Health Council of the Netherlands

Talc

Evaluation of the carcinogenicity and genotoxicity

Gezondheidsraad
Health Council of the Netherlands

Aan de staatssecretaris van Sociale zaken en Werkgelegenheid

Onderwerp : aanbieding advies *Talc*
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Geachte staatssecretaris,

Graag bied ik u hierbij het advies aan over de gevolgen van beroepsmatige blootstelling aan talk.

Dit advies maakt deel uit van een uitgebreide reeks waarin kankerverwekkende stoffen worden geclassificeerd volgens richtlijnen van de Europese Unie. Het gaat om stoffen waaraan mensen tijdens de beroepsmatige uitoefening kunnen worden blootgesteld.

Dit advies is opgesteld door een vaste subcommissie van de Commissie Gezondheid en beroepsmatige blootstelling aan stoffen (GBBS), de Subcommissie Classificatie van carcinogene stoffen. Het advies is getoetst door de Beraadsgroep Gezondheid en omgeving van de Gezondheidsraad.

Ik heb het advies vandaag ter kennisname toegezonden aan de staatssecretaris van Infrastructuur en Milieu en aan de minister van Volksgezondheid, Welzijn en Sport.

Met vriendelijke groet,

prof. dr. H. Obertop,
waarnemend voorzitter

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Evaluation of the carcinogenicity and genotoxicity

Subcommittee on the Classification of Carcinogenic Substances of
the Dutch Expert Committee on Occupational Safety,
a Committee of the Health Council of the Netherlands

to:

the State Secretary of Social Affairs and Employment

No. 2012/11, The Hague, July 24, 2012

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is "to advise the government and Parliament on the current level of knowledge with respect to public health issues and health (services) research..." (Section 22, Health Act).

The Health Council receives most requests for advice from the Ministers of Health, Welfare & Sport, Infrastructure & the Environment, Social Affairs & Employment, Economic Affairs, Agriculture & Innovation, and Education, Culture & Science. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.

Most Health Council reports are prepared by multidisciplinary committees of Dutch or, sometimes, foreign experts, appointed in a personal capacity. The reports are available to the public.

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Samenvatting

Op verzoek van de Minister van Sociale Zaken en Werkgelegenheid beoordeelt de Gezondheidsraad de kankerverwekkende eigenschappen van stoffen waaraan mensen tijdens de beroepsuitoefening kunnen worden blootgesteld. De evaluatie en beoordeling worden verricht door de subcommissie Classificatie van Carcinogene Stoffen van de Commissie Gezondheid en Beroepsmatige Blootstelling aan Stoffen van de raad, hierna kortweg aangeduid als de commissie. In het voorliggende advies neemt de commissie talk onder de loep. De commissie heeft haar oordeel gegoten in door de Europese Unie aangegeven termen. De beoordeling is gericht op talk dat geen asbest of asbestvormige vezels bevat en op talkpoeder. Mineraal talk wordt gebruikt in landbouwproducten, keramiek, verf en andere deklagen, papier, plastic, dakbedekking, rubber, cosmetica, geneesmiddelen en voor afvalbewerking. Cosmetische talk, wat meer dan 90% mineraal talk bevat, is aanwezig in vele cosmetische producten en wordt gebruikt voor vele doeleinden, inclusief baby poeder en hygiënische producten voor vrouwen.

Op basis van de beschikbare gegevens, hoewel deze veelal wijzen op afwezigheid van kankerverwekkende eigenschappen, is de commissie van mening dat de gegevens over talk onvoldoende zijn om de kankerverwekkende eigenschappen te beoordelen (categorie 3).*

* Volgens het nieuwe classificatiesysteem van de Gezondheidsraad (zie bijlage F).

Executive summary

At the request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands evaluates and judges the carcinogenic properties of substances to which workers are occupationally exposed. The evaluation is performed by the Subcommittee on Classifying Carcinogenic Substances of the Dutch Expert Committee on Occupational Safety of the Health Council, hereafter called the Committee. In this report the Committee evaluated talc. The evaluation is based on talc not containing asbestos or asbestiform fibres and talc used as body powder. Mineral talc is used in agricultural products, ceramics, paint and other coatings, paper, plastics, roofing, rubber, cosmetics and pharmaceuticals and for waste treatment. Cosmetic talc, which contains more than 90% mineral talc, is present in many cosmetic products and is used for many purposes, including baby powders and feminine hygiene products.

Based on the available information, although mainly indicating the absence of carcinogenicity, the Committee is of the opinion that the data are insufficient to evaluate the carcinogenic properties of talc (category 3).*

* According to the new classification system of the Health Council (see Annex F).

Chapter 1

Scope

1.1 Background

In the Netherlands a special policy is in force with respect to occupational use and exposure to carcinogenic substances. The Minister of Social Affairs and Employment has asked the Health Council of the Netherlands to study the carcinogenic properties of substances and to propose a classification (see Annex A). In addition to classifying substances, the Health Council also assesses the genotoxic properties of the substance in question. The assessment and the proposal for a classification are expressed in the form of standard sentences (see Annex E).

This report contains the evaluation of the carcinogenicity and genotoxicity of talc.

1.2 Committee and procedures

This document contains an evaluation by the Subcommittee of the Classification of Carcinogenic Substances of the Dutch Expert Committee on Occupational Safety of the Health Council, hereafter called the Committee. The members of the Committee are listed in Annex B. The submission letter (in English) to the State Secretary can be found in Annex C.

In 2012, the President of the Health Council released a draft of the report for public review. The individuals and organisations that commented on the draft are

listed in Annex D. The Committee has taken these comments into account in deciding on the final version of the report.

1.3 Data

The evaluation and recommendation of the Committee is standardly based on scientific data, which are publicly available. The starting points of the Committees' reports are, if possible, the monographs of the International Agency for Research on Cancer (IARC). This means that the original sources of the studies, which are mentioned in the IARC-monograph, are reviewed only by the Committee when these are considered most relevant in assessing the carcinogenicity and genotoxicity of the substance in question. In the case of metallic chromium, such an IARC-monograph is available, of which the summary and conclusion of IARC is inserted in Annex E. More recently published data were retrieved from the databases Medline, Toxline, Toxcenter (STN), Scisearch / Current Content (STN), Chemical Abstracts (STN) and Chembank using talc, talcum and CAS no. 14807-96-6 as key words in combination with key words representative for carcinogenesis and mutagenesis. The last updated online search was in June 2012. The new relevant data were included in this report.

Chapter 2

General information

2.1 Identity and physicochemical properties

Chemical name	:	Talc
CAS registry number	:	14807-96-6
EINECS number	:	238-877-9
RTECS-number	:	WW2710000
Synonyms	:	soapstone, steatite, talcum, French chalk
Appearance	:	white, very fine crystalline powder
Occurrence	:	talc is a very common metamorphic mineral in metamorphic belts.
Use	:	Mineral talc: used in agricultural products, for clarifying liquids by filtration; as pigment in paints, varnishes and rubber; as filler for paper, rubber and soap; in fireproof and cold-water paints for wood, metal and stone; in lubricating molds and machinery, as electric and heat insulator, in cosmetics and pharmaceuticals (filler for pills), as glove and shoe powder, and for waste treatment. Cosmetic talc (contains > 90% mineral talc): used in many cosmetic products and for many purposes, including baby powders and feminine hygiene products. Also used therapeutically (talc insufflation or talc pleurodesis) to treat non-malignant and malignant pulmonary disease.
Chemical formula	:	$Mg_3(OH)_2Si_4O_{10}$
Molecular weight	:	379.3
Boiling point	:	
Melting point	:	900-1,000 °C
Vapour pressure	:	
Vapour density (air = 1)	:	
Solubility	:	insoluble in water, cold acids or in alkalines

Conversion factor	:	
flash point		
Stability and reactivity	:	
EU Classification	:	Talc is not classified in the Annex I of Directive 67/548/EEC as such, but it may be included in one of the group entries.

