.00 ± 51.28**

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error
[b] n=4

Table 42: Lung talc burden (normalized to exposure concentration) of rats in the 4-week inhalation study of talc[a]

	0 mg/m³	2 mg/m³	6 mg/m³	18 mg/m³
Male				
n	5	5	5	5
	–[b]	34.25 ± 1.21**	44.22 ± 1.80**	49.52 ± 4.12**
Female				
n	5	4	4	5
	–	33.05 ± 1.40**	43.03 ± 2.41**	45.30 ± 3.01**

** Significantly different (P≤0.01) from the control group by Dunn's or Shirley's test
[a] Mean ± standard error; units are presented as µg talc/g control lung per mg/m³.
[b] Values of magnesium in sample pools of 2 to 3 control lungs were less than the limit of detectability (0.1 ppm). Therefore no equivalent of measurement of talc was calculated to be present in control lungs.

- histopathology findings: incidence and severity
    - There was a minimal increase in the number of intra-alveolar macrophages in the lung of male and female rats exposed to 18 mg/m^3 (incidence not specified). The lesion was diffuse in nature and in no instance were clusters of greater than three alveolar macrophages observed. The individual macrophages were slightly larger than normal and had cytoplasm which contained fine eosinophilic granules. Talc particles could be seen within macrophages under phase-contrast microscopy in lung tissue. The response was minimal in the high exposure group and therefore tissues from lower exposure groups were not examined. Based on these findings it was predicted that aerosol concentrations greater than 18 mg/m^3 would overwhelm lung clearance mechanisms, impair lung function, and possibly shorten survival.

- mortality and time to death (if occurring)
    - All rats survived to the end of the study.

1.2.1.2 Shim et al., 2015 – rat (4-week)

Study reference:

Inhalation of Talc Induces Infiltration of Macrophages and Upregulation of Manganese Superoxide Dismutase in Rats

I. Shim, H.M. Kim, S. Yang, M. Choi, G.B. Seo, B.W. Lee, B.I. Yoon, P. Kim, K. Choi

Int J Toxicol. Nov-Dec 2015;34(6):491-9

DOI: 10.1177/1091581815607068

RL 2

Detailed study summary and results:

Test type

Experimental study, no GLP.

Test substance

- Talc (non-asbestos form), provided as ultra-fine white talcum powder from Rex Material (Korea)
- Degree of purity: ≥96%
- Talc contained 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. The crystal structure of talc particles was monoclinic and prismatic after analysing by scanning electron microscopy.

Test animals

- Rat Sprague-Dawley
- 6 males and females per group.
- Age and weight at the study initiation: 7 weeks; weight at the study initiation not specified

Administration/exposure

- Inhalation (talc aerosol)
- 4-week study
- 0, 5, 50 and 100 mg/m^3 (overall mean concentrations were 0, 4.8 ± 0.7, 54.2 ± 7.5 and 101.5 ± 8.6 mg/m^3)
- Whole body exposure, 6 hours per day, 5 days per week
- After the terminal exposure, the rats were fasted for about 16 hours before necropsy.
- Aerosol size distribution
    - Mass median aerodynamic diameter: 3.88 ± 1.86 µm
- Aerosol generation
    - Talc aerosol was generated by a dust generator (Sibata) and was delivered into the chamber with air purified through a high-efficiency particulate air filter. The talc flow rate into the

chamber was maintained by continuously controlling talc particle counts per minute. Talc concentrations in the chamber were measured by collecting samples with a SIP-32L sampler (Sibata).

Results and discussion

- body weight and body weight changes
    - Body weight was slightly decreased on third day after exposure in 50 and 100 mg/m^3 exposure group of both male and female rats; however, there were no significance when compared with the control group (data not shown).
- food/water consumption
    - Not specified.
- description, severity, time of onset and duration of clinical signs (reversible, irreversible, immediate, delayed)
    - There were no treatment-related adverse symptoms associated with inhaled talc during the experimental period.
- sensory activity, grip strength and motor activity assessments (when available)
    - Not studied.
- ophthalmologic findings: incidence and severity
    - Not studied.
- haematological findings: incidence and severity
    - Haematology evaluations for the male and female rats at the end of the study are shown in Table 43 and Table 44, respectively. The mean plasma volume (MPV) in males exposed to 5 mg/m^3 of talc and platelet (PLT) count in females exposed to 50 mg/m^3 were increased significantly when compared with control rats. However, all haematological changes fell within the range of the historical control values. Clinical biochemistry findings: incidence and severity. No other haematological significant differences were evident in talc-exposed male and female rats.

