Safety Assessment of Talc as Used in Cosmetics

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All interested persons are provided 60 days from the above release date to comment on this safety assessment and to identify additional published data that should be included or provide unpublished data which can be made public and included. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a peer-reviewed scientific journal. Please submit data, comments, or requests to the CIR Director, Dr. F. Alan Andersen.

The 2012 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D., Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is F. Alan Andersen, Ph.D. This report was prepared by Monice M. Fiume, Senior Scientific Analyst/Writer, and Ivan Boyer, Senior Toxicologist, CIR.

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ABSTRACT

The CIR Expert Panel assessed the safety of talc for use in cosmetics and found that it is safe in the present practices of use and concentration; talc is reported to be used at up to 100% in cosmetics. Talc should not be applied to the skin when the epidermal barrier is not intact. Industry specifications state that cosmetic-grade talc must contain no detectable fibrous, asbestos minerals. Therefore, the large amount of available animal and clinical data the Panel relied on in assessing the safety of talc only included those studies on talc that did not contain asbestos. The Discussion of this safety assessment addressed a number of points that were deliberated.

INTRODUCTION

This assessment presents information relevant to the safety of talc as used in cosmetic formulations. Reported functions of talc in cosmetics include abrasive, absorbent, anticaking agent, bulking agent, opacifying agent, skin protectant, and slip modifier.[1]

Talc used in cosmetics does not contain asbestiform fibers; asbestiform refers to a crystallization product of a mineral in which the crystals are thin, hair-like fibers with enhanced strength, flexibility, and durability.[2] In 1976, specifications for cosmetic talc stating that it must contain no detectable fibrous, asbestos minerals.[3] Therefore, this report will only address the safety of talc that does not contain asbestos. Because the specification was developed in 1976, that year was used in determining what data are more likely relevant to the safety of cosmetic talc; because some studies performed prior to 1976 may not be relevant to talc as currently used in cosmetics, they might not be included in this assessment.

The following are conclusions from various workshops and review articles on talc. There have been a number of other published review papers on talc that are not cited here. The relevant primary references cited in the reviews were obtained and are included in this safety assessment. Reviews and responses specific to the National Toxicology Program (NTP) study are included in the section on Carcinogenicity. The non-cosmetic issue of the prohibition of the use of talc in medical examination gloves[4] will not be addressed in this safety assessment.

- In 1978, the Public Citizen Health Research Group contacted the Food and Drug Administration (FDA) with a letter stating their concern that talc is possibly carcinogenic and that the FDA should eliminate the use of talc in drugs and cosmetics even if the results are not conclusive.[5] The FDA responded that it was studying talc and believed that any risk from talc was related to contamination by asbestos.[6]

- In 1983, the FDA received a citizen's petition requesting that cosmetic talc be labeled with an asbestos warning statement, information on asbestos particle size, and the proportion of talc impurities in the product.[7] The FDA denied this request, stating that "there is no basis at this time for the agency to conclude that this is a health hazard attributable to asbestos in cosmetic talc. Without evidence of such a hazard, the agency concludes there is no need to require a warning label on cosmetic talc."

- In 1992, the Environmental Protection Agency (EPA) issued a "Health Assessment Document for Talc."[8] The review concluded that talc is not carcinogenic following inhalation exposure or intraperitoneal (i.p.), intrapleural, or intrabursal administration to rats, hamsters, and mice. However, these studies were not considered fully adequate to evaluate the carcinogenic potential of talc. The review noted that evidence from two studies suggests that talc may be an effective co-carcinogen when administered intratracheally with benzo[a]pyrene (B[a]P) to hamsters.[9,10] The Cosmetic Ingredient Review (CIR) Expert Panel determined that the results of these studies were not relevant to the cosmetic use of talc and that the study was not well-designed to study talc.

- In 1993, the NTP issued a report, "Toxicology and Carcinogenesis Studies of Talc (CAS No. 14807-96-6) in F344/N rats and $B6C3F_1$ Mice (Inhalation Studies)," that concluded there was *some evidence of carcinogenic activity* in male F344/rats, *clear evidence of carcinogenic activity* in female F344/N rats, and *no evidence of carcinogenic activity* in male or female $B6C3F_1$ mice exposed to aerosols of 6 or 18 mg/m^3 non-asbestiform cosmetic-grade talc in a lifetime study.[11] (This study and responses to the report will be described in detail later in this report).

- In 1994, a public workshop titled "Talc: Consumer Uses and Health Perspectives" was organized under joint sponsorship of the FDA, the CTFA (now, the Personal Care Products Council), and the International Society of Regulatory Toxicology and Pharmacology (ISRTP).[12,13] The purpose of the workshop was to provide a forum for an updated discussion of the origins, manufacture, characterization, toxicology, and epidemiology of talc and related products. The principle focus was the then-latest toxicological and epidemiological studies as they related to the safe uses of talc in cosmetic products. The characteristics of cosmetic-grade talc, the history of talc use, and quality-control measures for talc were discussed, as was an appraisal of the NTP inhalation study on talc. The regulatory history of talc was also reviewed. The workshop concluded that the NTP bioassay results could not be considered a relevant predictor of human risk, and in

regard to proposed association of talc exposure and ovarian cancer, the Panel found that the epidemiological data were conflicting and remain equivocal.

- In 1994, the Cancer Prevention Coalition (CPC) submitted a citizen petition to the FDA seeking labeling on all cosmetic talc products.[14] The requested labeling was a warning that talcum powder causes cancer in laboratory animals; frequent talc application in the female genital area increases the risk of ovarian cancer. This petition was denied.[15]

- In 2000, talc was nominated for review in the NTP 10th Report on Carcinogens because the NTP bioassay reported clear evidence of carcinogenic activity of talc (non-asbestiform) based on increased incidences of alveolar/bronchiolar adenomas and carcinomas of the lung in female rats and because published epidemiology studies suggested that talc exposure was associated with lung cancer in pottery workers and ovarian neoplasms in women. (65 FR 17891)[16] However, in 2005, the NTP deferred consideration of listing talc (cosmetic and occupational exposure; both asbestiform and non-asbestiform) as a carcinogen because of considerable confusion over the mineral nature and consequences of exposure to talc.(70 FR 60548)[17] Talc has been withdrawn from review.[18]

- In 2008, the CPC again submitted a petition to FDA seeking labeling on all cosmetic talc products.[15] The requested labeling was a warning that frequent application of talcum powder in the female genital area substantially increases the risk of ovarian cancer. It does not appear that FDA has responded to this petition.

- In 2010, the International Agency for Research on Cancer (IARC) Working Group determined that there is *limited evidence* in experimental animals for the carcinogenicity of talc not containing asbestos or asbestiform fibers.[19] The Working Group reviewed studies in which talcs of different grades were tested for carcinogenicity in mice by inhalation exposure or intrathoracic, i.p., or subcutaneous (s.c.) injection; in rats by inhalation exposure or intrathoracic or i.p. injection, oral administration, or intrapleural or ovarian implantation; and in hamsters by inhalation exposure or intratracheal injection.

- For humans, the determination of the IARC working group was that perineal use of talc-based body powder is *possibly carcinogenic to humans (Group 2B)*, and that inhaled talc not containing asbestos or asbestiform fibers is *not classifiable as to its carcinogenicity (Group 3)*.[19] In evaluating the carcinogenicity of talc in humans, the Working Group reviewed cohort studies of talc miners and millers, cohort and case-controlled studies examining the association of cosmetic talc use and the risk of ovarian cancer in humans, and the animal data and evidence regarding the potential mechanisms through which talc might cause cancer in humans. The Working Group found there is *inadequate evidence* in humans for the carcinogenicity of inhaled talc not containing asbestos or asbestiform fibers and there is *limited evidence* in humans for the carcinogenicity of perineal use of talc-based body powder.

Many occupational exposure studies are available that describe the effects reported in talc workers. Although the occupational exposure to talc is not at all similar to the cosmetic exposure to talc, these reports are summarized in this safety assessment to provide a total overview of available information. Occupational studies in which talc was known to contain asbestos are not included.

MINERALOGY AND CHEMISTRY

Definition and Structure

The term talc has two meanings: 1) as a mineral, the talc corresponding to the chemical formula for hydrous magnesium silicate, and 2) commercially, as a product that can be used industrially, in pharmaceuticals, and in cosmetics.[20] The mineral talc has the formula $Mg_3Si_4O_{10}(OH)_2$[21] and a theoretical chemical composition, expressed as oxides, of 31.7% by weight (wt) magnesium oxide (MgO), 63.5% silicon dioxide (SiO_2), and 4.8% hydrogen dioxide (H_2O).[22] As a cosmetic ingredient, talc (CAS No. 14807-96-6) is defined as a powdered native hydrous magnesium silicate, sometimes containing a small portion of aluminum silicate.[1]

Talc belongs to the silicate subclass phyllosilicates [23] and is a sheet silicate. The structural unit consists of three sheets, i.e., octahedrally-coordinated magnesium hydroxide groups (brucite layer) sandwiched between two layers of tetrahedrally-linked silica layers.[24,25] The apical oxygen atom positions of the tetrahedral layers are shared with one of the oxygen atom positions of the octahedral layer.[26] The composite sheets repeat every 9.4 angstroms (Å). Stacks of the triple-sheet crystalline units are held together by van der Waals forces.[27] (Figure 1.)

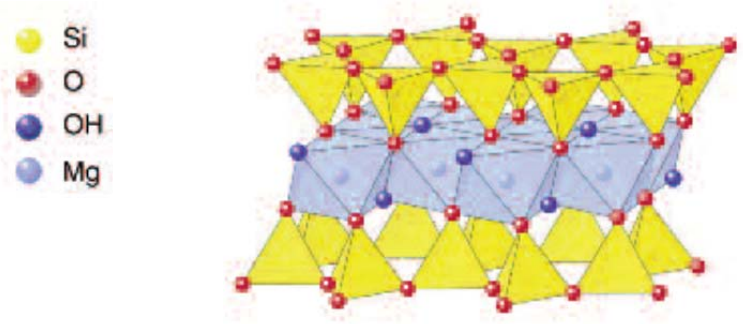


Figure 1. Schematic structure of talc[28]

Small amounts of aluminum and iron(III) can substitute for silicon in tetrahedral sites.[22] Trace amounts of nickel and small to moderate amounts of iron(II), iron(III), aluminum, and/or manganese can substitute for magnesium in octahedral sites. Such substitutions are bound within the crystal lattice and therefore do not exert any biological action. The replacement of hydroxyl groups (OH-) by fluorine may also occur.

The relationship between talc and asbestos is commonly misunderstood.[27] The presumption that asbestos and talc are commonly associated, or co-mined, is simply incorrect. Talc and asbestos (or even asbestiform materials) form under different geological conditions and are separated into adjacent, but disparate, strata. Accordingly, by utilizing proper mining methodologies, asbestos contamination is avoided. Moreover, the absence of asbestos in talc is routinely confirmed in ore samples through a battery of analytical techniques.

Physical and Chemical Properties

The mineral talc has a predominantly plate-like structure, with adjacent layers very weakly bonded by Van der Waals forces.[22] This allows talc to be easily sheared along the plane and gives it its natural slippery feel as well as its softness. Talc is the softest mineral with a hardness of 1 on a Mohs' scale of 1 to 10.

The physical form of talc rock is related to the source and geological conditions that exist during formation of the deposit.[22] The platelet size of talc determines its lamellarity, which, in turn, is related to the genesis of talc deposits. Highly lamellar talc (informally classified as macrocrystalline talc) has large individual platelets, whereas microcrystalline talc has small, randomly oriented platelets. The size of an individual talc platelet can vary from 1 μm to over 100 μm, depending on the formation of the deposit.[29]

The particle size of talc powder depends on the process used to make the powder.[22] Typical cosmetic talcs have average particle sizes ranging between 4 and 15 μm when measured by sedimentation method, with only minor fractions consisting of particles considered respirable. Another source recites that the "fineness" of talc used, characterized as 200 mesh, 325 mesh, or 400 mesh (i.e., particle size distribution that allows 95-99% of the product to pass through a 200-, 325-, or 400-mesh, respectively, [74, 44, or 37 μm, respectively], when wet-out with alcohol and dispersed in water) depends on the use in cosmetics.[27] For example, 200-mesh talc is preferred for body powders, while 400-mesh talc might be used for pressed powders. The cosmetic ingredient specifications for talc state that in a screen test, 100% passes through 100-mesh, 98% minimum passes through-200 mesh, and finer grades are as specified by the buyer.[30]

Physical and chemical properties of talc are summarized in Table 1.