Data from IARC[1-3], Merck[4], HSDB[5], EC-JRC[6], NIOSH[7] and Baan[8]

The term 'talc' refers to both mineral talc and industrial products that contain mineral talc in proportions that range from about 35% to almost 100% and are marketed under the name talc. Mineral talc is usually platy but may also occur occasionally and in exceptional cases as long, thin, asbestiform fibres in parallel bundles, which are easily separated from each other by hand pressure. It should be noted that the term "asbestiform" refers to a pattern of mineral growth (i.e., a habit) and not to the presence of other minerals. Therefore, asbestiform talc must not be confused with talc that contains asbestos. Talc products vary in their particle size, associated minerals and talc content depending on their source and application. Minerals commonly found in talc products include chlorite and carbonate. Less commonly, talc products contain tremolite, anthophyllite* and serpentine. The current evaluation is based on talc not containing asbestos or asbestiform fibres and on talc used as body powder.

2.2 IARC conclusion

Talc was evaluated by IARC in a Working Group in 2006[1], the actual monograph was published in 2010[2]. It was concluded that there was *limited evidence* in experimental animals for the carcinogenicity of talc not containing asbestos or asbestiform fibres. It was also concluded that there is *inadequate evidence* in humans for the carcinogenicity of inhaled talc not containing asbestos or asbestiform fibres, and *limited evidence in humans* for the carcinogenicity of perineal use of talc-based body powder.

Perineal use of talc-based body powder was classified as *possibly carcinogenic to humans (Group 2B).* Inhaled talc not containing asbestos or asbestiform fibres is *not classifyable as to its carcinogenicity (Group 3).*

* Tremolite and anthophyllite are members of the amphibole group of silicate minerals.

Chapter 3

Carcinogenicity

3.1 Observations in humans

3.1.1 Epidemiological studies on inhalation exposure to talc

Rubino et al. (1976) studied 1,514 miners and 478 millers employed for at least one year between 1921 and 1950 in talc mines and mills in the Germanasca and Chisone valleys (Piedmont) in Italy.[9] The talc in those mines is described as quite pure, with only some tremolite micro-inclusions; no other fibrous mineral was reportedly found. Significant increases in specific cause of death among miners were found for silicosis (62 observed/30.9 expected) and for silico-tuberculosis (18/9.1). Significant deficits in cause-specific mortality were reported for malignant neoplasms at other sites (23/39.9). Two cases of pleural mesothelioma and a high occurrence of silicosis and silico-tuberculosis were found in the comparison group. [The IARC Working Group noted that the method used to derive the number of expected deaths is not adequately described. It was considered that the lack of comparability between the worker and comparison groups could be the main explanation for the mortality increases and deficits observed in this study.]

The cohort of Piedmont talc workers (Rubino et al., 1976, 1979) was recently updated with a mortality analysis conducted among 1,244 miners and 551 millers who had worked ≥ 1 yr during 1946-1995.[9,10] Compared with regional or national rates, total mortality among the workers was increased (SMR (standard

mortality ratio), 1.2; 95% CI, 1.1-1.3), which was mainly due to nonmalignant respiratory disease among the miners. There was no excess mortality for total cancer or for lung cancer, and no case of pleural or peritoneal mesothelioma was reported (Coggiola et al., 2003).[11]

Selevan et al. (1979) carried out a study of talc exposures in five companies (two of which ceased operations in 1952 and 1960) in three regions in Vermont, USA.[12] Analysis of airborne dust samples and talc bulk samples revealed no asbestos, either by X-ray diffraction or analytical electron microscopy. Levels of respirable free silica were below 0.25% in nearly all ore and product samples, and free silica was only occasionably detectable in air samples. Insufficient information was available to estimate cumulative exposures, but the authors stated that past exposure levels for miners and millers 'far exceeded the present standard for nonfibrous talc of 20 mppcf '(million particles per cubic foot) (the statutory standard referred to was not further specified by the authors). They considered it probable that dust exposure for millers were higher than those for miners. In one mine, which 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 prior to milling. The cohort consisted of all white male talc workers who had been radiographed as part of annual voluntary surveys of the Vermont Health Department, who were employed in the Vermont talc industry between 1 January 1940 and 31 December 1969, and who had worked in the industry for at least one year. [Because of the voluntary nature of the survey, the cohort may not have been representative.] There were 90 deaths among the 392 members of this cohort; vital status was not established for four. For non-malignant respiratory disease and respiratory cancer, Vermont rates were used for comparison, because they are higher than national rates; for other causes of death, US rates were used. [The IARC Working Group noted this unconventional analytical approach.] While some increase was noted for malignant neoplasms, and specifically for respiratory neoplasms (6 observed /3.69 expected), these were not found to be significant. [The IARC Working Group noted that the results were not analysed by latency.] The excess of respiratory cancer occurred only among miners (5/1.15; $p<0.05$), and the significant excess for the non-malignant respiratory disease occurred only among millers (7/1.72; $p<0.01$). Most of those dying with non-malignant respiratory disease had radiographic evidence of pneumoconiosis (rounded opacities). Miners were also exposed to

radon daughters at mean levels ranging up to 0.12 working levels, with single peaks of 1.0 working level.*

Léophonte et al. (1983) reported on the mortality of talc workers in Luzenac, France. The talc in this region is said to contain no asbestos and levels of quartz varying from 0.5-3%.[13] The cohort comprised those who left employment between 1 January1945 and 31 December 1981 having worked for at least one year. Of 470 workers available for study, 256 were living, 209 had died and 5 were lost to follow-up; 192/204 with known occupational exposure had worked only at Luzenac. When compared with the regional population, the median age of death was not found to be influenced by dust exposure. There was no significant excess in cancer mortality in general, and, specifically, mortality from respiratory and digestive cancers was not increased. A significant increase in mortality was found for non-malignant respiratory disease, especially for pneumoconiosis and obstructive lung disease. [The IARC Working Group noted the unconventional definition of the cohort, that no data on smoking habits were available, and that causes of death were obtained for cases from local doctors, hospitals or families but for controls from regional or national records.]

A cohort study in Norway included 94 talc miners and 295 talc millers who had been employed for ≥ 1 yr during 1944-1972 (miners) or ≥ 2 yr during 1935-1972 (millers). The talc in this study is composed mainly of pure talc and magnesite, and contains < 1% quartz, tremolite and anthophyllite. The standardized incidence ratio (SIR) for all cancers was 1.4 (95% CI, 0.8-2.3; 15 observed cases) among the miners and 0.8 (95% CI, 0.5-1.1; 31 observed cases) among the millers. In the groups of 80 workers in the highest exposure category, a total of six cases of cancer were observed (SIR, 0.4 [95% CI, 0.2-1.1]), none of which were cancer of the lung. There was no case of mesothelioma (Wergeland et al., 1990).[14]

Mortality rates among workers employed in the talc quarry in Luzenac, France, were reported by Léophonte and Didier (1990).[15] The talc in this region contains chlorite and dolomite, 0.5-3% quartz, but no asbestos. The results described in this report confirm those of the previous publication by these authors (Léophonte et al., 1983).[13]

A cohort-mortality study at the Luzenac talc quarry and milling plant in France comprised 1070 men and 90 women employed ≥ 1 yr during 1946-1994.