Table 43: Haematological values of male rats exposed to talc for 4 weeks by inhalation

	Talc concentration (mg/m^3)			
Parameters	Control	5	50	100
WBC, $\times 10^9$/L	7.27 ± 1.57	6.32 ± 1.30	6.57 ± 2.79	7.43 ± 1.69
NE, $\times 10^9$/L	2.04 ± 0.46	1.78 ± 0.94	1.74 ± 0.13	2.51 ± 0.62
LY, $\times 10^9$/L	4.66 ± 1.08	4.02 ± 0.84	3.87 ± 1.55	4.48 ± 1.05
MO, $\times 10^9$/L	0.58 ± 0.19	0.70 ± 0.29	0.37 ± 0.27	0.40 ± 0.17
EO, $\times 10^9$/L	0.03 ± 0.01	0.01 ± 0.01	0.02 ± 0.00	0.03 ± 0.02
BA, $\times 10^9$/L	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.01
RBC, $\times 10^{12}$/L	7.62 ± 0.49	7.56 ± 0.40	7.66 ± 0.41	7.39 ± 1.43
HB, g/dL	13.42 ± 0.99	13.62 ± 1.08	13.53 ± 0.61	13.80 ± 1.15
HCT, %	43.50 ± 3.71	42.50 ± 3.21	42.93 ± 1.22	44.13 ± 6.14
MCV, fL	57.10 ± 2.88	56.60 ± 1.89	56.10 ± 1.67	55.40 ± 1.98
MCH, pg	17.62 ± 0.85	17.53 ± 1.18	17.67 ± 0.67	16.83 ± 1.14
MCHC, g/dL	30.87 ± 1.16	31.05 ± 2.58	31.50 ± 0.70	30.43 ± 2.57
RDW, %	14.62 ± 0.84	14.28 ± 0.52	14.03 ± 0.60	14.68 ± 1.25
PLT, $\times 10^9$/L	919.80 ± 73.51	842.00 ± 50.71	821.00 ± 52.33	1108.00 ± 169.71
MPV, fL	6.27 ± 0.48	7.27 ± 0.54[b]	6.97 ± 0.06	6.53 ± 0.40

Abbreviations: WBC, white blood cell; NE, neutrophil; LY, lymphocyte; MO, monocyte; EO, eosinophil; BA, basophils; RBC, red blood cell; HB, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, red blood cell distribution width; PLT, platelet; MPV, mean plasma volume.
[a]Size of each group (6).
[b]Significantly different with control ($P < 0.05$).

Table 44: Haematological values of female rats exposed to talc for 4 weeks by inhalation