Analytical Methods

The absence of asbestiform amphibole minerals in cosmetic talc is determined using the generally accepted method of x-ray diffraction and optical microscopy with dispersion-staining.[31] Other methods for the detection of fibrous amphibole, such as transmission electron microscopy with selected area diffraction and electron microprobe, were considered but were not adopted by the cosmetics industry trade association.

Talc can be analyzed for asbestos using polarized light microscopy and transmission electron microscopy.[32] Infrared spectrometry, which permits detection at a 0.1% w/w minimum detection level, also can be used.[22] Free crystalline silica (quartz) in talc can be detected using differential thermal analysis, which permits detection at a 0.5 – 1.0% w/w minimum detectable level,[33] or by x-ray diffraction.[34]

In early studies, the analytical methods used to identify the asbestos in talc were not performed and/or interpreted correctly. Misidentification of asbestos in talc can result from misinterpretation of the data obtained when performing an analytical procedure.[35]

Constituents/Impurities

Associated minerals found in commercial talc products vary from deposit to deposit depending on the conditions of formation of the deposit.[22] The most common minerals associated with talc are chlorite, magnesite, dolomite, calcite, mica, quartz, and fluorapatite. Amphiboles and serpentine are associated with certain specific talc deposits. These deposits are rare and historically were used for low-grade industrial applications due to the impurities present.

In 1976, the Cosmetic, Toiletry and Fragrance Association (CTFA; now known as the Personal Care Products Council [the Council]) issued purity standards for talc.[13] Cosmetic talc consists of a minimum of 90% hydrated magnesium silicate, with the remainder consisting of naturally associated minerals such as calcite, chlorite, dolomite, kaolin, and magnesite; it contains no detectable fibrous, asbestos minerals.[30] Additional specifications for cosmetic talc include: 6.0% max. acid-soluble substances; 3 ppm max. arsenic (as As); 20 ppm lead (as Pb); 0.1% max. water-soluble substances; no detectable fibrous amphibole (asbestiform tremolite, etc); free crystalline silica (quartz) as specified by the buyer.

As a color additive for drugs, talc sometimes contains a small proportion of aluminum silicate. (21CFR73.1550). It is required to meet the specifications for talc in the United States Pharmacopeia (USP), and it also must contain not more than 20 ppm lead (as Pb) and not more than 3 ppm arsenic (as As). The following are the acceptance criteria for USP-grade talc: 17.0-19.5% magnesium; not more than 0.1% water-soluble substances with neutral pH; no more than 0.25% iron; not more than 10 ppm lead; not more than 0.9% calcium; not more than 2.0% aluminum; and a demonstration of an absence of asbestos[21]. Talc intended for topical application is to have a total aerobic microbial count of not more than 100 cfu/g and a total combined molds and yeasts count of not more than 50 cfu/g; talc intended for oral administration is to have a total aerobic microbial count of no more than 1000 cfu/g and a total combined molds and yeasts count of not more than 100 cfu/g The acceptance criteria for food-grade talc are not more than 3 mg/kg arsenic and not more than 5 mg/kg lead, and the talc must be derived from deposits that are not associated with asbestos.[36]

Batches of cosmetic talc have been analyzed for asbestos and/or asbestiform minerals throughout the years. Analyses performed in the 1970s that indicated asbestos might be present in talc[37-40] may have used methodology that was unreliable or inaccurate. In the most recent analysis, which was performed by the FDA in 2012, nine cosmetic talc suppliers were asked for samples of their talc; four complied with the request.[32] The FDA also selected 34 talc-containing retail products. A contract laboratory analyzed the raw material and retail products using polarized light microscopy and transmission electron microscopy, finding no asbestos fibers or structures in any of the samples. It was indicated that the results were limited, however, because of the limited response by the suppliers and by the number of products tested.

Production

Talc is obtained from naturally occurring rock ore.[30] Talc commonly forms by hydrothermal alteration of rocks rich in magnesium and iron (ultramafic rocks) and by low-grade thermal metamorphism of siliceous dolomites.[26] Soapstone refers to impure, massive talc rock;[20] pure talc was once called steatite.[41] Talc is typically mined in open-pit operations,[27] and cosmetic talcs are mined in Italy, France, Norway, India, Spain, China, Egypt, Japan, and the United States.[42]

Crude talc ore can be sorted (beneficiated) to improve purity of commercial products by either dry or wet processing.[27] In either case, the talc ore is crushed and ground to a fineness suitable for specific end-uses. A dilute talc/slurry water is conditioned for flotation by the addition of a frothing agent (often a low molecular weight alcohol), and the slurry is then processed through a series of cells through which air is pumped. This processing causes bubbles to form, and as the bubbles rise to the surface, the talc particles attach to the bubbles due to their organophilic nature; the non-talc impurities are hydrophilic and do not tend to attach to the bubbles. The float (or froth) is then collected. The process is repeated until the desired purity levels are obtained. The talc particles can be further processed by magnetic separation or acid washing to remove iron-bearing minerals, soluble salts, and metals. The talc is then filtered, washed, and dried. Cosmetic talc is typically sterilized by heat treatment.[22]

USE

Cosmetic

Talc is reported to have the following functions in cosmetics: abrasive, absorbent, anticaking agent, bulking agent, opacifying agent, skin protectant, and slip modifier.[1] The FDA collects information from manufacturers on the use of individual ingredients in cosmetics as a function of cosmetic product category in its Voluntary Cosmetic Registration Program (VCRP). VCRP data obtained from the FDA in 2012[43] and data received in response to a survey of the maximum reported use concentration by category conducted by the Personal Care Products Council (Council) in 2009[44] indicate that talc is used in 2877 cosmetic formulations at concentrations up to 100%; it is used in almost every category of cosmetic

product. In 2012, the Council completed a survey to assess the use of talc in spray products; the highest reported concentration used in spray products was 35% in a makeup base (aerosol).[45] Frequency and concentration of use data are provided in Table 2.

Products containing talc may be applied to baby skin, used in products that could be incidentally ingested, or used near the eye area or mucous membranes. Additionally, talc is used in cosmetic sprays and powders; for example, talc is reported to be used in face powders at 100%, baby powders at 99%,[44] aerosol make-up bases at up to 35%, and in aerosol deodorants at up to 30%.[45] (Talc is not used in extremely high concentrations in spray or aerosol products because talc clogs the nozzle.[46]) These products could possibly be inhaled. In practice, 95 to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 μm.[47-50] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[47,49] There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aerodynamic equivalent diameters in the range considered to be respirable.[47] However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays.

The particle size of talc raw material varies widely by product type and by manufacturer but has "no practical significance with regard to human exposure since encapsulation by the other ingredients in the product matrices" (such as a lipstick or deodorant stick) "renders the talc constituents essentially nonrespirable".[27] Semi-solid matrix formulations (typically pressed powders such as blushes, eye shadows, pressed finishing powders, and base powders) incorporate binder systems. Fine talc with a larger than average particle size (200-mesh) is often preferred for use in blushes, eye shadows, and finishing powders. Loose-talc-based formulations, such as loose finishing makeup powders, baby powders, body powders, and foot powders, do not include a binder system. The majority of cosmetic talcs in loose-matrix powders contain talc particles that are of a larger diameter than those used in other cosmetic applications; for loose powders, a 200-mesh is normally used, and in these loose powders, substantial agglomeration occurs due to electrostatic and crystalline charges on the talc powders.

While some researchers state that the inclusion of a fragrance oil may act as a minimal binder system causing further agglomeration,[27] another researcher found that there was no evidence that the presence of perfume in adult or baby dusting powders containing Italian 00000 grade talc or Chinese talc influenced the level of respirable talc dust.[51]

In the European Union, the use of talc in powdery products intended to be used for children under 3 is restricted by the requirement of labeling that warns to keep powder away from children's nose and mouth. In Canada, the inner and outer label of preparations in powder form intended for infants and children shall carry cautionary statements to the effect: "Keep out of reach of children", "Keep powder away from child's face to avoid inhalation which can cause breathing problems."[52]

Non-Cosmetic

Sterile talc is approved as a sclerosing agent.[53] Sterile talc powder is indicated for administering intrapleurally via chest-tube to decrease the recurrence of malignant pleural effusions in symptomatic patients. Talc is not allowed for use on the surface of medical gloves.[54]

Talc is used as a color additive in drugs and is exempt from certification; it may be safely used in amounts consistent with good manufacturing practice to color drugs (21CFR73.1550). In foods, talc is used as an anticaking agent, coating agent, lubricating and release agent, surface-finishing agent, and texturizing agent.[36] Talc is a generally recognized as safe (GRAS) substance migrating from cotton and cotton fabrics used in dry food packaging (21CFR182.70) and as a substance migrating to food from paper and paperboard products (21CFR182.90). It is approved as an indirect food additive as a colorant (21CFR 176.170; 21CFR178.3297). The World Health Organization allocated talc (as magnesium silicate) an acceptable daily intake (ADI) of "not specified."[55]

FDA determined that data are inadequate to establish general recognition of the safety of talc as an active ingredient (astringent) in over-the-counter (OTC) drug products (21CFR310.545(e)(18)(ii)).

Talc is used as a dusting powder, alone or with starch or boric acid, for medicinal and toilet preparations.[56] It is used as an excipient and filler for pills and tablets, for dusting tablet molds, and for clarifying liquids by filtration. Talc is also used as a pigment in paints, varnishes, rubber; as filler for paper, rubber, soap; in fireproof and cold-water paints for wood, metal and stone; for lubricating molds and machinery; as glove and shoe powder; and as an electric and heat insulator. Talc is used in the leather industry, in the roofing and ceramic tile industry, as a carrier for insecticides and herbicides,[57] and it is used in plastics.[28]

TOXICOKINETICS

Inhalation

Non-Human

To determine the deposition, distribution, and clearance of talc, 44 female Syrian golden hamsters received a single 2-h nose-only exposure to a neutron-activated talc aerosol and sub-groups of 4 animals were then killed at 11 different intervals from 15 min to 132 days after exposure.[58] The talc tested was a commercial baby powder. (Chemical characterization data were not provided). Nine unexposed control animals were used; four were killed on the day the test animals were exposed and five were killed on the final day of the study. The aerosol exposure system had 7 tiers of exposure ports, and the talc aerosol was passed through a cyclone elutriator to remove particles that were larger than ~10 μm in diameter; the activity median aerodynamic diameter was 6.4-6.9 μm. The mean aerosol concentration was 40 and 75 μg/l at the 15-30 and 60-90 min sampling periods, respectively. In the presentation of the results, the γ-ray counts from the controls were expressed as μg talc equivalent, and the γ-ray counts of the exposed animals were not corrected for control values.

Variations among animals killed at the same time were attributed to variations in aerosol concentration at different tiers. The mean pulmonary talc content in the lungs of test animals at various time intervals was 33.08 (15 min after exposure), 24.08 (100 min), 42.70 (4 h), 18.75 (21 h), 21.30 (2 days), 21.03 (after 4 days), 13.85 (after 8 days), and 8.95μg (after 18 days); the mean for the day 0 control animals was 1.78 μg. The biological half-life of the talc deposited in the lungs was 7-10 days. At the time of termination of the final group, i.e. 132 days, there was no statistically significant difference in the talc burden of the lungs of test (3.70 μg) and control (2.30 μg) animals. The amount of talc in the liver, kidneys, and lungs was also determined; the only statistically significant differences compared to controls in any of these organs were found in the liver; there was a decrease at 4 h compared to day 0 controls, an increase at day 36 compared to both day 0 and day 132 controls, and an increase on day 68 compared to day 132 controls. Analysis of the data using the Kruskal-Wallis test showed that there were no significant differences among the mean talc burden values for the liver, kidneys, and ovaries, including the control values, and that there was no significant trend, indicating there was no translocation of talc to these tissues. As noted, no translocation from the respiratory tract to other tissues was found in this study, and the clearance of talc from the lungs was complete within 4 months after exposure.