* The concentration of radon daughters is measured in units of working level (WL) which is a measure of the potential alpha particles energy per litre of air. One WL of radon daughters corresponds to approximately 200 pCi/L of radon in a typical indoor environment.

No statistically significant excess mortality was found for any cancer (Wild, 2000).[16]

A combined analysis comprised the 1070 workers at Luzenac and 542 workers of three talc mines and mills in Austria, who had been employed ≥ 1 yr during 1972-1995. There was no excess of total cancer or lung cancer in the Austrian cohort. A nested-case control study was conducted with 30 lung cancer cases (23 from the French and 7 from the Austrian cohort) and 88 matched controls. Job tasks were categorized according to talc dust levels (no exposure; < 5 mg/m^3; 5-30 mg/m^3 and > 30 mg/m^3) and cumulative talc exposure (in mg/m^3-yr) was calculated for cases and controls. There was no evidence of increased lung cancer with increasing exposure. Adjusting for tobacco smoking, exposure to quartz or underground work did not change the results (Wild et al., 2002).[17]

A meta-analysis of lung cancer mortality studies among miners and millers processing non-asbestiform talc in the United States (Selevan et al., 1979)[12], France (Wild, 2000)[16], Austria (Wild et al., 2002)[17], Norway (Wergeland et al., 2003)[14] and Italy (Coggiola et al., 2003)[11] was performed by Wild (2006)[18]. Studies with populations in which no other occupational carcinogen was mentioned (only talc millers satisfied this criterion) reported no excess lung cancer mortality (overall SMR of 0.92; 95% CI, 0.67-1.25, 42 cases) (Wild, 2006[18]).

In a community-based case-control study in Canada (Siemiatycki, 1991), information on job histories and on potential confounders was obtained through interviews.[19] Over 4000 subjects were interviewed including patients with 20 different types of cancer and a population control series. Potential occupational exposures included industrial talc, notably among painters, car mechanics and farmers. There were no statistically significant increases in cancer risk associated with exposure to talc.

IARC (2006, 2010) summarises in their view on the abovementioned studies that he carcinogenic effect of exposure to talc not contaminated by asbestiform fibres has been investigated in five independent but relatively small cohort studies of talc miners and millers in the USA, Norway, Italy, France and Austria.[1,2] The miners and to a lesser extent the millers in these cohorts were also exposed to quartz. In the miners in the US study, an excess risk for lung cancer was found, which may have been due to exposure to radon daughters and quartz in the workplace. In all the other groups of workers studied, there was no increased risk for lung cancer. In the two studies from Norway and Italy, which included an estimate of cumulative exposure to talc dust, the risk for lung cancer in the

highest category was found to be close to or below unity. In a case-control study nested in the combined cohorts of talc workers from France and Austria, there was no tendency of higher risks for lung cancer by increasing cumulative exposure of workers to talc dust. In four of five studies, it was explicitly stated that no case of mesothelioma was observed [summary IARC 2006].

Churg and Wiggs (1985) analyzed the total fibrous and non-fibrous mineral content of the lung in 14 male lung cancer patients without history of occupational dust exposure and 14 controls, matched by sex, age, smoking history and general occupational class.[20] Lung cancer patients had an average of 114 ± 161 talc mineral particles and 1.1 ± 1.4 talc mineral fibres/g dry lung, while the controls had averages of 28 ± 20 talc mineral particles and 0.5 ± 0.5 talc mineral fibres/g dry lung [not clear whether the differences are statistically significant]. However, lung cancer patients also had increased amounts of kaolinite, mica, feldspars and crystalline silica mineral particles and mineral fibres in the lung.[20] Therefore, no conclusions can be drawn regarding the association of (talc) mineral particles and fibres and lung cancer.

Thomas and Stewart (1987, 1990) examined lung cancer mortality in a cohort study among 2055 white men employed in three ceramic plumbing fixture factories.[21,22] In a cohort mortality study, 2055 white men, employed for at least one year between 1939 and 1966 at three plants of a single USA company, were followed through January 1981. Lung cancer mortality was significantly higher than expected among workers whose jobs involved simultaneous exposure to high silica and non-fibrous talc (standardized mortality ratio 2.54), but not among workers exposed to only talc or only silica. In the group of workers simultaneously exposed to silica and non-fibrous (nonasbestiform) talc, lung cancer mortality risk increased with increasing number of years of exposure to non-fibrous talc, but showed no pattern by number of years of exposure to silica. Lung cancer risk increased with years since first non-fibrous talc exposure and decreased with age at first exposure.[21,22]

Chiazze et al. (1993) described a case-control study of malignant and non malignant respiratory disease among employees of a fiberglass manufacturing facility in Ohio.[23] Employment histories from the fiberglass facility provided information on employment characteristics (duration of employment, year of hire, age at first hire) and an interview survey obtained information on demographic characteristics (birthdate, race, education, marital state, parent's ethnic background, and place of birth), lifetime residence, occupational and smoking histories, hobbies, and personal and family medical history. Matched, unadjusted odds ratios (ORs) were used to assess the association between lung cancer or non-malignant respiratory disease and the cumulative exposure history,

demographic characteristics, and employment variables. Adjusted ORs for lung cancer and non malignant respiratory disease after talc use versus never exposed were 1.355 (95% CI 0.407-4.515) and 0.760 (95% CI 0.175-3.298), respectively.[23] It must be noted that data may be difficult to interpret, since employees were also exposed to respirable fibers, fine fibers, asbestos, formaldehyde, silica, and asphalt fumes.

Honda et al. (2002) evaluated mortality among workers at an industrial (tremolite) talc mining and milling facility in New York.[24] Subjects were white men actively employed between 1948 and 1989 and known to have been alive in or after 1950. Analyses assessed cancer mortality during the period 1950-89 (809 subjects) and non-cancer mortality during 1960-89 (782 subjects). Comparisons with regional general population death rates for 1960-89 indicated that the workers had more than expected deaths from all causes combined [209 observed/ 160 expected, standardized mortality ratio (SMR) = 1.31, 95% confidence interval (CI) = 1.14-1.50], due mainly to increased mortality from lung cancer (31/13, SMR = 2.32, CI = 1.57-3.29) and non-malignant respiratory disease (NMRD) (28/13, SMR = 2.21, CI = 1.47-3.20). The median estimated exposure to respirable dust was 511 mg/m^3-days for all exposed employees, 739 mg/m^3-days for mine workers and 683 mg/m^3-days for mill workers. Employees with high, compared with low, estimated exposure to talc dust had a rate ratio of 0.5 (CI = 0.2-1.3) for lung cancer and of 11.8 (CI = 3.1-44.9) for pulmonary fibrosis.[24] It must be noted that the facility contains a high amount of non-asbestiform amphibole.