	Talc concentration (mg/m^3)			
Parameters	Control	5	50	100
WBC, $\times 10^9$/L	4.90 ± 2.15	4.29 ± 1.12	5.27 ± 0.82	6.53 ± 0.49
NE, $\times 10^9$/L	1.34 ± 0.53	0.83 ± 0.23	1.03 ± 0.16	1.49 ± 0.22
LY, $\times 10^9$/L	3.64 ± 1.43	3.82 ± 0.24	4.32 ± 0.82	4.19 ± 1.37
MO, $\times 10^9$/L	0.40 ± 0.25	0.19 ± 0.06	0.27 ± 0.12	0.34 ± 0.20
EO, $\times 10^9$/L	0.03 ± 0.01	0.01 ± 0.01	0.01 ± 0.01	0.02 ± 0.01
BA, $\times 10^9$/L	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
RBC, $\times 10^{12}$/L	6.98 ± 0.39	7.36 ± 0.18	7.22 ± 0.14	7.37 ± 0.50
HB, g/dL	12.52 ± 0.82	13.05 ± 0.58	12.67 ± 1.06	13.18 ± 1.32
HCT, %	40.18 ± 2.16	40.98 ± 0.48	41.37 ± 1.95	41.03 ± 2.15
MCV, fL	57.63 ± 2.19	55.70 ± 1.04	57.33 ± 1.83	56.02 ± 1.07
MCH, pg	17.95 ± 0.79	17.75 ± 0.62	17.53 ± 1.21	17.83 ± 0.74
MCHC, g/dL	31.17 ± 1.19	30.08 ± 4.01	30.60 ± 1.15	32.08 ± 1.56
RDW, %	12.90 ± 0.31	12.90 ± 0.64	12.93 ± 0.42	12.86 ± 0.53
PLT, $\times 10^9$/L	798.33 ± 50.93	910.00 ± 90.51	872.67 ± 23.69[b]	893.67 ± 13.87
MPV, fL	6.80 ± 0.60	6.76 ± 0.48	7.40 ± 0.85	7.40 ± 1.28

Abbreviations: WBC, white blood cell; NE, neutrophil; LY, lymphocyte; MO, monocyte; EO, eosinophil; BA, basophils; RBC, red blood cell; HB, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, red blood cell distribution width; PLT, platelet; MPV, mean plasma volume.
[a]Size of each group (6).
[b]Significantly different with control ($P < 0.05$).

- clinical biochemistry findings: incidence and severity
    - Glucose was decreased significantly (not dose-dependent) in male rats exposed to 50 and 100 mg/m^3 (Table 45). Triglyceride was decreased in all male rats exposed to talc, with a significant difference only in the 50 mg/m^3 exposure group (Table 45). Aspartate aminotransferase and gamma-glutamyl transferase (GGT) were increased significantly in female rats exposed to 50 mg/m^3 compared with the control group (Table 46), but was not dose-dependent and not statistically significantly increased in other dose groups. No other biochemical significant differences were evident in talc-exposed male and female rats.

Table 45: Biochemical serum values in male rats exposed to talc for 4 weeks by inhalation

	Talc concentration (mg/m^3)			
Parameters	Control	5	50	100
ALP, mg/dL	439.50 ± 77.41	451.60 ± 68.07	527.20 ± 79.17	525.00 ± 75.45
LDH, U/L	808.20 ± 134.21	768.00 ± 188.10	890.00 ± 22.36	865.25 ± 59.31
GLU, mg/dL	199.00 ± 35.41	159.50 ± 31.63	136.80 ± 23.64[b]	146.17 ± 25.80[b]
TCHO, mg/dL	53.00 ± 16.79	53.50 ± 9.71	51.40 ± 8.08	54.00 ± 8.88
AST, U/L	90.00 ± 17.03	68.17 ± 11.65	122.00 ± 15.00	88.75 ± 25.55
TG, mg/dL	61.75 ± 15.61	58.80 ± 18.99	31.50 ± 5.00[b]	39.50 ± 9.33
ALT, U/L	25.67 ± 5.28	22.50 ± 3.51	25.00 ± 4.85	20.17 ± 0.98
BUN, mg/dL	14.20 ± 0.96	13.57 ± 1.23	14.52 ± 1.49	15.37 ± 1.63
GGT, U/L	8.67 ± 1.03	9.50 ± 0.84	7.40 ± 0.55	7.83 ± 0.98
ALB, g/dL	3.70 ± 0.13	3.60 ± 0.24	3.64 ± 0.18	3.65 ± 0.08
TP, g/dL	6.07 ± 0.30	5.82 ± 0.46	5.94 ± 0.25	6.10 ± 0.18
CRE, mg/dL	0.30 ± 0.06	0.25 ± 0.05	0.22 ± 0.04	0.27 ± 0.04
TBIL, mg/dL	0.43 ± 0.10	0.52 ± 0.18	0.48 ± 0.08	0.42 ± 0.04

Abbreviations: ALP, alkaline phosphatase; LDH, lactate dehydrogenase; GLU, glucose; TCHO, total cholesterol; AST, aspartate aminotransferase; TG, triglyceride; ALT, alanine aminotransferase; BUN, urea nitrogen in blood; GGT, gamma-glutamyl transferase; ALB, albumin; TP, total protein; CRE, creatinine; TBIL, total bilirubin.
[a]Size of each group (6).
[b]Significantly different with control ($P < 0.05$).