Oral

Non-Human

Six female Syrian golden hamsters (outbred Ela:ENG strain) were dosed by gavage with 1 ml neutron-activated talc suspended in physiological saline containing 0.6% (w/w) 1% methyl cellulose, and the animals were killed 24 h after dosing.[59] The talc used was a commercial baby powder. (Chemical characterization data and particle size were not provided). Four hamsters were dosed similarly with a non-irradiated talc solution. The neutron-activated talc was exposed to an integrated neutron flux of 7×10^{16} n/cm^2 30 days prior to dosing. The skinned carcass, gastrointestinal (GI) tract, lungs, liver, kidneys, and excreta were analyzed for ^{60}Co and ^{46}Sc by γ-ray spectrometry, and the γ-ray counts were compared with those of four hamsters that were not dosed with talc.

The γ-ray counts of the tissue and excreta of the dose animals were equivalent to a total of 2.94 mg talc. Based on γ-ray counts, 74.5% of the neutron-activated talc was recovered in the feces and 23.5% was recovered in the GI tract, while 1.91% was recovered in the skinned carcass, 0.09% in the urine, 0.04% in the kidneys, and 0.02% in the liver. The amount found in the urine of the hamsters given irradiated talc was statistically significantly increased compared to the controls. No talc was recovered in the lungs.

The absorption, distribution, and excretion of orally administered talc was determined in mice, rats, and guinea pigs.[60] (Chemical characterization data were not provided). With all species, [^{3}H]talc was administered as a suspension in aqueous (aq.) glycerol jelly solution (10 mg/ml; 1 μCi/ml). Four LACA female mice were given a single oral dose of 40 mg/kg [^{3}H]talc. Two mice were killed at 6 h and two at 24 h after dosing. In the mice killed 6 h after dosing, 95 and 96% of the radioactivity was recovered in the large intestines and feces, 9 and 7% was recovered in the small intestines and stomach, and 0.7 and 0% in the urine of each mouse. In the two mice killed 24 h after dosing, 99 and 101% of the radioactivity was recovered in the large intestines and feces, 4 and 6% was recovered in the small intestines and stomach, and 1.3 and 1.5% in the urine of each mouse. Less than 0.005% of the radioactivity was found in the carcass of any of the mice.

Three male Wistar albino rats were given a single oral dose and three rats were given six daily oral doses by gavage of 50 mg/kg body wt [^{3}H]talc. After the last dose, urine and feces were collected every 24 h for 4 days and on day 10; the rats were then killed. Within 24 h after administration of the single dose, approximately 75% of the radioactivity was recovered in the feces and only 1% was recovered in the urine. After 96 h, a total of 95.8% of the dose was excreted in the feces and 1.7% in the urine, with a total excretion of 97.5% of the dose. No radioactivity was recovered in the liver or kidneys 10 days after a single dose of talc. On day 10 in the rats given six daily doses of [^{3}H]talc, there was no radioactivity found in the feces or livers, and there was a trace of radioactivity (<0.02%) in the kidneys of these rats.

Three female Dunkin Hartley guinea pigs were administered a single oral dose of 25 mg/kg [^{3}H]talc, and urine and feces were collected as described above; all animals were killed on day 10. Talc was excreted more slowly in the guinea pig than in the rat. Within 24 h after dosing, 31% of the radioactivity was recovered in the feces, and 0.2% was recovered in the urine. At 24-48 h and 48-72 h after dosing, 39% and 19% of the radioactivity, respectively, was recovered in the feces, with <0.01% of the dose being recovered in the urine at each of these time periods. Within 96 h of dosing, a total of 94.4% of the radioactivity was recovered in the feces and 0.2% was recovered in the urine, with a total of 94.6% of the dose being excreted over 96 h.

Intrapleural

Non-Human

Wistar rats were used to determine the systemic distribution of talc following intrapleural administration.[61] Groups of 20 rats (sex not specified) were administered 10 or 20 mg talc in 1 ml of saline as a slurry into the pleural cavity. (Chemical characterization data were not provided). Ten animals of each group were killed 24 h after instillation, and the remaining 10 animals were killed 48 h after instillation. The lungs, chest wall, liver, kidneys, spleen, heart, and brain of each animal were removed for examination. There were no gross lesions in the examined tissues. Microscopic examination revealed that the chest wall had the most common lesions, and these lesions were represented by an early pneumoconiosis characterized by stellate interstitial collections of dust-laden macrophages containing pale yellow particles associated with inflammatory infiltrate of lymphocytes with mild fibroblastic proliferation. Polarized light used to locate birefringent particles revealed "large numbers of irregular, strongly birefringence platy, acicular, and "Maltese Cross" crystals that varied in length from 5.7 – 70 μm" in the chest wall. The deposition index of talc crystals was greater in the chest wall and the lungs after administration of 10 mg (3.90 in the chest and 3.18 in the lungs) than 20 mg talc (3.58 in the chest and 2.50 in the lungs); this difference was statistically significant. (It is not stated whether these values were from the 24 h group, 48 h group, or an average of the two). Pneumoconiosis reactions were not observed in the other organs; however talc crystals were present inside of the microvessels. The researchers suggested talc was absorbed rapidly through the pleura, reaching the systemic circulation with deposition in other organs within 24 h after administration, and that the distribution was not dose-related.

TOXICOLOGICAL STUDIES

Single Dose Toxicity

Oral

The LD_{50} of talc in rats was determined to be 920 mg/kg.[62] Ten male rats were dosed by gavage with 5000 mg/kg talc suspended in 0.85% saline; all 10 rats died within 24 h. Groups of 5 rats were then intubated with 50, 100, 500, 1000, 2000, or 3000 mg/kg talc in saline. All five animals dosed with 3000 mg/kg, four dosed with 2000 mg/kg, three with 1000 mg/kg, and one with 500 mg/kg talc died. (Chemical characterization data were not provided).

In another single-dose study in rats, the LD_{50} was >5000 mg/kg.[62] All the animals survived dosing with 5000 mg/kg talc in 0.85% saline.

The oral LD_{50} of 18.3% talc in saline was >5000 mg/kg.[62] A single oral dose of 5000 mg/kg of talc prepared as an 18.3% (w/v) suspension in saline was administered to 10 male rats. All animals survived, and there were no signs of toxicity.

Inhalation

Eight mice were placed in a box with baby powder that was circulated with compressed air.[63] (Details regarding the composition of the baby powder, the amount of baby powder, or the size of the box were not provided). Two mice were removed from the box at 30-min intervals, i.e. after 30, 60, 90, or 120 min. The mice removed after 30 and 60 min recovered completely; symptoms that were observed were not specified. The mice removed after 90 min died in 5-6 h; the mice exposed for 2 h died immediately after exposure. The mice that died were necropsied, and the mucous membrane of the airway was found covered with baby powder. Microscopically, hemorrhage, edema, and desquamation of bronchial epithelium admixed with baby powder were observed.

Intrabursal

Groups of 10 anesthetized female Sprague-Dawley rats (10-15 wks of age) were given a single bilateral intrabursal injection of 100 mg/ml talc in phosphate-buffered saline (PBS) into the bursa around the ovaries, and groups of 3 age-matched, sham-operated, and sham-treated rats were used as controls.[64] Asbestos-free Italian 00000 talc, composed of platy crystals ranging in size from 0.3-14 μm, was used. The animals were killed 1, 3, 6, 12, or 18 mos after dosing. There was no effect on the production of physiological concentrations of steroid hormones. Gross examination was made for all animals, and microscopic examination was performed 12 mos after dosing. One or both ovaries of rats dosed with talc were cystic in appearance at all time periods; no gross changes were seen in the ovaries of the control animals; the cystic structures were not derived from the ovaries but were due to distention of the bursal sac. Focal areas of papillary change were seen in the surface epithelium of four injected ovaries, but not in any of the controls. There was no correlation between the presence of foreign body granulomas and the presence of the papillary changes. No evidence of cellular lesions or of mitotic activity was seen in

the non-papillary areas of the surface epithelium of injected ovaries, and neoplasia was not observed. Foreign body granulomas, without surrounding inflammation, were seen in the cortical area of five of the injected ovaries, with similar lesions in the supracapsular fat in the connective tissue matrix of the capsule. Talc was observed in the granulomas.

Intraperitoneal

The induction of fibrosis following an i.p. injection of 50 mg/kg bw non-fibrous talc in physiological saline was evaluated in six male and six female Wistar rats.[65] A granulomatous reaction in which foreign-body giant cells containing refractile materials was observed in the rats at 1 mo after dosing; this lesion was still observed at 3 mos, but there was no fibrosis.

Groups of five female Wistar rats were used to evaluate the toxicity of talc following a single i.p. injection of 0.02, 0.1, or 0.5 g in 5 ml normal saline.[66] Although the talc was described as irregular crystalline plates, it was also stated that it could vary from all plates to all fibers. The talc was composed of 49-56% silicon dioxide, 20-22% magnesium oxide, 6-8% calcium oxide; the particle size range from 10-120 μm, with a mode of 20 μm. The control group was administered saline only. The animals were killed 7 days after dosing. There were no adhesions in the control group, but adhesions were observed, mainly in the upper abdomen, of the test animals; three animals of the 0.5 g group had mild/intermediate adhesions and four animals in the 0.5 g group had four intermediate adhesions. Talc particles could be seen in the adhesions. The parietal peritoneal mesothelium was examined microscopically using the Hautchen technique, and clusters of foci of inflammatory cells were observed scattered on the surface of the peritoneum. Again, talc particles were seen in the center of each focus of inflammatory cells. Powder deposits adherent to the viscera or omentum without adhesions were reported in three animals dosed with 0.02 g talc and in all animals dosed with 0.1 or 0.5 g talc; ascites did not occur in any of these animals.

Cellular Effects

Cellular effects in various systems are described in Table 3. There were no remarkable results found in studies examining the cellular effect of talc, such as cytotoxicity assays, assays examining the effect of talc on cell viability, or studies on the induction of apoptosis (among others).[65,67-74]

Repeated Dose Toxicity

Repeated dose animal toxicity studies are summarized in Table 4. Dermal application of talc to shaved rabbit skin for 6 wks resulted in dryness of the skin and skin erosion.[75] Oral administration to rats for 5 days produced minimal toxicity;[62] no toxicologically significant effects were noted in a 5-mos study in which rats were fed a diet containing 100 mg/day Italian talc.[76] In inhalation studies, exposure of mice and rats for 4 wks (25 μm particle size) resulted in macrophages in the alveolar space, with more found in the mice than the rats.[11,77] In rats exposed for 3, 6, or 12 mos, minimal to slight fibrosis resulted.[76] In hamsters, exposure by inhalation to baby powder (95% talc; 4.9 -6.0 μM) for 30 days did not result in clinical toxicity, and no trends were observed.[78] Intrapleural administration of talc (25 μm) to rats did not result in mesotheliomas; granulomas at the injection site were common.[76] Infections occurred, but no neoplastic or perineal changes, when talc was instilled intravaginally or perineally in rats.[79] Upon intravenous (i.v.) injection of talc (<5 μm) once weekly for 3 wks in guinea pigs, talc was found in the lungs and the liver throughout the study.[80]

Ocular Irritation

Two unpublished ocular irritation studies were briefly summarized in the IUCLID dataset on talc.[81] Talc was not irritating to the eyes of rabbits in one study and was slightly irritating to the eyes of rabbits in the other study. No details were provided.

A case study was reported in which a woman presented with a foreign body sensation and inflammation of the conjunctiva of both eyes.[82] Following a biopsy and electron microscopy and electron diffraction analysis of the sample, a diagnosis of foreign body granuloma secondary to talc was made. It was postulated that the talc originated from surgical gloves from a surgery performed decades earlier.