Ramanakumar et al. (2008) analyzed lung cancer risk in relation to talc exposure, adjusted for several potential confounders, including smoking, in two large population based case-control studies of lung cancer carried out in Montreal. Detailed lifetime job histories were elicited, and a team of hygienists and chemists evaluated the evidence of exposure to a host of occupational substances. Several analyses were carried out separately in four study populations: Study I – using population controls, Study I – using cancer controls, Study II – males and Study II – females and a pooled analysis. Subjects with occupational exposure to industrial talc and cosmetic talc did not experience any detectable excess risk of lung cancer (ORs and 95%CIs in study I: 0.6; 0.2-2.7 and 0.7; 0.3-1.7 for industrial talc using population controls and cancer controls, respectively; 0.3; 0.1-2.0 and 0.4; 0.3-3.6 for cosmetic talc using population controls and cancer controls, respectively; ORs and 95%CIs in study II: 1.4; 0.4-3.1 for industrial talc in males; 0.4; 0.1-2.1 for cosmetic talc in females; pooled ORs and 95%CIs: 0.9; 0.5-1.3 for industrial talc and 0.7; 0.3-1.8 for cosmetic talc).[25]

Langseth and Andersen (1999) investigated the cancer risk among female Norwegian pulp and paper workers.[26] The cohort included a total of 4,247 workers employed for at least one year between 1920 and 1993 and the follow-up period for cancer was from 1953-1993. During the follow-up period, 380 new cases of cancer were observed vs. 322 expected (standard incidence ratio (SIR) 1.2, 95% CI 1.07-1.30). An excess risk of ovarian cancer was found (SIR 1.5, 95% CI 1.07-2.09). The SIR was highest among those younger than 55 years, and mostly among those working in paper departments. Short-term workers showed increased risk of lung and bladder cancer (SIR 3.0, 95% CI 1.29-5.89 and SIR 3.7, 95% CI 1.00-9.38, respectively)[26]. It should be noted that, besides to talc, the women might also have been exposed to asbestos and different types of paper dust as well as to other chemicals used in the pulp and paper industry.

Among others based on the previous cohort study, Langseth and Kjaerheim (2004) investigated the association between ovarian cancer and occupational talc exposure among Norwegian pulp and paper workers in a case-control set-up. Forty-six cases of ovarian cancer, with four controls each, were included in the study. No association between ever talc exposure in the Norwegian pulp and paper industry and ovarian cancer was found (odds ratio 1.10, 95% CI 0.56-2.18).[27] It is not clear from the study description if there was an overlap in the study populations from the two Langseth studies.

Hartge and Stewart (1994) investigated the occupational exposure to talc in relation to ovarian cancer risk. Job histories of 296 women aged 20-79 who were diagnosed with epithelial ovarian cancer in the Washington DC area in 1978-1981 were compared to 343 hospital controls, matched for age and race. Occupational exposure to talc for more than 10 years resulted in a relative risk of 0.5 (95% CI 0.2-1.5) when compared to no occupational exposure to talc, indicating that occupational exposure to talc is not associated with an altered risk of ovarian cancer.[28]

3.1.2 Epidemiological studies on perineal use of talc-based body powders

Talc-based body powder has been used by women on the perineum (or genital area) and on sanitary napkins. In total, data from one prospective cohort study and over 20 case-control studies are available to date (June 2012) to evaluate the association of use of talc-based body powder and risk for ovarian cancer. Also a number of meta-analyses are available as yet.

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.[29] This analysis was conducted among

participants in the Nurses' HealthStudy. The study population included 78,630 women who responded to the questions on powder use in 1982 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. 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).

IARC (2010[2], based on the activities of the working group in 2006[1]) summarizes their view on the 19 of the case-control studies. They included between 77 and 824 cases and between 46 and 1,105 controls. Five were hospital-based designs and the others were population-based studies. The IARC Working Group selected a subset of 8 of these studies as being more informative based on the following characteristics: whether the study was population-based, was of a reasonable size, had acceptable participation rates and included information to allow control for potentially important confounders (Cramer et al. 1982[30], Harlow BL et al. 1992[31], Chan & Risch 1997[32], Cook et al. 1997[33], Green et al. 1997[34], Cramer 1999[35], Ness et al. 2000[36], Mills et al. 2004[37]).

Cramer et al. (1982) reported a case-control study of ovarian cancer and talc exposure in the Boston, Massachusetts, USA, area between November 1978 and September 1981.[30] Two-hundred-and-fifteen women with pathologically-confirmed epithelial ovarian cancers were identified and matched randomly by residence, race and age. Ninety-two (42.8%) cases regularly used talc either as a dusting powder on the perineum or on sanitary napkins compared with 61 (28.4%) controls. Adjusted for parity and menopausal status, this difference yields a relative risk of 1.9 ($p<0.003$). Women who had regularly engaged in both practices had an adjusted relative risk of 3.3 ($p<0.001$) compared to women with neither exposure.

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).[31] 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. A total of 526 women were contacted as potential controls. 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).

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).[34] [The analysis by Green et al. (1997) used the same number of cases but five fewer controls than Purdie et al. (1995).] 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.

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.[32] 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).

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.[33] 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. Three hundred twenty nine cases were interviewed (64.3%) and 313 were included in the analysis [61.1%]. Fivehundred twenty one controls were interviewed and 422 were included in the analysis [58.5%]. 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. The authors also evaluated the association between any genital use of powder and the risk for the major histological subtypes of ovarian cancer. 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.

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.[35] 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).

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.[36] The study was conducted among 767 recently diagnosed cases of epithelial ovarian cancer and 1,367 population-based controls. 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). 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.

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.[37] 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 1,122 controls identified by random-digit dialling. Controls were frequency-matched to the cases by age and ethnicity. 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).

These 8 studies selected by IARC included at least 188 cases and had participation rates generally ranging from 60 to 75%. Among these eight studies, the prevalence of perineal use of talc-based body powder among controls ranged from 16 to 52%; however, information on exposure was not collected in a comparable manner across studies. In addition, frequency and duration of use or total lifetime applications were reported in several studies as well as consideration of prior tubal ligation or hysterectomy. Only sparse data were available on whether women had used body powder prior to or after the mid-1970s.

The relative risks for ovarian cancer among body powder users (versus non-users) were homogenous across this relatively diverse set of eight studies, each of which indicated a 30-60% increase in risk [significance not mentioned]. Among the other 11 case-control studies, most also reported relative risks of this

magnitude or higher. The subset of studies that assessed use of talc on a diaphragm was relatively uninformative due to low precision.

Results on exposure-response relationships were presented in the cohort study (Gertig et al. 2000)[29] and in seven of the more informative case-control studies. In the cohort study, no exposure-response trend was apparent. Positive exposure-response trends were apparent in the two Boston-based studies, which presented the most comprehensive analysis. In the remaining five studies, consistent trends were not observed.

Several meta-analyses were performed with regard to the association of perineal talc use and ovarian cancer which were not included in the IARC monography. Meta-analyses of nine case-control studies that have been published that address the purported association between talc use and an increased risk of ovarian cancer were performed by Gross & Berg (1995). Meta-analyses were performed for crude and adjusted risk, and for malignant and borderline tumors together and epithelial tumors only. Crude risk, both tumor types: RR 1.27 (1.09-1.48); adjusted risk, both tumor types: 1.31 (1.08-1.58); crude risk, epithelial tumors: 1.20 (1.01-1.44); adjusted risk, epithelial tumors: 1.29 (1.02-1.63).[38]

According to Cramer et al. (1999), the combined OR from 14 case control studies on the risk for ovarian cancer with genital use of talc was 1.36 (95% CI 1.24-1.49), which is statistically significant.[35]

Huncharek et al. (2003) performed a meta-analysis to evaluate the association between perineal cosmetic talc use and increased risk of epithelial ovarian cancer (never vs. ever or none vs. any). Data from 16 observational studies were pooled using a general variance based meta-analytic method. This resulted in a RR of 1.33 (95% CI 1.16-1.45), a statistically significant result. Nevertheless, the data showed a lack of a clear dose-response relationship. Since hospital-based studies did not show a significant relationship between talc use and ovarian cancer risk (RR 1.19, 95% CI 0.99-1.41), in contrast to population-based studies (RR 1.38, 95% CI1.25-1.52), the authors suggest that selection bias and/or uncontrolled confounding may account for the positive association observed in many studies.[39]