Table 46: Biochemical serum values in female rats exposed to talc for 4 weeks by inhalation

	Talc concentration (mg/m^3)			
Parameters	Control	5	50	100
ALP, mg/dL	292.40 ± 39.97	397.00 ± 103.52	375.20 ± 64.55	347.75 ± 93.25
LDH, U/L	853.00 ± 94.00	883.33 ± 28.87	891.67 ± 20.41	890.00 ± 22.36
GLU, mg/dL	106.20 ± 21.23	140.50 ± 19.12	112.33 ± 27.29	118.20 ± 26.53
TCHO, mg/dL	72.40 ± 19.15	77.50 ± 17.08	78.00 ± 14.52	73.00 ± 16.61
AST, U/L	71.17 ± 12.09	69.00 ± 20.51	117.80 ± 14.32[b]	95.75 ± 8.66
TG, mg/dL	36.60 ± 7.99	25.75 ± 7.89	30.60 ± 10.21	26.00 ± 2.83
ALT, U/L	18.50 ± 3.89	17.75 ± 3.40	17.50 ± 3.89	17.60 ± 3.78
BUN, mg/dL	14.30 ± 1.14	15.70 ± 2.20	14.75 ± 1.79	14.10 ± 1.71
GGT, U/L	8.50 ± 0.55	8.50 ± 0.58	10.83 ± 1.83[b]	8.60 ± 1.52
ALB, g/dL	4.17 ± 0.23	4.20 ± 0.22	4.23 ± 0.25	4.20 ± 0.24
TP, g/dL	6.80 ± 0.34	6.58 ± 0.59	6.78 ± 0.42	6.84 ± 0.59
CRE, mg/dL	0.33 ± 0.05	0.28 ± 0.05	0.30 ± 0.06	0.28 ± 0.04
TBIL, mg/dL	0.48 ± 0.04	0.60 ± 0.24	0.68 ± 0.21	0.60 ± 0.07

Abbreviations: ALP, alkaline phosphatase; LDH, lactate dehydrogenase; GLU, glucose; TCHO, total cholesterol; AST, aspartate aminotransferase; TG, triglyceride; ALT, alanine aminotransferase; BUN, urea nitrogen in blood; GGT, gamma-glutamyl transferase; ALB, albumin; TP, total protein; CRE, creatinine; TBIL, total bilirubin.
[a]Size of each group (6).
[b]Significantly different with control ($P < 0.05$).

- gross pathology findings: incidence and severity
    - There were no significant differences in the relative weight of the heart, thymus, kidney, liver, lung, and spleen compared to body weight (data not shown).
- histopathology findings: incidence and severity
    - In male and female rats exposed to 50 and 100 mg/m^3 of talc, infiltration of foamy macrophages (minimal to moderate; Table 47) on the alveolar walls and spaces near the terminal and respiratory bronchioles occurred in a concentration-dependent manner (Figure 4 and Figure 5). Interstitial pneumonitis (minimal to mild), bronchial epithelial hyperplasia and hypertrophy (minimal to mild), and arterial medial hypertrophy (mild) were observed in both sexes, with no relation to the exposure concentration (Table 47).

- In lung tissue, a statistically significant fold-induction of protein expression of superoxide dismutase 2 (SOD2) was evident between the control group and both the low and the high talc inhalation groups of male rats and in the high dose group in females (Figure 6). Protein expression of glutathione peroxidase (GPxI) was statistically significantly increased in low-dose males, but not in females or in other dose groups (Figure 6).