Granuloma Formation in the Skin

Application of talc on wounds can give rise to scab formation, possible infection, and foreign body granulomas in the dermis.[83] In one case study, talc powder applied to post-varicella lesions resulted in granulomas. In another case study, hundreds of granulomas of the skin developed in a patient that had open, draining furuncles and who had liberally applied talc daily.[84]

Occupational Exposure

Talc has a threshold limit value (TLV) (respirable fraction) of 2 mg/m^3 as a 10-h time-weighted average (TWA).[85] The National Institute for Occupational Safety and Health (NIOSH) states the immediately-dangerous-to-life-or-health (IDLH) concentration is 1000 mg/m^3. The Occupational Health and Safety Administration (OHSA) mineral dust limit for talc is 20 millions of particles per cubic foot (mppcf) of air, if containing less than 1% quartz; if ≥1% quartz is present, then the quartz limit is used (250/(%SiO_2 + 5) mppcf) (29CFR1910.1000 Table Z-3).

Human pulmonary effects of chronic occupational inhalation of talc include diffuse interstitial fibrosis and progressive massive fibrosis (often called complicated pneumoconiosis).[86] Depending on the composition and contaminants of talc, three forms of talc-related pulmonary effects have been described: pure talcosis, produced by exposure to talc that is free of silica and asbestiform minerals; talco-asbestosis, produced by the inhalation of talc with asbestiform fibers; and talco-silicosis, produced by exposure to talc associated with silica and other non-asbestiform fibers.[87] A fourth talc-related disease, stemming from i.v. administration of talc, is not related to occupational exposure, but instead is usually associated with abuse of oral medications. Each form has a distinctly different radiographic appearance. The radiographic abnormalities associated with pure talcosis consist of small nodules that are usually seen in the lower pulmonary fields. Reticulations may occur, but this is less common. Pure talcosis results in pulmonary function test results that are consistent with restrictive pulmonary disease.

Effects of Occupational Exposure

Studies examining the pulmonary effects of occupational exposure to talc by talc miners and millers and by workers in industries that use talc are summarized in Table 5. Statistically significantly elevated standardized mortality ratios (SMRs) for silicosis and silico-tuberculosis were observed in an early study of talc miners and millers in the Italian Piedmont region.[88] The miners were employed for at least one year and the millers for at least two years in their respective occupations. Talc in this region reportedly contained no fibrous material, except for tremolite micro-inclusions. This study also found statistically significantly reduced SMRs for malignant neoplasms, including lung, bronchial and tracheal cancers. Updates of this study reported similar results, including statistically significant increases in mortality, which were attributable primarily to non-malignant respiratory diseases among the miners, no increases in SMRs for cancer, including lung cancer, and no mesothelioma cases.[89,90]

A cohort study of talc miners and millers employed for at least one year found no statistically significant SMRs for all causes, all cancers, or diseases of the circulatory system or respiratory tract.[91] These workers were exposed to talc and magnesite containing trace amounts of quartz, tremolite, and anthophylite. There were no lung cancer or mesothelioma cases even among the workers in the highest exposure category.

The results of several other epidemiological studies were likely confounded by the presence of up to 3% silica or 6% actinolite in the talc, exposures to high concentrations of silica with or without exposures to fibrous talc or tremolite, or concurrent exposures to radon daughters.[92-98]

A meta-analysis of studies of miners and millers who worked with non-asbestiform talc reported summary SMRs for lung cancer of 0.92 (95% confidence interval (CI): 0.67-1.25) for millers in five countries exposed to high levels of talc without exposure to other occupational carcinogens, and 1.2 (95% CI: 0.86-1.63) for miners in 3 countries exposed to high levels of talc as well as to silica or radon and radon daughters.[2] The corresponding SMRs for death from all causes were 0.95 for the millers and 1.10 for the miners.

Studies examining radiological, lung-function, and clinical (e.g., wheezing, coughing, bronchitis) parameters in talc miners and millers and rubber workers found some statistically significant decreases in lung function.[93,99-103]

Respirable Particles During Use

Studies on exposure during use of cosmetic talc are summarized in Table 6.[51,57,104] Many of the researchers noted that there was a wide variation in talcing times and methods, often by the same volunteer during different applications. Reported talcing times ranged from 17 sec to 31 sec.

Case Reports

A 70-yr old non-smoking female was determined to have intense endobronchitis and airway stricture following inhalation of large amounts of cosmetic talc.[105] The subject frequently poured a "small pile of talcum powder" into her hand and applied it to her face. Bronchoscopy showed diffuse, severe endobronchitis that extended throughout both main stem bronchi. Chest radiography and computed tomography (CT) imaging showed complete collapse of the right upper and middle lobes of the lung; the right lung was normal with the exception of scattered areas of mild bronchial wall thickening, bronchial plugging, and a few non-specific nodules. Bronchial biopsies showed edema, chronic inflammation, and fibrosis, and there were confluent foreign-body granulomata that contained birefringent crystalline material. Spectral analysis confirmed the crystals were the same composition as the talc used by the subject.

A case of chronic pulmonary granulomatous reaction was reported in a woman who applied "non-powdering talc" to her face for 20 yrs, followed by use of talcum powder 2-3 times a day during a 10-yr period, usually in an unventilated room.[106] The subject had smoked for 20 yrs. The amount of powder used per year was described as two boxes, but the amount per box was not stated. Chest x-rays showed fine diffuse opacities, and anterolateral thoracotomy showed a diffuse nodular consistency. A heavy intra-alveolar and interstitial granulomatous inflammation was found at biopsy, and numerous birefringent particles were found inside the giant cells. The foreign body material contained in the granulomas was characteristic of talc. After 2

yrs follow-up, a biopsy of an enlarged lymph node showed granulomatous inflammation. It was the opinion of the investigators that this was a case of not true talc pneumoconiosis, but chronic sarcoidosis and coincidental talc deposition in the lung.

Pulmonary talcosis was reported in several cases of misuse of talcum powder in which the subjects dusted their entire body with large amounts of powder at least once a day,[107,108], including one in which an individual also dusted the bed sheets every day,[109] and in a case in which the powder was purposefully inhaled.[110] A woman that excessively used talc for herself and her children died from rapidly progressive disease and pulmonary hypertension. Cases of accidental inhalation of large amounts of talc by infants and children have been reported, and consequences have ranged from complete recovery to death.[63,111-115] Specifics of these cases are not included because the results are not from normal, intended use of the product. Also not included in this safety assessment are reports of adverse effects due to injection of talc with i.v. drug abuse.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Oral

Orally administered talc was not a developmental toxicant in mice, rats, hamsters,[116] or rabbits. [117] Chemical characterization of the talc was not provided in any of these studies.

Groups of 20-22 gravid albino CD-1 mice and groups of 20-24 gravid Wistar rats were dosed by gavage with 0, 16, 74, 350, or 1600 mg/kg bw talc as an anhydrous corn oil suspension on days 6-15 of gestation.[116] Aspirin was used as a positive control in both species. The mice were killed on day 17 and the rats on day 20 of gestation and the number of implantation sites, resorptions sites, and live and dead fetuses, and the live pup body weights were recorded. In both mice and rats, the administration of up to 1600 mg/kg bw talc in corn oil had no effect on reproductive or developmental parameters and had no effect on maternal or fetal survival.

In hamsters, groups of 20-23 gravid female golden hamsters were dosed by gavage with 0, 12, 56, 260, or 1200 mg/kg bw talc as an anhydrous corn oil suspension on days 6-10 of gestation.[116]. The animals were killed on day 14 of gestation and examined as described previously. The administration of up to 1200 mg/kg bw talc in corn oil had no reproductive or developmental effects and had no effect on maternal or fetal survival.

Groups of 12-15 gravid Dutch-belted female rabbits were dosed orally with 9, 42, 195, or 900 mg/kg talc in corn oil on days 6-18 of gestation.[117] Eight gravid negative controls were given only vehicle and 9 gravid positive controls were dosed with 2.5 mg/kg of 6-aminonicotinamide on day 9 of gestation. The dams were killed on day 29 of gestation. A total of 1/8, 4/15, 2/12, 5/15, and 2/13 dams of the negative control, 9, 42, 195, and 900 mg/kg dose groups, respectively, died or aborted before day 29 of gestation, and the number of live litters for these groups was 6/7, 10/11, 8/10, 10/10, and 7/11, respectively. The researchers concluded that administration of up to 900 mg/kg talc on days 6-18 of gestation "had no discernible effect on nidation or on maternal or fetal survival." The researchers also stated the number of abnormalities did not differ between test and control animals.

In a dominant-lethal study, groups of 10 male rats were dosed by gavage with a single dose or once daily for 5 days with 30, 300, 3000, or 5000 mg/kg talc.[62] Saline was used as the negative control and 0.1 μg/ml triethyl melamine (TEM) (i.p.) was the positive control. (The results of the reproductive portion of the study are presented here; the genotoxicity results are presented in that section of the safety assessment). Each treated rat was mated with two previously unmated females, and 2 wks after mating, the female rats were killed and the effects on fertility and preimplantation loss were determined. In the single-dose study, significant dose-related decreased in average corpora lutea and preimplantation losses were reported in the test groups at wks 4 and 5. In the repeated dose study, significant increases in average implantations and corpora lutea were reported in the test groups at wk 6, as were significant differences in the proportions of females with 1+ or 2+ dead implants. However, the results observed at the highest dose did not vary significantly from the negative control, and no dose-response or time-trend patterns were indicated.

GENOTOXICITY

In Vitro

Talc was not genotoxic in an unscheduled DNA synthesis (UDS) assay or a sister chromatid exchange (SCE) assay in rat pleural mesothelial cells (RPMC). [118,119] Three samples of European talc (French, Italian, and Spanish talc) were tested. The samples, which contained 90-95% talc with chlorite and dolomite, were asbestos-free; the mean particle size of the samples ranged from 2.6 μm (Spanish and French talc) to 4.0 μm (Italian talc). In the UDS assay, the cells were treated with 0, 10, 20, or 50 μg/cm^2 of each sample of talc for 24 h. A negative reference particle controls, anatase, and two positive controls reference particles, Rhodesian chrysotile and crocidolite were used; mean particle sizes of the three talc samples were 0.7, 3.2, and 3.1 μm, respectively. The particles were dispersed in culture medium at a concentration of 560 μg/ml by sonication. None of the talc samples enhanced UDS. The negative and positive particles yielded the expected results.

In the SCE assay, RPMC were treated with 0, 2, 5, 10, and 15 μg/cm^2 of each talc sample for 48 h. Two negative reference particle controls, anatase and attapulgite, and the two positive controls reference particles named previously were used, as were the chemical controls mitomycin C in water and K_2CrO_4 in culture medium. Talc did not cause a statistically significant increase in SCEs and was not clastogenic. The negative particle controls and chemical controls gave expected results; chrysotile and crocidolite statistically significantly increased SCEs in 2/4 and 3/8 experiments, respectively.

In Vitro/In Vivo

Talc was not genotoxic in a host-mediated assay or cytogenetic assay. (Chemical characterization data were not provided in either assay). In the host-mediated assay, male ICR mice served as the host and groups of 10 animals were dosed by gavage with a single dose or once daily for 5 days with 30, 300, 3000, or 5000 mg/kg talc.[62] *Salmonella typhimurium* TA1530 and G46 and *Saccharomyces cerevisiae* D3 were the indicator organisms. Saline was the negative control and 100 mg/kg dimethyl nitrosamine and intramuscular administration of 350 mg/kg ethyl methane sulfonate were the positive controls. For comparison, a microdrop of solution, 0.01-0.25 ml, of talc was evaluated in an Ames test using *S. typhimurium* TA1530 and G46 and *S. cerevisiae* D3. Talc caused no significant increase in mutant or recombinant frequencies in the host-mediated assay, and it was not mutagenic in the Ames test.