In addition, Huncharek et al. (2008) performed another meta-analysis, in which 9 observational studies were included which have studied the association of ovarian cancer risk and direct exposure of the female genital tract to talc via dusting of contraceptive diaphragms. [Some of the studies included were also used for the meta-analysis of 2003.] Adjusted ORs ranged from 0.5-1.56 and none of the studies reached a significant effect on ovarian cancer risk. Data were

pooled using a general variance based meta-analytic method. The results yielded a non-statistically significant summary relative risk of 1.03 (95% CI 0.8-1.37).[40]

In addition, Muscat and Huncharek (2008) reported in a review that in 7 studies that gathered information on (talc-dusted) condom use, none of these studies found an increased risk with ovarian cancer. Crude RRs ranged from 0.49-1.0.[41]

More recently, a review was published by Langseth et al. (2008).[42] This review included the association between talc use in the perineal region and ovarian cancer investigated in one cohort study, and 20 case-control studies. In the cohort study, there was no association between cosmetic talc use and risk of all subtypes of ovarian cancer combined. The various case-control studies provided indications of either a significant excess risk (10 studies) or non-significant excess risk or null (10 studies), with odds ratios (ORs) ranging from 1.0 to 3.9 (see Table 1). None of the studies reported relative risks below 1.0. Pooled odds ratios, calculated by fixed effects model, were 1.40 (95% CI 1.29-1.52), 1.12 (95% CI 0.92-1.36) and 1.35 (95% CI 1.26-1.46) for population-based, hospital-based and all case control studies combined, respectively. No clear trend of exposure-response associations, in terms of frequency of use or length of use in years was found in the studies. Before 1976, talc was to some extent contaminated with asbestos, so that the early studies relating talc to ovarian cancer may have been confounded by the asbestos. However, the association between talc exposure and ovarian cancer is as strong in recent studies, as in earlier ones, diminishing the likelihood that all these results are influenced by contamination of talc by asbestos.[42]

3.2 Carcinogenicity studies in animals

3.2.1 Inhalation studies

The IARC Working Group noted that in most of the studies of talc described below, no or limited characterization of the mineralogy of the sample employed was given, and, in particular, there was a lack of information on fibre content or particle size. In most studies, information was insufficient to determine whether the talc contained asbestiform fibres.

Wistar-derived rats (24/sex/group), six to eight weeks of age, were exposed by inhalation to a mean respirable dust concentration of 10.8 mg/m^3 Italian talc (grade 00000; ready milled; mean particle size, 25 μm; containing 92% talc, 3% chlorite, 1% carbonate minerals and 0.5-1% quartz) for 7.5 h per day on five days a week for six (24 rats) or twelve (24 rats) months (cumulative exposures, 8,200

and 16,400 mg/m^3 × h, respectively). Ten days after the end of each exposure period, six rats in each group were killed; a further four rats were killed in each group one year later. Within 28 months of the start of the study, a further 12 animals in each group had died. No lung tumours were observed in rats exposed to talc for six months, while one lung adenoma occurred among those exposed for twelve months. No lung tumour was found in the controls (Wagner et al., 1977).[43] [The IARC Working Group noted the limited number of animals allowed to survive longer than 12 months after the end of each exposure period.]

Syrian golden hamsters (50/sex/group), four weeks old, were exposed to an aerosol of talc body powder, prepared from Vermont talc by flotation (95% w/w platy talc with trace quantities of magnesite, dolomite, chlorite and rutile), for 3, 30 or 150 min per day on five days a week for 30 days. The mean total aerosol concentration was 37.1 mg/m^3, with a mean respirable fraction of 9.8 mg/m^3 and a mass median aerodynamic diameter of 4.9 μm. Two further groups of hamsters, seven weeks old, were exposed to talc aerosol for 30 or 150 min per day for 300 days or until death. The mean total aerosol concentration was 27.4 mg/m^3, with a mean respirable fraction of 8.1 mg/m^3 and a mass median aerodynamic diameter of 6 μm. Two control groups (25/sex/group) were sham exposed. No primary neoplasm was found in the respiratory system of any hamster. The incidence of alveolar-cell hyperplasia was 25% in the groups exposed to aerosol for 30 or 150 min per day for 300 days, compared with 10% in the control group (Wehner et al., 1977, 1979).[44,45][The IARC Working Group noted the inadequate duration of the study.]

Syrian golden hamsters (24/sex/group), nine weeks old, received 18 weekly intratracheal injections of 3 mg talc (United States Pharmacopeia grade; 93.3% below 25 μm) in 0.2 ml saline, with or without 3 mg benzo[α]pyrene, or 0.2 ml saline only, or were untreated. The animals were allowed to live out their lifespan (average 50% survival, 46-55 weeks). No respiratory-tract tumour was observed in animals exposed to talc alone or in saline-treated or untreated controls. In hamsters exposed to talc with benzo[α]pyrene, 33/45 animals had benign and malignant tumours of the respiratory tract (larynx to lung) (Stenbäck and Rowland, 1978).[46] [The IARC Working Group noted that no group received benzo[α]pyrene alone and that the survival in all groups was relatively short.]

Male and female Fischer 344N rats were exposed by inhalation to aerosols of 0, 6, or 18 mg/m^3 talc (MP 10-52; maximum particle size, 10 μm) for 6 h/day on 5 days/wk for up to 113 wk (males) and 122 wk (females). MP 10-52 grade talc is a high-purity microtalc from a Montana strip mine that is reported to contain no tremolite or any asbestiform minerals; it was found to be free of asbestos by polarized light microscopy and transmission electron microscopy. The survival

of the exposed rats was similar to that of the controls. No clinical findings were attributed to exposure to talc. Exposure to talc produced a spectrum of inflammatory, reparative and proliferative processes in the lungs. The incidences of alveolar/bronchiolar carcinoma or adenoma and carcinoma (combined) in female rats were control, 1/50; low-dose, 0/48; and high-dose, 13/50 (carcinoma, 5/50), and were significantly higher in the high-dose group than in controls ($p < 0.001$). The incidences of pulmonary neoplasms in exposed male rats were similar to those in controls. Adrenal medulla phaeochromocytomas (benign and malignant combined) occurred with a significant positive trend in males (control, 26/49; low-dose, 32/48; high-dose, 37/47; $p = 0.006$) and females (control, 13/48; low-dose, 14/47; high-dose, 23/49; $p = 0.02$). Incidences of malignant phaeochromocytomas in females were: control, 0/48; low-dose, 1/47; high-dose, 10/49 ($p = 0.001$) (revisited).[47] [The IARC Working Group discussed the high background incidence of the phaeochromocytomas in this strain of rats and noted that this type of tumor was not reported in particle inhalation studies other than those of the National Toxicology Program. The IARC Working Group did not consider it probable that the increased incidence of phaeochromocytomas was causally related to talc, but based on the experimental data available, neither can talc-related effects be excluded.]