Table 47: Incidence of histopathological findings in the lungs of the rats exposed to talc

Sex	Male				Female			
Talc concentration (mg/m^3)	0	5	50	100	0	5	50	100
Number of rats examined	3	3	3	3	3	3	3	3
No specific lesion	3	3	0	0	3	2	0	0
Foamy histiocytes	0	0	3	3	0	0	3	3
Grades: Minimal	0	0	2	0	0	0	3	0
Mild	0	0	1	2	0	0	0	3
Moderate	0	0	0	1	0	0	0	0
Interstitial pneumonitis, diffuse	0	0	0	1	0	1	0	0
Grades: Minimal	0	0	0	0	0	1	0	0
Mild	0	0	0	1	0	0	0	0
Bronchial epithelial hyperplasia and hypertrophy	0	0	0	1	0	1	0	0
Grades: Minimal	0	0	0	0	0	1	0	0
Mild	0	0	0	1	0	0	0	0
Arterial medial hypertrophy	0	0	0	1	0	0	0	0
Grades: Minimal	0	0	0	0	0	0	0	0
Mild	0	0	0	1	0	0	0	0

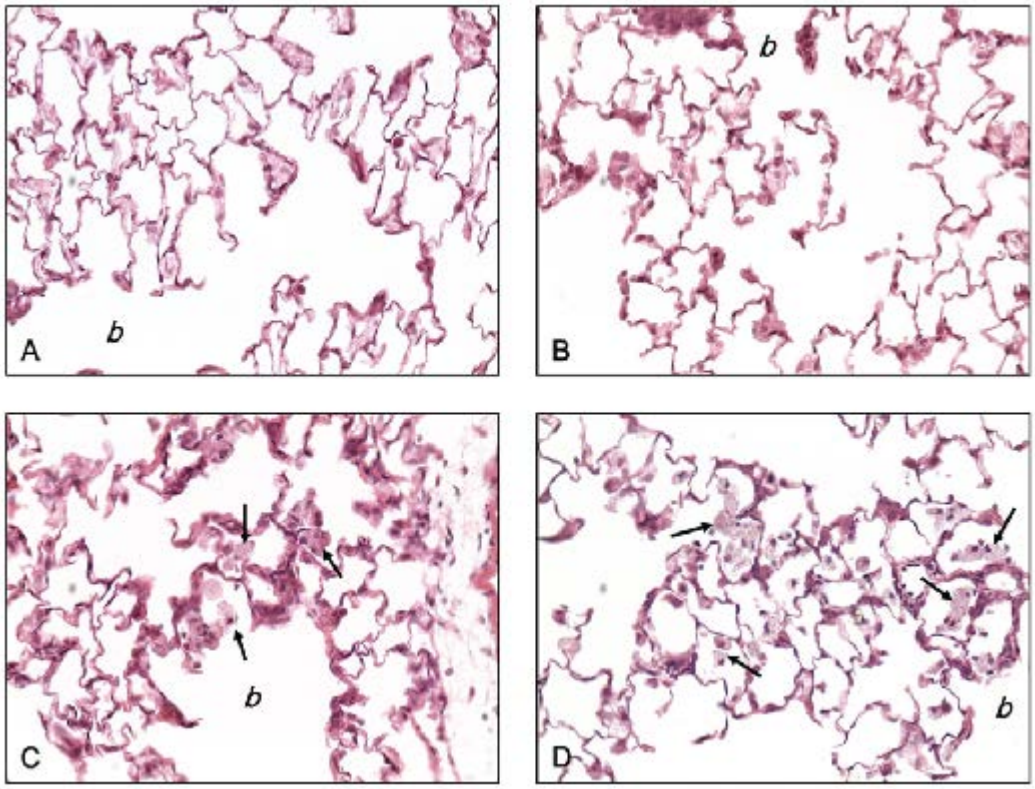


Figure 4: Histopathological findings in the lungs of male rats after exposure to talc for 4 weeks. A, Control and (B) low (50 mg/m^3) exposure group. In the middle (C, 50 mg/m^3) and high (D, 100 mg/m^3) exposure group, the foamy macrophages (arrows) were infiltrated on the alveolar walls and spaces near

the terminal bronchioles (b). After haematoxylin and eosin (H&E) staining, the image was taken at 400× magnification.