Groups of 15 male albino rats were given a single dose by gavage and groups of 5 rats were dosed once daily for 5 days with 30, 300, 3000 , or 5000 mg/kg talc in the cytogenetics assay.[62] Saline was used as the negative controls and 0.3 mg/kg TEM (i.p.) was the positive control. The concentrations used during the in vitro aspect of the study were 2, 20, and 200 μg/ml in human embryonic lung culture (WI-38) cells. Talc produced no significant aberrations during the in vivo or in vitro phase and was not genotoxic.

In Vivo

Talc was not genotoxic in a rat dominant lethal assay.[62] (Chemical characterization data were not provided). Groups of 10 male rats were dosed by gavage with a single dose or once daily for 5 days with 30, 300, 3000, or 5000 mg/kg talc. Saline was used as the negative controls and 0.1 μg/ml TEM (i.p.) was the positive control. There were no dose-response or time-trend patterns; talc did not induce dominant lethal mutations in this assay.

CARCINOGENICITY

In 2010, the IARC Working Group determined that there is *limited evidence* in experimental animals for the carcinogenicity of talc not containing asbestos or asbestiform fibers.[19] The Working Group reviewed studies in which talc of different grades was tested for carcinogenicity in mice by inhalation exposure or intrathoracic, i.p., or subcutaneous (s.c.) injection, in rats by inhalation exposure or intrathoracic or i.p. injection, oral administration, or intrapleural or ovarian implantation, and in hamsters by inhalation exposure or intratracheal injection.

For humans, the evaluation of the IARC working group was that perineal use of talc-based body powder is *possibly carcinogenic to humans (Group 2B)*, and that inhaled talc not containing asbestos or asbestiform fibers is *not classifiable as to its carcinogenicity (Group 3)*.[19] In evaluating the carcinogenicity of talc in humans, the Working Group reviewed cohort studies of talc miners and millers, cohort and case-controlled studies examining the association of cosmetic talc use and the risk of ovarian cancer in humans, and the animal data and evidence regarding the potential mechanisms through which talc might cause cancer in humans. The Working Group found there is *inadequate evidence* in humans for the carcinogenicity of inhaled talc not containing asbestos or asbestiform fibers and there is *limited evidence* in humans for the carcinogenicity of perineal use of talc-based body powder.

The references cited by the IARC in their review were obtained by the CIR and are cited as appropriate in this safety assessment.

Inhalation

Exposure of hamsters to talc via inhalation did not produce carcinogenic effects.[78] Groups of 50 male and 50 female Syrian golden hamsters were exposed for 30 or 150 min/day, 5 days/wk, to 27.4 ± 3.4 μg/l mean total aerosol concentration commercial baby powder (95% w/w platy talc with trace quantities of carbonates and platy chlorite and rutile) until natural death, or, for a maximum of 300 days. A group of 25 male and 25 female guinea pigs served as the control group. A single tier exposure was used. There was no statistically significant difference in survival time among groups, but there was a significant difference between males and females within all groups. No clinical signs of toxicity to talc were observed. The type, incidence, and severity of lesions indicated no trend toward a dose-response and no statistically significant differences between exposed and control groups. The incidence of focal alveolar cell hyperplasia (25% in treated groups; 10% in controls) appeared to be affected by treatment, but a two-way weighted analysis showed no significant association.

A bioassay using mice and rats was performed by the NTP to determine the carcinogenic potential of non-asbestiform, cosmetic-grade talc following exposure by inhalation.[11] There was *no evidence of carcinogenic activity* in male or female B6C3F$_1$ mice, *some evidence of carcinogenic activity* in male F344/rats, and *clear evidence of carcinogenic activity* in female

F344/N rats. The talc used was asbestos-free and virtually silica-free microtalc; scanning electron microprobe analysis of one lot of talc indicated that 1/1466 particles examined was silica, 136/1466 particles tremolite, and 1241/1466 particles were talc. More than 75% of the particles were in the 1.0 – 3.0 μm range. This study is discussed in greater detail below.

A 2-yr study was performed in mice; groups of 50 male and 50 female $B6C3F_1$ mice (7 wks old) were exposed to target concentrations of 0, 6, or 18 mg/m^3 talc for 6 h/day, 5 days/wk, for 103-104 wks. The concentrations were selected based on the results of a 4-wk inhalation study in $B6C3F_1$ mice; that study is presented in Table 4. These exposure concentrations provided a dose equivalent of 0, 2, or 6 mg/kg/day for male mice, respectively, and 0, 1.3, or 3.9 mg/kg/day for female mice, respectively. The MMAD was 3.3 ± 1.9 μm in the 6 mg/m^3 chamber and 3.6 ± 2.0 μm in the 18 mg/m^3 chamber. Groups of 40 male and 40 female mice were similarly exposed and killed at 6, 12, and 18 mos for interim microscopic evaluations. Some problems were experienced in maintaining control of the chamber concentrations, and there was a 12-wk period beginning at wk 70 during which the chamber concentrations were substantially lower than the target concentrations. Mean body wts were similar for test and control animals, and there were no clinical findings attributable to talc exposure.

Compared to the 6 mos value, the lung talc burden (normalized to control lung wt) was statistically significantly increased at 24 mos in 6 mg/m^3 males, at 12 and 24 mos in 18 mg/m^3 males, at 18 and 24 mos in 6 mg/m^3 females, and at 12, 18, and 24 mos in 18 mg/m^3 females. When lung talc burdens were normalized to exposure concentration, a statistically significant difference was observed between the 6 and 18 mg/m^3 males at 12 and 24 mos but not at 6 and 18 mos. The mouse lung talc burdens are provided in Table 7.

Changes in enzymatic activities in bronchoalveolar lavage fluid were noted mostly in the 18 mg/m^3 males and females; measured enzymatic activity was increased in the high-dose animals at 18 and 24 mos. A statistically significant increase in β-glucuronidase activity was seen as of 12 mos in the high dose animals, and at 24 mos, the activity was increased in all test groups. Lavage fluid polymorphonuclear cells were statistically significantly increased in males and females of the 18 mg/m^3 group at all times except at 12 mos; statistically significant increases were observed in some 6 mg/m^3 interim groups. The population of bronchoalveolar lavage fluid macrophages was significantly decreased in the female test groups at 24 mos. The phagocytic activity of the macrophages recovered from the lavage fluid at 12, 18, and 24 mos was statistically significantly decreased by exposure to 18 mg/m^3 talc. At 24 mos, there was no effect on the viability of the macrophages. Lung tissue collagen and proteinase activity were significantly increased in exposed male and female rats. At 24 mos, collagen and lung fluid collagenous peptides were statistically significantly increased in the 18 mg/m^3 group, and most proteinase activity was increased as well.

Chronic active inflammation without alveolar epithelium hyperplasia, squamous metaplasia, or interstitial fibrosis was reported in exposed mice. An accumulation of macrophages was observed in the lungs, and talc-containing macrophages were found in the bronchial lymph nodes. The incidence of pulmonary neoplasms was similar for test and control animals. In the upper respiratory tract, cytoplasmic eosinophilic droplets in the nasal mucosal epithelium occurred and were concentration-dependent. There was *no evidence of carcinogenic activity* in male or female B6C3F1 mice exposed to talc.

A lifetime study was performed in rats; groups of 50 male and 50 female F344/N rats (6-7 wks old) were exposed to the same dosing regimen and target concentrations of talc as mice until mortality reached 80% in any exposure group, i.e., males were exposed for 113 wks and females for 122 wks. (The concentrations selected were based on the results of a 4-wk inhalation study in F344/N rats; that study is described in Table 4). The MMAD was 2.7 ± 1.9 μm in the 6 mg/m^3 chamber and 3.2 ± 1.9 μm in the 18 mg/m^3 chamber. As with the mice, there was difficulty in maintaining the chamber concentrations for the rats; there was a 7-wk period beginning at wk 11 during which time the concentration for the 18 mg/m^3 group varied from 30-40 mg/m^3 and there was a 12-wk period beginning at wk 70 during which the chamber concentrations were substantially lower than the target concentrations for both groups. Groups of 22 male and 22 female rats were exposed similarly and killed at 6, 11, 18, and 24 mos for interim evaluations. Survival was similar for test and control animals. Body weights of the low dose animals were similar to controls and final body weights of the high dose animals were slightly (14%) lower than controls. Compared to controls, the absolute and relative lung weights in high dose males were statistically significantly increased in at 6, 11, and 18 mos and at study termination, in high-dose females at 11, 18, and 24 mos and at study termination, and in low dose females at 18-mos and study termination.

A concentration-related impairment of respiratory function was observed in exposed male and female rats, and the severity increased with increasing duration of exposure. In the 6 and 18 mg/m^3 males and in the 6 mg/m^3 females, the lung talc burden (normalized to control lung wt) was statistically significantly increased at 11, 18, and 24 mos compared to the 6 mos value. In the 18 mg/m^3 females, the 18 and 24 mos values were statistically significantly increased compared to the 6 mos values. When lung talc burdens were normalized to exposure concentration, a statistically significant difference was observed between the 6 and 18 mg/m^3 males at 6 and 11 mos but not at 18 and 24 mos. At 24 mos, the lung talc burden (normalized to exposure concentration) was higher in the 6 mg/m^3 males than in the 18 mg/m^3 males. In the females, the only statistically significantly difference between the low and high dose groups was at 6 mos. The interim rat lung talc burdens are provided in Table 8.

Pulmonary function was impaired (i.e., restricted) in a concentration-related manner, increasing in severity with exposure duration. After 24 mos of exposure, changes in enzymatic activities in bronchoalveolar lavage fluid were noted compared to controls; statistically significant increases in β-glucuronidase were seen in all test animals. Also, lavage fluid polymorphonuclear cells were statistically significantly increased and macrophage cells were statistically significantly decreased in all test animals; a statistically significant increase in lymphocyte cell populations was reported in all test group females. The viability and phagocytic activity of the macrophages recovered from the lavage fluid were not affected by exposure to talc. Lung tissue collagen and proteinase activity was significantly increased in exposed male and female rats.

Granulomatous inflammation occurred in most test animals, and severity increased with duration and concentration. Hyperplasia of the alveolar epithelium and focal interstitial fibrosis was statistically significantly increased at study termination; squamous metaplasia of the alveolar epithelium and squamous cysts were significantly increased in the 18 mg/m^3 females only. Talc-containing macrophages were reported in the peribronchial lymphoid tissue of the lung and in the bronchial and mediastinal lymph nodes. In the full study, the incidences of pulmonary neoplasms in male rats of the test group were similar to controls. However, in female rats of the 18 mg/m^3 group, the incidences of alveolar/bronchiolar adenoma, carcinoma, and adenoma/carcinoma (combined) were statistically significantly greater than controls; one squamous cell carcinoma was reported in this group. In the upper respiratory tract, hyperplasia of the respiratory epithelium of the nasal mucosa was observed in male test animals and accumulation of cytoplasmic eosinophilic droplets in the nasal mucosal epithelium was observed in males and female test animals; the incidence of these lesions was concentration-dependent. Benign, malignant, or complex (combined) adrenal medulla pheochromocytomas occurred with a significant positive trend in male and female rats, and the incidences in the 18 mg/m^3 group were statistically significantly increased compared to controls. The incidence of adrenal medulla hyperplasia was statistically significantly decreased in exposed males, but not exposed females, compared to controls. It was concluded that there was *some evidence of carcinogenic activity* of talc in male F344/rats based on an increased incidence of benign or malignant pheochromocytomas of the adrenal gland and *clear evidence of carcinogenic activity* of talc in female F344/N rats based on increased incidences of alveolar/bronchiolar adenomas and carcinomas of the lung and benign or malignant pheochromocytomas of the adrenal gland.

Responses to/Reviews of the NTP Inhalation Bioassay

- One member of the NTP Board of Scientific Counselors, Technical Reports Review Subcommittee, voted against the NTP conclusions on the carcinogenic potential of non-fibrous talc in rats.[120] This board member asserted that talc-induced lung tumors occurred only in the group of animals that experienced the most chronic toxicity and inflammation, and that the lung toxicity data were presented as an empirical observation rather than related to the risk assessment implications of the bioassay. Additionally, it was the opinion of the board member that the evaluation of the pheochromocytomas was inadequate because the spontaneous incidence of this tumor in rats was not sufficiently addressed and that the incidence of pheochromocytomas were not treatment-related.