In a parallel study, male and female $B6C3F_1$ mice were exposed by inhalation (6 h/day on 5 days/wk for up to 104 wk) to 0, 6, or 18 mg/m^3 MP 10-52 talc. Survival and final mean body weights of the exposed mice were similar to those of the controls, and no clinical findings were attributed to exposure to talc. No significant increase in the incidence of neoplasms was observed and the incidence of pulmonary neoplasms was similar in exposed and control groups.[47]

[According to Oberdörster and the ILSI Risk Science Institute, the lung tumours found in the rat study are a secondary effect of chronic pulmonary overload and not a direct carcinogenic effect of talc. In mice and hamsters, tumorigenesis has not been observed after lung overload. It is still not known with certainty whether high lung burdens of poorly soluble particles as talc can lead to lung cancer in humans via mechanisms similar to those of the rat.[48,49]]

3.2.2 Oral studies

Wistar rats (25/sex/group), ten weeks of age, received about 50 mg/kg bw per day commercial talc [characteristics unspecified] in the diet or standard diet for life (average survival, 649 days). No significant difference in tumour incidence was found in comparison with controls (Gibel et al., 1976).[50]

Wistar-derived rats (16/sex/group), 21-26 weeks of age, were exposed to 100 mg Italian talc (grade 00000; ready milled; mean particle size, 25 μm; containing 92% talc, 3% chlorite, 1% carbonate minerals and 0.5-1% quartz) per day per rat in the diet for five months and then maintained on basal diet for life (average survival, 614 days). A control group of 16 rats was fed basal diet. No difference in tumour incidence was found between the two groups (Wagner et al., 1977).[43] [The IARC Working Group noted the limited exposure period and the advanced age of the animals at the start of exposure.]

3.2.3 Other studies

In one study in rats (Pott et al. 1974)[51] and two studies in mice (Bischoff & Bryson, 1976)[52] of intraperitoneal administration of talc, no increase in the incidence of mesotheliomas was observed. Two other studies of intraperitoneal administration, one in rats and one in mice, were found to be inadequate for evaluation. One study in rats and one study in mice by intrathoracic administration were found to be inadequate for evaluation. In one study by intrapleural injection of talc in rats (Wagner et al.,1977)[43] and in another study by intrapleural implantation of various talcs in rats, tumour incidence was not increased (Stanton et al.,1981)[53]. A single subcutaneous injection of talc in mice did not produce local tumours (Neukomm & de Trey, 1961)[54]. No tumour was produced in rats in one study of administration of talc in the diet or in another study by implantation of talc into the ovary Hamilton et al.,1984).[55] Tumour incidence was not increased following administration of talc to hamsters by inhalation or intratracheal administration (Stenbäck & Rowlands, 1978).[46]

3.3 Cell transformation tests

Normal human epithelial (OSE2a) and granulosa ovarian (GC1a) cell lines and polymorphonuclear neutrophils (PMN) were incubated with talc (0-500 μg/mL) from 24 to 120 h. Talc significantly increased proliferation, induced neoplastic transformation (in the OSE2a cells at 5 and 20 μg/mL talc and in the GC1a cells at 5, 20 and 100 μg/mL talc). In addition, talc increased reactive oxygen species (ROS) generation time-dependently in the ovarian cells (at 20 μg/mL (72 and 120 h) and 50 μg/mL in OSE2a cells and with 0.5, 20 and 50 μg/mL (72 and 120 h), as well as 5 and 100 μg/mL (120 h) in GC1a cells, compared with the respective 24 h values), and dose-dependently in the PMN (significant at 0.5, 5, 20, 50 μg/mL (24 h) and 100 and 500 μg/mL (24 and 72 h)).[56]

Chapter 4

Mode of action

4.1 Genotoxic mode of action

4.1.1 Gene mutation assay

In vitro

Talc was not mutagenic to *Salmonella typhimurium* TA1530 or *his* G46 or to *Saccharomyces cerevisiae* D3 in vitro [full details not given].[3]

In vivo

Talc was not mutagenic in host-mediated assays in mice (30-5,000 mg/kg bw)[3]. Neither chromosomal aberrations nor dominant lethal mutations were induced in rats following oral administration of 30-5,000 mg/kg bw talc.[3]

4.1.2 Cytogenetic assays

In vitro

Chromosomal aberrations were not induced in human WI38 cells treated with talc at 2-200 µg/mL.[3] Endo-Capron and colleagues (1993) tested the genotoxicity of 3 talc samples (French, Italian and Spanish talc) in cultures of rat pleural

mesothelial cells (RPMC) using genotoxicity assays for unscheduled DNA synthesis (UDS) and sister chromatid exchanges (SCEs). Each talc sample contained 90-95% talc, other compounds being chlorite and dolomite. For UDS, cells were treated with talc concentrations of 0, 10, 20 and 50 μg/cm^2 (or 0, 50, 100 and 250 μg/L) for 24 hours. For the SCE assay, cells were treated with 0, 2, 5, 10 or 15 μg/cm^2 (or 0, 15, 37.5, 75 or 112.5 μg/L) for 48 hours in the dark. None of the talc samples induced enhancement of UDS or SCEs in treated cultures, in contrast to the positive controls (Rhodesian chrysotile and crocidolite asbestos).[57]

In vivo

Single intraperitoneal injections of 20 mg talc plus 2 mg particulate prednisolone acetate in saline into mice induced significant numbers of multinucleated giant cells within 48 h. Neither compound alone induced this response. The multinucleate cells arose by cell fusion and the resultant polykarions exhibited severe structural chromosomal abnormalities (bridges, acentrics and dispersed chromosomes). Prednisone in combination with talc also elicited the formation of multinucleated giant cells. Polykarions were not observed when talc was injected in combination with cortexone acetate, cortisone or testosterone isobutyrate (Dreher et al., 1978).[58]

Chapter 5

Classification

5.1 Evaluation of data on carcinogenicity and genotoxicity

No data with regard to the carcinogenic effects of ingestion of talc were available in humans.

Carcinogenicity following the inhalation of talc (not containing asbest or asbestiform fibers, although sometimes contaminated with other dusts) has been extensively studied in workers of talc mines, mills or factories chronically exposed to talc dusts. A meta-analysis of lung cancer mortality studies among miners and millers processing non-asbestiform talc in the United States (Selevan et al., 1979)[12], France (Wild, 2000)[16], Austria (Wild et al., 2002)[17], Norway (Wergeland et al., 2003)[14] and Italy (Coggiola et al., 2003)[11] was performed by Wild (2006)[18]. This analysis indicates that studies with populations of talc millers exposed to high levels of relatively pure talc in which no other occupational carcinogen was mentioned, no excess lung cancer mortality was reported (overall SMR of 0.92; 95% CI, 0.67-1.25, 42 cases). These studies are in support of the view that talc is not carcinogenic to man. On the other hand, in some population studies of talc miners and talc workers in other industrial settings the cancer mortality risks were in excess. However, in these studies coexposures to carcinogens such as quartz may obscure either the presence or absence of a carcinogenic effect of talc. Therefore, the results of these studies are not sufficient to exclude talc as a carcinogen.

Twenty case-control studies were identified on the association between perineal use of talc-based body powders and risk of ovarian cancer and used for a meta-analysis. Six were hospital-based designs and the others were population-based studies. While none of the hospital-based studies showed a significant increase in the risk of ovarian cancer following perineal talc use, 10 of the population-based studies did. Moreover, a meta-analysis of all population-based studies as well as a meta-analysis of all hospital- and population-based studies combined showed a significant increase in risk of ovarian cancer (1.40; 95% CI 1.29-1.52 and 1.35; 95% CI 1.26-1.46) (Langseth et al., 2008).[42] In contrast, in a cohort study no indications for an association between perineal talc use and ovarian cancer were found. A clear exposure-response relationship (either frequency based or length in years based) was lacking in most of the studies or not even investigated. Several factors have to be kept in mind, such as the possibility of recall bias, selection bias and uncontrolled confounding. In addition, adequate mechanistic data are still absent, and the fact that several studies, including a cohort study are negative do raise questions regarding the exact association of perineal talc use and risk of ovarian cancer. The Committee considers the association between perineal exposure and ovarial cancer not very convincing but taken together the data are not sufficient to exclude talc as a carcinogen.