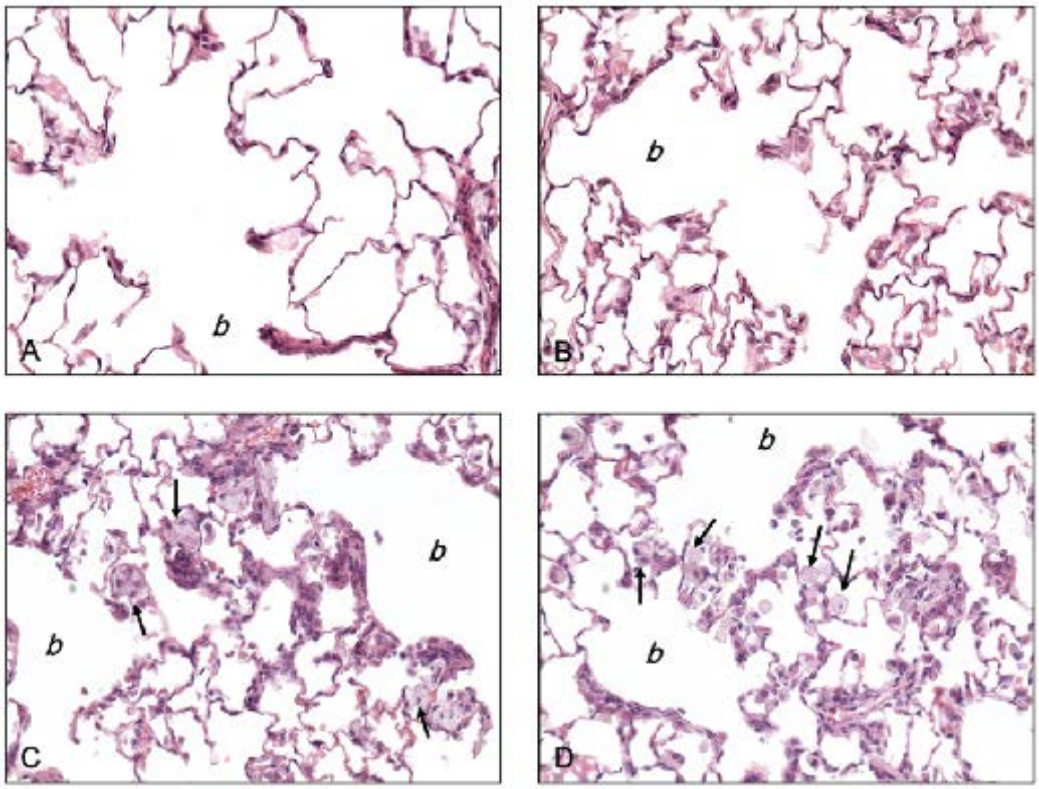


Figure 5: Histopathological findings in the lungs of female rats after exposure to talc for 4 weeks. A, Control and (B) low (50 mg/m^3) exposure group. Note the foamy macrophages (arrows) infiltrated on the alveolar walls and spaces near the terminal bronchioles (b) in the middle (C, 50 mg/m^3) and high (D, 100 mg/m^3) exposure group. After haematoxylin and eosin (H&E) staining, the image was taken at 400× magnification.

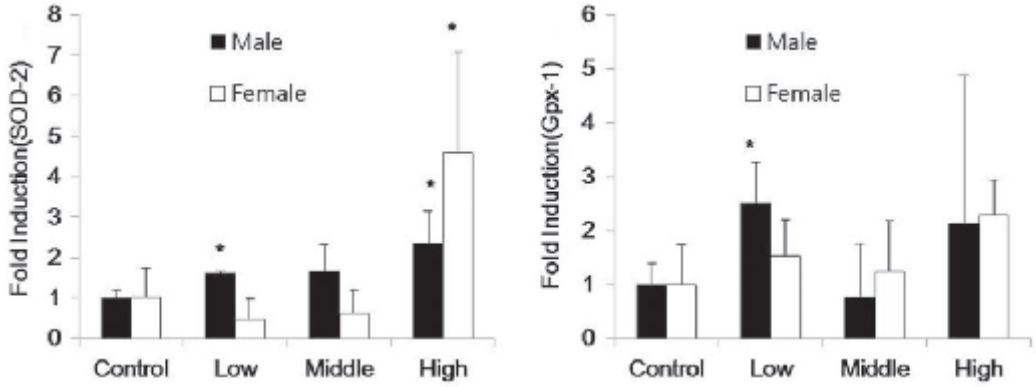


Figure 6: Expression of superoxide dismutase 2 (SOD2) and glutathione peroxidase (GPxI) in the lungs of male and female rats after exposure to talc for 4 weeks. *$p < 0.05$ versus control group.