- At a talc workshop that was co-sponsored by the FDA, CTFA (now, the Council), and ISRTP, a unanimous consensus was reached regarding the NTP talc bioassay.[12] It was the opinion of the Panel at the workshop that "because of the extreme doses and the unrealistic particle sizes of the talc that was used, because of the negative results in mice and male rats, because of the lack of tumor excess at the low doses, and because of the clear biochemical and cytological markers of excessive toxicity in the female rats, the positive talc bioassay results in female F344/N rats were the likely experimental artifacts and nonspecific generic response of a dust overload of the lungs and not a reflection of a direct activity of talc. Given the gross differences of rodent and human lungs, the lung clearance capabilities of humans, and the possible conditions of customary human exposures, the NTP bioassay results in F344/N female rats cannot be considered as relevant predictors of human risk."

- A critical appraisal of the NTP study discussed test concentration selection and the effect of lung particle overload.[121] The appraisal noted that a 4-wk study, rather than a subchronic study, was used to determine the test concentrations used in the bioassay; additionally, only two test concentrations were used and exposure at these concentrations impaired lung clearance in the 4-wk study. The appraisal cited a recommendation that, instead, the long-term bioassay should be performed using three concentrations and that only the highest concentration tested should show interference with lung defense mechanisms; the two lower concentrations should not interfere with clearance and particle accumulation. It was the opinion of this appraisal that lung particle clearance in both rats and mice was impaired, resulting in altered accumulation kinetics, with long-term exposure at concentrations of 6 and 18 mg/m^3. Therefore, the maximum tolerated dose (MTD) was exceeded at both exposure concentrations, and because the MTD was exceeded, "classification of such particles with respect to human pulmonary carcinogenicity should be considered carefully". Finally, the appraisal stated that the NTP conclusion of clear carcinogenicity in female rats should be qualified by a statement indicating that the lung tumors that occurred were mostly likely produced secondary to particle overload and related chronic toxicity.

- The human exposure to respirable talc particles during normal product use (values obtained from studies by Russell et al. (1979)[104] and/or Aylott (1979)[51]) was compared to the exposure of rats and mice in the NTP study.[27] According to these

researchers, based upon the determinations reported in the literature, human exposure to respirable talc particles during normal product use is approximately 2000 – 20,000 times lower than that used for rats and mice in the NTP study.

- The International Life Sciences Institute (ISLI) convened the Workshop on Relevance of the Rat Lung Response to Particle Overload for Human Risk Assessment.[122] The workshop addressed studies reporting lung tumors in rats resulting from chronic inhalation of poorly soluble, nonfibrous particles (PSPs) that are of low acute toxicity and not directly genotoxic, including non-asbestiform talc. The workshop noted that PSP-induced tumors in rats are associated with the following sequence of responses: particle accumulation, chronic active inflammation, epithelial cell hyperplasia, and metaplasia; the chronic active inflammation is associated with the emergence of neoplastic cells. It was stated that, although for direct-acting mutagens the rat appears to be a good qualitative predictor of the human lung cancer, for PSPs it appears to be more sensitive than humans and other rodent species at doses and exposure intervals that result in particle overload in the rat lung. However, because it is not known whether high lung burdens of PSPs can lead to lung cancer in humans via mechanisms similar to those in rats, "it was the consensus view of the workshop that there are insufficient data at present to conclude that the PSP-induced tumor response in the rat model is not relevant for human hazard identification. In other words, in the absence of mechanistic data to the contrary, it must be assumed that the rat model of tumorigenicity can identify potential carcinogenic hazards to humans."

- Another comment paper discussed the use of micronized talc in the NTP study, which resulted in a significantly reduced particle size compared to cosmetic talc, i.e., 2.7-3.2 μm instead of 6.0-6.9 μm.[123] The commenter stated that the use of micronized talc significantly affected the bronchopulmonary deposition and clearance characteristics of the inhaled aerosol; the micronized talc particles were deposited deeper in the lung where clearance depended on alveolar macrophages, whereas cosmetic talc particles would have deposited in the ciliated portion of the respiratory tract. The commenter also remarked on the difficulty in controlling aerosol concentrations and that the 7-wk period in which the rats were exposed to twice the intended aerosol concentration most likely aggravated an existing overload condition.

Parenteral

Intrapleural

Talc did not induce pleural tumors in rats following intrapleural injection.[118] A group of 35 Sprague-Dawley rats were given an intrapleural injection of 20 mg talc (mean size 2.6 ± 2.3 μm; no other chemical characteristics provided) and control groups were given an intrapleural injection of saline (40 rats) or no injection (38 rats). The animals were killed when moribund. No pleural tumors were observed in the test or control group. As a comparison, the researchers examined the effect of Canadian chrysotile (90% of the fibers were <8 μm in length) in 39 rats and found that 25.6% of the rats developed mesothelioma.

Intratracheal

Groups of 24 male and 24 female Syrian golden hamsters were dosed weekly with intratracheal instillations of 0 or 3 mg talc in 0.2 ml saline for 18 wks.[9] The chemical composition of talc was 61-63% silicon dioxide, 32-34% magnesium dioxide, and 0.85-1.06% other dusts; the particle size distribution was 93% <25 μ, 86% <16 μ, 54% <10 μ, 26% <5 μ, and 2% <1 μ. An untreated control group was also included. The animals were allowed to live until natural death or until killed when moribund. Animals given talc had a shorter lifespan (46 wks) when compared to the saline controls (55 wks). The talc-treated animals showed signs of minor respiratory disorders during treatment, and at necropsy, microscopic examination revealed pulmonary congestion and interstitial fibrosis, but no detectable dust deposits, granulomas, or mesothelial proliferations. There were three tumor-bearing animals; no tumors were in the respiratory tract, although three benign lung lesions (mucoepidermoid lesions) were reported. Two forestomach papillomas, 1 thyroid adenoma, and 1 adrenal adenoma were also found.

In a lifetime study, groups of 48 Syrian golden hamsters were dosed once weekly with intratracheal instillations of 3 mg talc.[10] The talc was defined as USP-grade and contained 64-66% SiO_2, 34-36% MgO_2, and <1% other dusts. Dust-laden macrophages and an accumulation of interstitial cells and were observed in the talc-treated animals. A proliferation of fibrillar material, primarily elastic fibers, and multinucleated giant cells with foreign material were observed in the alveolar and interstitial spaces, and occasional accumulation of proteinaceous exudate was seen in the alveoli. No increase in collagen fibers or granulomas was observed. The severity of premalignant lesions was evaluated in the tracheobronchial and alveolar zone of the animals. No dysplasia was observed with talc in either zone. Slight metaplasia and moderate epithelial destruction were observed in the tracheobronchial zone. Moderate hyperplasia was observed in the alveolar zone. The number of lesions induced by talc was not given.

Both intratracheal studies also examined the effects of administering 3 mg talc + 3 mg B[a]P in 0.2 ml saline to hamsters for the 18 wk period[9] or for a lifetime.[10] Although the researchers reported that results of the study indicated that talc + B[a]P had a co-carcinogenic effect, the Expert Panel noted that appropriate controls were not used.

Intraperitoneal

Forty 6-wk old Swiss albino mice were given an i.p. injection of 20 mg of UV-sterilized commercial talc (composition not stated) in 1 ml saline, and the animals were observed until there were obvious signs of a tumor or spontaneous death.[124] Fifty-five control animals were injected with 1 ml physiological saline. Animals that died before 9 mos elapsed were not included. Twenty-four treated mice were included in the results. Three (12.5%) developed mesothelioma; no lymphomas were reported. Forty-six of the control animals were included in the results; three mesothelioma and one lymphoma developed (8.7% total tumors).

Forty Wistar rats were given weekly i.p. injections of 25 mg talc suspended in 2 ml saline weekly for 4 wks, and the animals were allowed to live until natural death.[125] It is stated that the talc was composed of magnesium silicate, but no other components are given; the particle size was not known. Eighty control animals were injected with saline only. Few tumors developed in the test animals; the tumor rate was 2.5%. The time to first tumor was 587 days.

Ovarian Cancer Risk

Particulate Migration in the Genital Tract

Migration of particles through the female genital tract has been examined as a possible explanation of the presence of talc in the ovaries. However, at the "Talc: Consumer Uses and Health Perspectives" workshop, it was stated that "available histologic and physiologic studies provide no basis to conclude that talc can migrate to the ovaries from the perineal region."[12] Because whether or not translocation is a viable theory in general, several studies on the transport of particulate matter other than talc are briefly summarized below; mixed results were found. Studies specifically relating to talc migration then follow.

Non-Human

No translocation of bone black from the vagina to the oviducts was found in monkeys.[126] Cynomolgus monkeys were restrained so that their pelvis was elevated, and 0.3 ml of a suspension of 4% bone black in 30% dextran was placed in the vaginal posterior fornix of four monkeys and 0.3 ml of a suspension of 4% bone black in physiological saline containing carboxymethyl cellulose (CMC) was placed in the vaginal posterior fornix of one monkey. Ten units of oxytocin were administered by intramuscular (i.m.) injection at the same time. The monkeys were released after 20 min. One h after deposition of the bone black, two monkeys that received suspensions in dextran and the one that received the saline with CMC suspension were anesthetized and the reproductive tract of each animal was removed; the oviducts were flushed. The remaining two monkeys were processed in the same manner 72 h after deposition. The test samples, the solutions without bone black (negative controls), and samples with a suspension of bone black (positive control) were filtered with Millipore membrane filters (0.45 μm). Particles resembling bone black were found on filters used for oviduct flushing solutions as well as the solution blanks; the numbers ranged from very few to occasional on all filters and no distinct differences in numbers or shape of these particles were apparent. The new filter blank that was examined immediately upon removal was the only sample on which no bone black particles were found. The researchers stated that these results suggest that there was no translocation of bone black from the vagina to the oviducts.

Twenty-six New Zealand white rabbits were used to examine whether starch particles migrate from the vagina to the peritoneal cavity.[127] Anesthetized rabbits were divided into an untreated control group, a group given 50 mg of a glove lubricant powder intravaginally, and a group given 50 mg of the lubricant powder and *Chlamydia trachomatis* (an inclusion former). Ovulation was then induced in all groups. After 1-4, 17, and 25 days, the rabbits were anesthetized and the peritoneal cavity was rinsed; the lavage fluids were analyzed for starch particles. Small numbers of starch particles were found on all slides. Retrograde migration was found after 3 days. The number of small particles between the treated and control groups was not statistically significantly different. Large starch particles were statistically more numerous in the two test groups compared to the controls.

Human

Sterile carbon particles were suspended in 30% dextran and 3-4 ml of the suspension was deposited into the posterior fornix of three women placed in the lithotomy position (i.e., head tilted downward at a 15° angle for horizontal) that were undergoing abdominal surgery; 1 ml (10 U) of oxytocin given simultaneously via i.m. injection.[128] During surgery, 20-34 min after deposition of the particles, the Fallopian tubes were sutured 1 cm lateral to the uterus, excised, and then flushed with saline. Carbon particles were found in the rinsate from two of the three subjects. In a study using India ink, it was found that India ink (0.2 ml) that was injected into the uterine cavity 15 min – 24 h prior to abdominal surgery was transferred to the Fallopian tubes in 27/50 women in the proliferative phase and in 23/35 women in the secretory phase of the menstrual cycle.[129] Injection of ink into the cervical canal often resulted in immediate back flow into the vagina; the ink reached the Fallopian tubes in 17/56 women. However, when the ink was placed into the vagina, the ink was transferred to the Fallopian tubes in only 1/18 women in the proliferative phase in 12-24 h. The ink was found to pass from the vagina to the uterus in 2/37 women; one of these woman where the ink was transferred had a lacerated cervix. (In this study, some of the women had received an i.m. injection of 2 units of oxytocin at the same time the ink was administered, but it did not appear to affect the results, and the women were placed in the Trendelenburg position after the abdomen had been opened.)