The Committee is of the opinion that, if only the results of the occupational studies in talc millers were to be evaluated, talc could be classified as not carcinogenic to humans. However, the Committee is also aware of the occupational studies on talc miners and other industrial populations which do not justify to exclude talc as a lung carcinogen. In addition, the Committee is aware of the human studies on perineal exposure which do not exclude talc in talc-based body powder as an ovarian carcinogen. Taken together, the Committee is of the opinion that the epidemiological studies not sufficiently prove that talc is not a carcinogen.

Oral studies in rats do not indicate that talc is carcinogenic. In addition, subcutaneous, intraperitoneal, intrathoracic and intrapleural injections in mice and/or rats did not increase the incidence of tumors. Also, no tumours were induced in rats in one study where talc was implantated into the ovary.

Inhalation of aerosols of talc (18 mg/m^3, 6h/d, 5d/w, 122w) resulted in a significantly higher incidence of adrenal medulla phaeochromocytomas (benign and malignant combined) in male (37/47 vs 26/49 in controls) and female Fischer rats (23/49 vs 13/48 in controls). However, it is not probable that this is causally related to talc, since Fischer rats show a high background incidence of

phaeochromocytomas, and phaeochromocytomas were not observed in other (NTP) studies. In female rats (but not in male rats) a significantly higher incidence of alveolar/bronchiolar carcinoma or adenoma and carcinoma (combined) was observed. Tumour incidence (either local or not local) was not increased following repeated inhalation exposure in other studies in rats, mice and hamsters (doses up to 10.8 mg/m^3, 7.5h/d, 5d/w, 12 m; 18 mg/m^3, 6h/d, 5d/w, 104w; 9.8 mg/m^3, 2.5h/d, 5d/w, 30d). The lung tumours found in the first rat study are suggested to be a secondary effect of chronic pulmonary overload and not a direct carcinogenic effect of talc. However, currently it cannot be excluded that a similar mechanism could also occur in humans. Thus, in spite of the adrenal medulla phaeochromocytomas observed in one inhalation study in rats, which are probably not talc-related, further animal data do not indicate a direct carcinogenic potency of talc not containing asbest or asbestiform fibers. Nevertheless, alveolar/bronchiolar carcinomas were observed in rats due to lung overload with talc particles, indicating that carcinogenesis might occur as a secondary effect to inhalation exposure to talc. This secondary carcinogenic effect of talc may also be relevant for humans.

With respect to the animal studies the Committee is of the opinion that, in spite of one reliable (NTP) study, their number is limited and their quality is not sufficient to conclude on the carcinogenic potential of talc.

No data on the genotoxicity of talc in humans were available. The results of the few in vitro studies and the single in vivo study available on the genetic toxicology of talc were negative. Therefore, the available data indicate that talc is not genotoxic.

5.2 Recommendation for classification

Based on the available information, although mainly indicating the absence of carcinogenicity, the Committee is of the opinion that the data are insufficient to evaluate the carcinogenic properties of talc (category 3).*

* According to the new classification system of the Health Council (see Annex F).

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A	Request for advice
B	The Committee
C	The submission letter (in English)
D	Comments on the public review draft
E	IARC Monograph
F	Carcinogenic classification of substances by the Committee

Annexes

Annex **A**

Request for advice

In a letter dated October 11, 1993, ref DGA/G/TOS/93/07732A, to, the State Secretary of Welfare, Health and Cultural Affairs, the Minister of Social Affairs and Employment wrote:

Some time ago a policy proposal has been formulated, as part of the simplification of the governmental advisory structure, to improve the integration of the development of recommendations for health based occupation standards and the development of comparable standards for the general population. A consequence of this policy proposal is the initiative to transfer the activities of the Dutch Expert Committee on Occupational Standards (DECOS) to the Health Council. DECOS has been established by ministerial decree of 2 June 1976. Its primary task is to recommend health based occupational exposure limits as the first step in the process of establishing Maximal Accepted Concentrations (MAC-values) for substances at the work place.

In an addendum, the Minister detailed his request to the Health Council as follows:

The Health Council should advice the Minister of Social Affairs and Employment on the hygienic aspects of his policy to protect workers against exposure to chemicals. Primarily, the Council should report on health based recommended exposure limits as a basis for (regulatory) exposure limits for air quality at the work place. This implies:

- A scientific evaluation of all relevant data on the health effects of exposure to substances using a criteria-document that will be made available to the Health Council as part of a specific request

for advice. If possible this evaluation should lead to a health based recommended exposure limit, or, in the case of genotoxic carcinogens, a 'exposure versus tumour incidence range' and a calculated concentration in air corresponding with reference tumour incidences of 10^{-4} and 10^{-6} per year.

- The evaluation of documents review the basis of occupational exposure limits that have been recently established in other countries.
- Recommending classifications for substances as part of the occupational hygiene policy of the government. In any case this regards the list of carcinogenic substances, for which the classification criteria of the Directive of the European Communities of 27 June 1967 (67/548/EEG) are used.
- Reporting on other subjects that will be specified at a later date.

In his letter of 14 December 1993, ref U 6102/WP/MK/459, to the Minister of Social Affairs and Employment the President of the Health Council agreed to establish DECOS as a Committee of the Health Council. The membership of the Committee is given in Annex B.

Annex **B**

The Committee

- R.A. Woutersen, *chairman*
  Toxicologic Pathologist, TNO Innovation for Life, Zeist; Professor of Translational Toxicology, Wageningen University and Research Centre, Wageningen
- J. van Benthem
  Genetic Toxicologist, National Institute for Public Health and the Environment, Bilthoven
- P.J. Boogaard
  Toxicologist, SHELL International BV, The Hague
- G.J. Mulder
  Emeritus Professor of Toxicology, Leiden University, Leiden
- Ms M.J.M. Nivard
  Molecular Biologist and Genetic Toxicologist, Leids University Medical Center, Leiden
- G.M.H. Swaen
  Epidemiologist, Dow Chemicals NV, Terneuzen
- E.J.J. van Zoelen
  Professor of Cell Biology, Radboud University Nijmegen, Nijmegen
- G.B. van der Voet, *scientific secretary*
  Toxicologist, Health Council of the Netherlands, The Hague

The Health Council and interests

Members of Health Council Committees are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the chairperson and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the Committee's work. It is the responsibility of the President of the Health Council to assess whether the interests indicated constitute grounds for non-appointment. An advisorship will then sometimes make it possible to exploit the expertise of the specialist involved. During the inaugural meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.

Annex **C**

The submission letter (in English)

Subject : Submission of the advisory report *Talc*
Our reference : DGV/MBO/U-932342
Your Reference : U-7257/BvdV/fs/246-M16/E
Enclosed : 1
Date : 24 July 2012

Dear State Secretary,

I hereby submit the advisory report on the effects of occupational exposure to *Talc*.

This advisory report is part of an extensive series in which carcinogenic substances are classified in accordance with European Union guidelines. This involves substances to which people can be exposed while pursuing their occupation.

The advisory report was prepared by the Subcommittee on Classifying Carcinogenic Substances, a permanent subcommittee of the Health Council's Dutch Expert Committee on Occupational Safety (DECOS). The advisory report has been assessed by the Health Council's Standing Committee on Health and the Environment.