- mortality and time to death (if occurring)
    - There were no treatment-related deaths associated with inhaled talc during the experimental period.

1.2.1.3 NTP, 1993/Pickrell et al., 1989 – mouse (4-week)

Study reference:

Toxicology and Carcinogenesis Studies of Talc (CASRN 14807-96-6) in F344/N Rats and B6C3F1 Mice (Inhalation Studies). National Toxicology Program (NTP)Technical Report (TR) 421[5]

RL 1

Detailed study summary and results:

Test type

NTP 4-week inhalation study, similar to OECD test guideline study 412. The study is GLP compliant.

Test substance

- Talc (MP 10-52 grade) lot W101882, for more details see 1.1.1.1
- Degree of purity: ≥96%

Test animals

- $B6C3F_1$ mice
- 10 males and females per group. Groups of 5 males and females were evaluated for lung talc burden. Animals were sacrificed within 24 h after the last exposure.
- Age and weight at the study initiation: 6-7 weeks; male: 25.8 ± 0.2 g, female: 20.7 ± 0.2 g

Administration/exposure

- Inhalation (talc aerosol)
- 4-week study
- 0, 2, 6 or 18 mg/m^3 (overall mean concentrations were 0, 2.2, 5.7 and 20.4 mg/m^3)
- Whole body exposure, 6 hours per day, 5 days per week
- Aerosol size distribution
    - Mass median aerodynamic diameter: 2.7 ± 0.1 µm
    - Geometric standard deviation: 1.9
- Aerosol generation, see 1.1.1.1

Results and discussion

- body weight and body weight changes
    - The final mean body weights of exposed male (final weight relative to controls (%) at 2, 6, 18 mg/m^3: 98, 97, 96%) and female (99, 104, 100%) mice were similar to controls.
- food/water consumption
    - Not specified.
- description, severity, time of onset and duration of clinical signs (reversible, irreversible, immediate, delayed)
    - No clinical signs were observed in mice prior to sacrifice 24 hr after the last exposure day.
- sensory activity, grip strength and motor activity assessments (when available)
    - Not studied.

- ophthalmologic findings: incidence and severity
    - Not studied.
- haematological findings: incidence and severity
    - Not studied.
- clinical biochemistry findings: incidence and severity
    - Not studied.
- gross pathology findings: incidence and severity
    - There were no significant changes in any organ-weight-to-body-weight ratios in exposed male or female mice. Talc lung burdens increased with talc exposure level (Table 48). However, the ratio of lung burden to exposure concentration was constant at all exposure levels (Table 49). In contrast to rats, the maximum ability of the respiratory tract to clear particles was apparently not exceeded at the 18 mg/m^3 level.

Table 48: Lung talc burden of mice in the 4-week inhalation study of talc[a]

	0 mg/m^3	2 mg/m^3	6 mg/m^3	18 mg/m^3
Male				
n	5	5	5	5
µg talc	–[b]	19.60 ± 1.29	50.20 ± 2.84	197.00 ± 5.75
µg talc/g lung	–	128.0 ± 9.7	322.0 ± 19.6	1,138.0 ± 10.7
Female				
n	5	5	5	5
µg talc	–	15.40 ± 1.21	49.80 ± 1.66	180.60 ± 6.61
µg talc/g lung	–	101.6 ± 8.4	328.0 ± 13.6	1,162.0 ± 66.4

[a] Mean ± standard error
[b] Values of magnesium in sample pools of 2 to 3 control lungs were less than the limit of detectability (0.1 ppm). Therefore no equivalent of measurement of talc was calculated to be present in control lungs.