In a study using a radionuclide procedure, the migration of a particulate radioactive tracer from the vagina to the peritoneal cavity and ovaries was determined in 24 women scheduled to undergo gynecological surgery.[130] The day prior to surgery, the women were placed in a supine position, and less than 3 ml of 10-15 mCi [^{99m}Tc]-labeled human albumin microspheres (HAM) with a size range of 30-50 µm were deposited in the posterior fornix. Each subject remained in a supine position for 24 h. The radionuclide material remained in place for 21 women, and in 16 of these women, "sufficiently high radioactivity levels" were determined as evidence of migration to the uterus or the Fallopian tubes and ovaries. In 14 of the 21 subjects, radioactivity was measured in adnexa separately from the uterus. Nine of the 14 subjects had "marked" radioactivity in the tubes and ovaries; the five subjects that did not had severe tubal occlusions. Another group of researchers stated that this finding may be misleading because only one radioactive label was used.[126]

The migration of starch particles from powdered gloves was examined in groups of female subjects that were undergoing abdominal surgery.[131] A group of 17 females was examined with powdered gloves 1 day prior to surgery and a group of 12 females was examined with powdered gloves 4 days prior to surgery. Corresponding control groups of 15 and 14 females, respectively, were examined with powder-free gloves. Peritoneal fluid was collected during surgery. The number of starch particles found in patients examined with powered gloves 1 day prior to surgery was statistically significantly increased for both small and large particles at all locations of the genital tract and for large particles in the peritoneal fluid. No particles were found in two subjects examined with powdered gloves and a few particles were found in three subjects examined with powder-free gloves 1 day prior to surgery. In subjects examined with powdered gloves 4 days prior to surgery, there were statistically significantly more small and large starch particles in the cervix and uterus, but not in the Fallopian tubes or peritoneal fluid, compared to subjects examined with powder-free gloves.

A catheter was used to apply 1-2 ml of 10 ± 2 MBq-TC-99m-labeled macroaggregates of human serum albumin, 5-20 Hm in size, into the posterior vaginal fornix of 1000 women with primary or secondary infertility in the follicular phase of the menstrual cycle; 15 women were examined during the early to mid-luteal phase.[132] The women were in a supine position, and hysterosalpingoscintigraphy (HSS) scans (a method to evaluate the transport function of uterus and Fallopian tubes) were obtained immediately and at various intervals for 4 h after application. Labeled particles were detected in the uterus at the time of the first HSS scan of every woman examined; women in both the follicular and luteal phase were examined. In women in the follicular phase, radioactivity entered the Fallopian tubes on both in 15% of the subjects and on one side in 64% of the subjects; significant radioactivity entered the pelvis of 6% of the subjects. Radioactivity was not found to migrate to the Fallopian tubes of the remaining women that were in the follicular phase or in any of the women examined during the luteal phase.

Talc Migration in the Genital Tract

Non-Human

Particles of talc were identified in the ovaries of rats that received intrauterine instillation(s) of talc.[133] In a pilot study, one group of four female ex-breeder Sprague-Dawley rats received one intrauterine instillation of 100 mg/ml talc in 250 µl PBS; these rats were killed 5 days after dosing. A second group of four rats received intrauterine instillations of the talc suspension on days 0, 6, and 15; two animals were killed on day 20. (Spectral analysis reported a 3:1 ratio of silicon to magnesium; it is not stated whether the talc was non-fibrous). The remaining two animals were dosed again on days 22 and 30, and killed on day 49. The ovaries of each animal were analyzed by an ashing procedure.

Two groups of 12 female ex-breeder Sprague-Dawley rats were then dosed intravaginally with 250 µl of the same talc suspension or PBS only, and two animals per group were killed 24 h, 48 h, or 4 days after dosing. Their ovaries were removed and analyzed as above. Particles of talc were found in the ovaries of the two rats of the talc group that were killed after 4 days, but not in those killed at 24 or 48 h or in the PBS-treated animals.

Radioactivity was not found in the ovaries of rabbits dosed intravaginally with talc.[60] Three female Large White rabbits received a single intravaginal instillation of 0.5 ml of [^{3}H]talc administered as a suspension in aq. glycerol jelly solution (10 mg/ml; 1 µCi/ml) and three were given six daily doses of the talc suspension. (Chemical characterization data were not provided). In the single-dose rabbits, urine was collected every 24 h for 3 days; the animals were then killed, the urogenital tract was dissected out, and the total radioactivity was determined in the urine, ovaries, Fallopian/ uterine tubes and cervix, the bladder, and the vagina. In the urogenital tract 72 h after dosing, radioactivity (0.004% of the dose) was only detected at the site of administration. (The limit of detection was 0.25 µg). Total recovery was not quantitated.

In the multiple-dose group, the rabbits were killed 72 h after the final dose; radioactivity was determined as described for the single-dose animals. In the urogenital tract at 72 h after the final dose, 0.035% of the radioactivity was found at the site of administration and 0.006% was found associated with the cervix and Fallopian/uterine tubes. No radioactivity was found in the ovaries.

Talc was not found to translocate from the vaginas of female cynomolgus moneys to the ovaries.[126] A pilot study was first performed with two female cynomolgus monkeys. Talc samples were exposed to a calculated neutron fluency of 1.2×10^{17}

n/cm^2, and 125 mg neutron-activated talc suspended in 0.3 ml deionized water containing 1% CMC was placed into the vaginal posterior fornix of each monkey. (Deposition was similar to that of bone black, described previously). Three days after talc deposition, the animals were anesthetized and peritoneal lavage was performed; when the peritoneal cavity was opened to collect the fluid, the lavage was repeated through the abdominal incision. Peritoneal lavage was also performed on a control animal. Radionuclide activity was determined with ^{46}Sc, ^{59}Fe, and ^{60}Co. There was no measurable translocation of activated talc from the site of deposition to the uterine cavity, oviducts, ovaries, or peritoneal cavity. (The vagina and the cervix were analyzed together). It appeared that detectable amounts of ^{60}Co were found in a portion of the oviducts of each test animal, but this was not supported by ^{46}Sc or ^{59}Fe data. Approximately 0.3 and 2.3 mg talc were found in the vaginas of the two test monkeys 3 days after instillation.

In the definitive study, six monkeys were dosed with a neutron-activated purified blend of cosmetic talc for 30 consecutive workdays.[134] The animals were restrained and dosed as defined in the pilot study; additionally, 10 units of oxytocin were administered by i.m. injection once weekly. ^{46}Sc, ^{59}Fe, ^{60}Co, and ^{61}Cr were used as tracers. The peritoneal lavage was performed as above 2 days after the last talc deposition. Measurable quantities of talc were observed in the vagina + cervix sample, and the quantities ranged from 0.006 – 117 mg talc. (The researchers theorized that the wide variations were most likely due to different menstrual cycle phases). No measurable levels of talc (> ~0.5 μg) were present in the samples from the peritoneal lavage fluid, ovaries, oviducts, or body of the uterus.

Human

Talc particles were found in approximately 75% (10 of 13) of the ovarian tumors and 50% (12 of 21) of the cervical tumors during an extraction-replication technique used to examine tissue from patients with ovarian or cervical cancer.[135] The particles found in the ovarian tumors were located deep within the tumor tissue and were not universally dispersed; some of the particles were 1000 Å, but most ranged from 1000 Å to 2 μ. The particles found in the cervical tumor tissue were generally larger than those in the ovarian tumors; some crystals were as large as 5 μ. Additionally, many particles of talc were found concentrated in the deeper layers of a primary carcinoma of the endometrium; however, talc was not found in a secondary tumor in the ovary of the same patient. Talc particles were also found in 5 of 12 normal ovarian tissue samples removed from patients with breast cancer. (Chemical characterization data were not provided for the talc that was found; the researchers noted that no asbestos fibers were found in any of the tissues studied.)

In 100 consecutive cases of women operated on for pelvic disease at Johns Hopkins Hospital, a total of 175 normal ovaries were removed and examined for particulate matter.[136] Seventy-two cases were classified as having laminated calcifications referred to as psammoma bodies. Six examples of crystalline foreign bodies were found and examined by scanning electron microscopy; computer-assisted microscopic x-ray analysis was used to determine the elemental composition of the foreign bodies in four cases. The particles were composed primarily of magnesium and silicon; the researchers stated that in industrial North America, the most common compounds containing magnesium and silicate are talc and asbestos. Nine percent (9%) of the patients appeared to have magnesium silicate granulomas in their normal ovaries, and an additional 9% contained very similar histologic entities.

The ovaries of 24 women with benign ovarian neoplasms who were undergoing surgery at Columbia Presbyterian Medical Center between 1992 and 1993 were examined for the presence of talc using both light and electron microscopy.[137] Twelve women reported talc application directly to the perineum or underwear and 12 women were age-matched controls. The mean number of lifetime exposures for women reporting talc use was 14,820, with a range of 4784 – 39,312 lifetime exposures. The ovaries of two stillborn fetuses were analyzed as negative controls; no talc was found in these ovaries. Sections of normal ovary from the 12 women who reported the talc use were analyzed. A linear relationship between ovarian talc particle burden and exposure was not found. Neither light nor electron microscopy values correlated with perineal talc usage. Electron microscopy counts were 0 for about half of the subjects exposed to talc as well as half of the controls; talc was observed with light microscopy in all subjects exposed to talc and 11/12 of the controls. There was a negative correlation between the values obtained by light microscopy and electron microscopy. The mean electron microscopic particle count was higher in those exposed to talc and the mean light microscopic particle count was higher in the women that did not report talc use. In one subject for which both ovaries were analyzed, both talc counts varied greatly between the right and left sides (0 vs. 1,669,000 particles/g wet tissue wt by electron microscopy and 556 vs. 6 particles by light microscopy, respectively). Asbestos was detected in the ovaries of four talc-exposed subjects and five of the control subjects.

The pelvic lymph nodes of a woman with stage III ovarian papillary serous carcinoma, with metastatic serous carcinoma in two of six right external iliac and obturator nodes, were examined using polarized light microscopy and scanning electron microscopy and x-ray spectroscopy.[138] The subject applied talc daily for 30 yrs to the perineum, and also applied it to underwear and sanitary napkins. She had three term deliveries followed by a tubal ligation and she did not smoke, use oral contraceptives, or, with the exception of 6 mos of progesterone therapy, use postmenopausal hormone therapy. Birefringence was seen using polarized light; three of four nodes that did not contain metastases displayed polarizing material. Examination of lymph nodes by combined scanning electron microscopy and x-ray spectroscopy revealed plate-like particulates in the 5-10 μm range within the lymph nodes; the energy dispersive x-ray spectroscopy showed a magnesium and silicate signature that

was compatible with talc. Nodes from 12 other patients were examined; this case was strongest for birefringence. (Electron microscopy or x-ray spectroscopy had not been performed).

Epidemiological Studies

Numerous epidemiological studies have been performed examining the risk of ovarian cancer following talc exposure.[139-171] These studies are summarized in Table 9. There is a large amount of information presented in these studies, and a variety of parameters were examined. Table 10 is a summary of the relative risk for ovarian cancer presented in case-control studies; this table only includes those studies that indicated "ever" use of talc in the perineal area, independent of the manner of use.[140-143,145,146,149-152,154,156,158-160,162-164,167,170,171]

Analysis of Ovarian Cancer Risk in the Epidemiological Studies

Concerns about cosmetic talc are based on reports suggesting that talc may migrate from the perineum to the ovaries and epidemiological studies suggesting a fairly consistent association between perineal dusting and ovarian cancers.[13]

The possibility that using cosmetic talc powder can cause ovarian cancer was suggested when talc particles were found in or on human ovarian tissues.[128-130,135,172,173] The translocation of talc particles from the perineum to the ovaries would require that these particles pass from the perineum through the vagina and cervical canal, move across the uterus and against the ciliary motion of the Fallopian tubes, cross the peritoneal space between the fimbriae and ovaries, escape phagocytosis in the peritoneal space, and attach to the surface of the ovaries to accumulate in the ovaries.[174,175]

However, there is evidence that talc particles found in ovaries is attributable to sample contamination, rather than to particle translocation.[13,176] This view is supported by studies finding talc in 100% of women with no known talc exposure, for example, as well as in 85% of women reporting frequent perineal talc applications.[137]

Further, many translocation studies have been criticized for using particles with only a single radionuclide,[130] because the radiolabel leaches from such particles, leading to the untenable assumption that the leached radioactive marker represents translocated particles.[13,58,134,176-182] In a study conducted to help address this issue, ^{46}Sc, ^{60}Co, ^{59}Fe and ^{51}Cr served as tracers in 125 mg neutron-activated talc deposited intravaginally 30 times over 45 days to ensure exposure through at least one menstrual cycle in cynomolgus monkeys.[13,134,176,179] The tracers were not detected in the uterus, Fallopian tubes, ovaries, or peritoneal lavage fluid 2 days after the 30th talc application.