I have today sent copies of this advisory report to the State Secretary of Infrastructure and the Environment and to the Minister of Health, Welfare and Sport, for their consideration.

Yours sincerely,

(signed)
Prof. H. Obertop,
Acting President

Annex **D**

Comments on the public review draft

A draft of the present report was released in February 2012 for public review. The following organisations and persons have commented on the draft document:

- Scientific Association of the European Talc Industry (EUROTALC aisbl), Brussels, Belgium
- Talc/Wollastonite Section of the Industrial Minerals Association North America (IMA-NA), Washington DC, USA
- IMERYS Talc America Inc, San Jose, CA, USA

Annex **E**

IARC Monograph

Talc (perineal use of talc-based body powder and inhaled talc not containing asbestos or asbestiform fibres) has been evaluated by IARC in 2006.

The summary and evaluation of IARC on the perineal use of talc-based body powder and inhaled talc not containing asbestos or asbestiform fibres in IARC monograph 93 (2010) is provided.

D.1 VOL: 93

CAS No.: 14807-96-6

Summary of Data Reported and Evaluation

Exposure data

The term ‘talc’ refers to both mineral talc and industrial products that contain mineral talc in proportions that range from about 35% to almost 100% and are marketed under the name talc. Mineral talc occurs naturally in many regions of the world where metamorphosed mafic and ultramafic rocks or magnesium carbonates occur. Mineral talc is usually platy but may also occur as asbestiform fibres. (Asbestiform refers to a habit, i.e. a pattern of mineral growth and not to the presence of other minerals. Asbestiform talc must not be confused with talc

that contains asbestos.) Together with platy talc, asbestiform talc is found in the Gouverneur District of New York State, USA, and occasionally elsewhere; it may be associated with other minerals as observed by transmission electron microscopy.

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

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

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

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

Human carcinogenicity data

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

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

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

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

The 19 case-control studies were conducted in the USA, Canada, the United Kingdom, Australia, Greece, Israel and China and included between 77 and 824 cases and between 46 and 1105 controls. Five were hospital-based designs and the others were population-based studies. The Working Group selected a subset of these studies as being more informative based on the following characteristics:

whether the study was population-based, was of a reasonable size, had acceptable participation rates and included information to allow control for potentially important confounders.

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

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

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

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

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

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

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

recall bias could result from the fact that women with a cancer may be more likely to remember or over-report a habit, such as body powder use, if they thought that it may have played a role in their illness. The Working Group believes this source of bias is a possibility inherent in the case-control studies and cannot be ruled out. The Working Group also considered publication and selection biases and these were not judged to have substantially influenced the pattern of findings.

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

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

- The eight more informative case-control studies, as well as most of the less informative ones, provided overall estimates of excess risk that were remarkably consistent; seven of these eight case-control studies examined exposure-response relationships: two provided evidence supporting such a relationship and five did not.
- The cohort study neither supports nor strongly refutes the evidence from the case-control studies;
- Case-control studies were susceptible to recall biases, which could tend to inflate risk estimates but to an unknown degree;

- All studies were susceptible to other potential biases, which could increase or decrease the association;
- All studies involved some degree of non-differential misclassification of exposure that would tend to underestimate any true underlying association.

Animal carcinogenicity data

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

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

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

Mechanistic considerations and other relevant data

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

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

In humans and experimental animals, the effects of talc are dependent on the route of exposure, the dose and the properties of the talc. Talc pneumoconiosis is somewhat more prevalent and severe among miners exposed to talc containing asbestiform minerals and/or asbestos than among those exposed to talc without such contaminants. The role of quartz and asbestos in the observed pneumoconiosis could not be ruled out. Inadvertent exposure to talc in intravenous drug users results in microembolization in a variety of organs and alterations in pulmonary function.

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

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

Perineal exposure to cosmetic talc in women is of concern because of its possible association with ovarian cancer. A number of studies have been conducted to assess potential retrograde movement of particles through the reproductive tract to the ovaries. These studies have been conducted in women about to undergo

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

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

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

Evaluation

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

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

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

Overall evaluation

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

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

Rationale

In making this evaluation the Working Group considered the human and animal

evidence as well as evidence regarding the potential mechanisms through which talc

might cause cancer in humans.The Working Group found little or inconsistent evidence of an increased risk for cancer in the studies of workers occupationally exposed to talc. The studies of talc miners and millers were considered to provide the best source of evidence, but no consistent pattern was seen. One study observed an excess risk for lung cancer among miners, but confounding from exposure to other carcinogens made it difficult to attribute this to talc and no excess risk was seen in millers. Other studies also found no increased cancer risk or no higher risk with increasing cumulative exposure. Overall, these results led the Working Group to conclude that there was *inadequate evidence* from epidemiological studies to assess whether inhaled talc not containing asbestos or asbestiform fibres causes cancer in humans. For perineal use of talc-based body powder, many case-control studies of ovarian cancer found a modest, but unusually consistent, excess in risk, although the impact of bias and potential confounding could not be ruled out. In addition, the evidence regarding

exposure-response was inconsistent and the one cohort study did not provide support for an association between talc use and ovarian cancer. Concern was also expressed that exposure was defined in a variety of ways and that some substances called talc may have contained quartz and other potentially carcinogenic materials. A small number of Working Group members considered the evidence to be inadequate. Despite these reservations, the Working Group concluded that the epidemiological studies taken together provide *limited evidence* of an association between perineal use of talc-based body powder and an increased risk for ovarian cancer.

In one study of rats that inhaled talc, an excess incidence of malignant lung tumours was seen in females. The same study observed an excess incidence of pheochromocytomas in the adrenal medulla in both sexes, but the Working Group was divided as to whether these rare tumours could be attributed to exposure to talc. Other

studies in rats and mice using different routes of administration did not find an excess of cancer, and two studies in rats were considered to be inadequate for evaluation. Based on the one positive study, the Working Group found that there was *limited evidence* of carcinogenicity of inhaled talc in experimental animals. There was no agreement within the Working Group as to whether the evidence on pheochromocytomas should be taken into account in the evaluation of animal data.

Annex **F**

Carcinogenic classification of substances by the Committee

The Committee expresses its conclusions in the form of standard phrases:

Category	Judgement of the Committee (GR_{GHS})	Comparable with EU Category	
		67/548/EEC before 12/16/2008	EC No 1272/2008 as from 12/16/2008
1A	The compound is known to be carcinogenic to humans. • It acts by a stochastic genotoxic mechanism. • It acts by a non-stochastic genotoxic mechanism. • It acts by a non-genotoxic mechanism. • Its potential genotoxicity has been insufficiently investigated. Therefore, it is unclear whether the compound is genotoxic.	1	1A
1B	The compound is presumed to be as carcinogenic to humans. • It acts by a stochastic genotoxic mechanism. • It acts by a non-stochastic genotoxic mechanism. • It acts by a non-genotoxic mechanism. • Its potential genotoxicity has been insufficiently investigated. Therefore, it is unclear whether the compound is genotoxic.	2	1B
2	The compound is suspected to be carcinogenic to man.	3	2
(3)	The available data are insufficient to evaluate the carcinogenic properties of the compound.	not applicable	not applicable
(4)	The compound is probably not carcinogenic to man.	not applicable	not applicable

Source: Health Council of the Netherlands. Guideline to the classification of carcinogenic compounds. The Hague: Health Council of the Netherlands, 2010; publication no. A10/07.[59]