Table 49: Lung talc burden (normalized to exposure concentration) of mice in the 4-week inhalation study of talc[a]

	0 mg/m³	2 mg/m³	6 mg/m³	18 mg/m³
Male				
n	5	5	5	5
	–[b]	58.170 ± 4.405	56.480 ± 3.443	55.240 ± 0.512
Female				
n	5	5	5	5
	–	46.180 ± 3.820	57.540 ± 2.372	56.400 ± 3.223

[a] Mean ± standard error; units are presented as μg talc/g control lung per mg/m³.
[b] Values of magnesium in sample pools of 2 to 3 control lungs were less than the limit of detectability (0.1 ppm). Therefore no equivalent of measurement of talc was calculated to be present in control lungs.

- histopathology findings: incidence and severity
    - The only lesions related to inhalation of talc aerosols were observed in the lung of male and female mice exposed to 18 mg/m³ (incidence not specified). The changes were minimal and consisted of a diffuse increase in the number of intra-alveolar macrophages. In most cases, pulmonary macrophages did not exceed two per alveolus, but occasional clusters of up to 10 alveolar macrophages were observed. The individual macrophages were two to three times normal size with foamy granular cytoplasm. Talc particles could be seen within macrophages under phase-contrast microscopy in lung tissue. The response was minimal in the high exposure group and therefore tissues from lower exposure groups were not examined. Based on these findings it was predicted that aerosol concentrations greater than 18 mg/m³ would overwhelm lung clearance mechanisms, impair lung function, and possibly shorten survival.
- mortality and time to death (if occurring)
    - One male mouse exposed to 2 mg/mg³ and one male mouse exposed to 6 mg/m³ died before the end of the study.

1.2.1.4 Summary other animal repeated dose toxicity studies

An overview of repeated dose toxicity studies investigating other than subacute, subchronic and chronic studies can be found in Table 50.

Table 50: Summary table of animal studies on repeated exposure to talc

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
Oral prenatal developmental toxicity studies			
Similar as OECD TG 414 Wistar rats (n = 20-24/group, female) Predates GLP RL 2	Talc (purity not stated; as suspension in corn oil; FDA 71-43) 0, 16, 74, 350 and 1600 mg/kg bw/day on GD 6-15 via gavage	No reproductive or developmental effects and no effects on maternal or foetal survival were observed at any dose levels.	Food and Drug Research Labs Inc. (1973a)
Similar as OECD TG 414 CD-1 mice (n = 20-22/group, female) Predates GLP RL 2	Talc (purity not stated; as suspension in corn oil; FDA 71-43) 0, 16, 74, 350 and 1600 mg/kg bw/day on GD 6-15 via gavage	No reproductive or developmental effects and no effects on maternal or foetal survival were observed at any dose levels.	Food and Drug Research Labs Inc. (1973a)
Similar as OECD TG 414 Dutch-belted rabbits (n = 14-29/group, female) Predates GLP RL 2	Talc (purity not stated; as suspension in corn oil; FDA 71-43) 0, 9, 42, 195 and 900 mg/kg bw/day on GD 6-18 via gavage	No dose-response effects on maternal mortality and abortion rates. Fertility was similar in all group, but slightly higher at 900 mg/kg bw (87% vs. 57% in control). Number of live litters per group was decreased at 900 mg/kg bw (64% vs. 86% in control), although no effects on total number of live foetuses in this dose group compared to control were observed. No foetal abnormalities in soft or skeletal tissues were noted. It was concluded in this report that talc had no clear discernible effects on nidation or on maternal and foetal survival.	Food and Drug Research Labs Inc. (1973b)
Similar as OECD TG 414 Golden hamster (n = 20-23/group, female) Predates GLP RL 2	Talc (purity not stated; as suspension in corn oil; FDA 71-43) 0, 12, 56, 260 and 1200 mg/kg bw/day on GD 6-10 via gavage	No reproductive or developmental effects and no effects on maternal or foetal survival were observed at any dose levels.	Food and Drug Research Labs Inc. (1973a)
GD: gestational day			

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