The migration of many different types of materials from the vagina through the cervix has been demonstrated in patients in a supine or in the Trendelenburg position or with a lacerated or a dilated cervix. In addition, retrograde menstrual flow is a well-known phenomenon that could help explain the movement of particles to the ovaries in some cases. However, the findings of at least one study[129] has been interpreted as demonstrating the formidable barrier that the cervix presents to the translocation of particles from the vagina to the ovaries.[179,183]

Many women may have been exposed to talc in infancy.[137] Infants are typically placed in a supine position and their legs separated during diapering, which could facilitate the passage of talc into the vagina. This may help explain the ubiquitous presence of talc in ovarian tissue. However, it has not been determined whether the hymen blocks exposure to the infant genital tract, or otherwise to what extent, if any, talc can enter the genital tract during diapering.[23]

Several epidemiological studies suggested that medical procedures that would be expected to prevent the translocation of talc to the ovaries, such as tubal ligation or hysterectomy, reduce the relative risks estimated for talc use.[145,151,169,184] However, in one of these studies, women who were exposed to talc for one to nine years before tubal ligation or hysterectomy appeared to have an increased risk of ovarian cancer, but not women who had talc exposure for ten or more years before their surgery.[169] Other studies found no difference in relative risk between women who had tubal ligation or hysterectomy and women who did not have these procedures.[140,170] One study reported inverse exposure-effect trends with duration of talc exposure after adjusting for tubal ligation.[162] Thus, the literature provides no clear, convincing support for the hypothesis that procedures that would preclude the passage of talc particles from the perineum to the ovaries reduce the risk of ovarian cancer.

The use of talc-dusted condoms or diaphragms, which would clearly result in exposure close to the cervical opening, was not associated with an increased relative risk estimate for ovarian cancer.[143,145,164] A meta-analysis found no association between talc-dusted diaphragm use and ovarian cancer risk. Overall, these studies do not support the hypothesis that talc can migrate from the perineum or the vagina to the ovaries.

Numerous case-control studies have reported small increases in relative risk estimates of all ovarian cancers combined in women using cosmetic talc products, compared to women with minimal or no exposure, including population-based and hospital-based case-control studies (Tables 9 and 10; Chart 1). Other investigations found no statistically-significant increase in risk estimates for ovarian cancer (all subtypes combined), including many case-control studies and one prospective cohort study.[148] Presumably the subjects in all of these studies used products that contained cosmetic grade talc, but information on fibrous content is generally lacking.

Some studies found statistically-significant associations between talc use and invasive cancer[140,145,148] while another study reported an association only between talc use and tumors of low malignant potential.[151] Some studies found no statistically-significant associations with all subtypes of ovarian cancer considered together, but reported statistically-significant associations only with specific subtypes of ovarian cancer or endometrioid tumors.[142,145,148,151]

Among the epidemiological investigations reporting statistically-significant associations, the relative risk estimates ranged between 1.0 and 2.0 and were barely statistically significant (Tables 9 and 10; Chart 1). For such low estimates, epidemiological methods generally cannot distinguish causality from even minor confounding risk factors or biases.[185-188] Age, race, low parity, infertility, and a family history of ovarian, endometrial or breast cancer are among the most likely risk factors in the etiology of epithelial ovarian cancer.[13,189] Others have suggested that the effects of cancer treatment, smoking, and consuming coffee regularly could explain the small increases in the relative risk estimates reported for ovarian cancer in women using cosmetic talc products perineally.[169,190,191] Many physiological, sociological, and exposure factors have been linked to ovarian cancer, a number of them with a stronger association than the hygienic use of cosmetic talc, but causality has not been established for any of them.[179] The etiology of the majority of ovarian cancer cases is still unknown.

Prospective cohort studies do not suffer from recall bias because the exposures are recorded before the cancers were diagnosed. The single cohort study available found no statistically-significantly association between perineal talc use and all ovarian cancer subtypes combined, but did report such an association with invasive serous ovarian cancer (RR=1.4; 95% CI: 1.02-1.91)[148] The odds ratios for serous ovarian cancer were also elevated in several case-control studies.[140,145,151,170] All of the odds ratio estimates reported in these studies were less than 1.7.

Talc exposure probably varies over time as women age and their reasons for deciding to use talc change. Talc use might be sporadic, seasonal, or change with circumstances (e.g., sexual activity and parity). However, no studies have characterized either the feminine hygiene habits involving the use of cosmetic talc products in the general population or the latency of purported talc-induced ovarian cancer to enable resolving these issues.[187] Moreover, the epidemiological studies used questionnaires that did not focus specifically on the subjects' use of talc or talcum powders, as distinct from non-talc powders or sprays of known (e.g., corn-starch based) or unknown compositions.[174] It is not clear that all of the subjects understood the distinction between talc or talcum powders and talc-free powders when answering the questions. These factors contribute substantially to the uncertainties associated with the risk estimates of the prospective study, and well as the case-control studies.

An early meta-analysis found a statistically-significant adjusted pooled odds ratio of 1.27 (95% CI: 1.09-1.48) for ovarian cancer in women who ever used talc in the perineal or abdominal region compared to women who never used talc[192] However, the authors cautioned that this result does not provide the basis for inferring causality because many of the studies had substantial design limitations.

A more recent meta-analysis yielded a statistically-significant overall summary relative risk of 1.33 (95% CI: 1.16–1.45).[191,193] However, a sensitivity analyses revealed clear differences in outcome based on study design. Population-based case-control studies yielded a statistically-significant increase in the risk of ovarian cancer for hygienic use of talc, but hospital-based case–control studies showed no statistically significant difference. There were no differences in the frequency of talc use in the respective control groups. The authors suggested that the difference in outcomes may be attributable to a bias, such as a "treatment effect" among the cases (i.e., side effects from treatments for ovarian cancer may make talc use more likely in the patients than in the controls).

A still more recent meta-analysis reported a statistically-significant overall summary relative risk of 1.35 (95% CI: 1.26–1.46).[191,194] However, a statistical test for data heterogeneity indicated substantial inconsistencies among the pooled studies and an invalid pooled summary relative risk estimate. Thus, the outcome provided no support for a causal association between perineal talc use and ovarian cancer.[185,195]

Most of the epidemiological studies found no trend of increasing ovarian cancer risk with increasing exposure duration or frequency or cumulative exposure, despite a fivefold difference between the lowest and the highest exposure groups (Table 10).[196] Several of these studies reported an apparent inverse trend.[139,140,145,148,193,197] In one study, suggestions of an exposure-effect relationship were obtained only after excluding exposures during pregnancy, during oral contraceptive use, and after sterilization.[145] Overall, however, the results of the epidemiological studies are not consistent with known mechanisms of carcinogenesis, which would be expected to yield positive exposure-effect trends. The inverse trends, in particular, are not compatible with a causal relationship between perineal talc exposure and ovarian cancer.[190,193]

No plausible biological mechanism has been identified to explain how exposure to talc containing no asbestos or other asbestiform fibers could cause ovarian cancer. If perineal talc use can cause ovarian cancer in a dose-dependent manner, then there should be also be associations between such talc use and both cervical and uterine cancer, where talc exposure would be expected to be greater than ovarian exposure. No such associations have been reported..

Thirty or more years ago, cosmetic talc was thought to contain substantial amounts of asbestos fibers,[24,198] which would clearly represent a carcinogenic risk. However, FDA and IARC found that this contention could not be substantiated.[19,38,198-201] Further, stringent quality criteria have been in place for cosmetic talc since 1976.[202] Meeting these criteria requires the elimination of detectable asbestos and other asbestiform fibers. Thus, the increased ovarian cancer risks associated with cosmetic talc use reported in some of the more recent epidemiological studies have generally not been attributed to contamination with asbestiform fibers.

However, the potential carcinogenicity of talc has been attributed by some authors to the chemical similarity of talc to asbestos. Both substances are magnesium silicates, but they share no other characteristics in common.[13,23,202] The aspect ratio of the fibrils is generally considered to be critical for the carcinogenicity of asbestos. In contrast, talc consists of three-layer silica-brucite-silica sheets stacked together to form small platy packets with highly insoluble, hydrophobic surfaces. Cosmetic talc does not contain fibrils.

Alternatively, some researchers have suggested that talc in the ovaries could cause cancer, indirectly, through a talc-induced inflammatory response, analogous to the action of asbestos fibers in the lungs.[203] However, pelvic inflammatory diseases, such as endometriosis, peritonitis, and tubo-ovarian abscess formation, have not been found to be associated with increased risks of ovarian cancer. In addition, anti-inflammatory drug use did not reduce ovarian cancer risk estimates in several studies.[158,204]

Most recently, one group proposed that elevated expression of anti-MUC1 antibodies induced by perineal talc in the peritoneal lymph nodes might explain the reported associations between talc exposure and ovarian cancer.[146] However, the application of talc powder to other parts of the body appears to induce anti-MUC1 antibody expression as well, and elevated anti-MUC1 antibody levels generally have not been associated with increased risks of ovarian cancer. Thus, this proposal remains highly speculative.

Talc is commonly used clinically as the active agent for pleurodesis. This procedure involves introducing a talc slurry directly into the pleural space to induce fibrogenesis. No increase in the incidences of lung or pleural cancers has been found in multiple clinical studies involving hundreds of patients followed for decades after pleurodesis.[190,205,206]

The results of these clinical studies are consistent with epidemiological investigations reporting no statistically significant increase in mortality from lung cancer or mesothelioma in workers occupationally exposed to "pure" talc.[88,91,93] As stated by one author, "the likelihood that talc could selectively induce ovarian cancer and not lung cancer at exposure concentrations orders of magnitude lower than that experienced in occupational settings, argue against its toxicity."[23] Others have noted the absence of reports suggesting that talc inhalation is associated with either lung cancers or mesothelioma in consumers[13].

Accordingly, animal cancer bioassays using rodents exposed to high concentrations of talc in air indicate that talc is not a primary carcinogen. The NTP life-time inhalation carcinogenesis bioassay found no ovarian lesions in female mice or rats, and no malignant respiratory-tract lesions in male rats or male or female mice.[11] Further, the lung cancers found in female rats can be plausibly attributed to chronic pulmonary particle overload, rather than to the possible carcinogenicity of talc.[121,207] The use of micronized talc in the NTP study probably contributed to the pulmonary overloading. This interpretation is supported by the results of an earlier lifetime inhalation study in hamsters. The animals were exposed to a talc baby powder aerosol at rates that exceeded those measured in infant-dusting simulations (mg-h/m^3) by 30 to 1,700 fold.[13,78] The exposures had no effect on the type, incidence or degree of histopathological findings in the lungs or other tissues examined, or on body weight, survival, or any other parameter evaluated, compared with the sham-exposed controls.

Further, the injection of talc into ovarian bursa of rats in one study (100 µl/ovary of 100 mg 0.4-14 µm platy talc crystals/ml buffered saline) induced no cancers[64]

In summary, critical issues that call into question the validity of the statistically-significant associations reported in some of the epidemiological studies include:

- Absence of persuasive evidence that talc can migrate from the perineum to the ovaries;
- Lack of consistent statistically-significant positive associations across studies;
- Uniformly small relative risk estimates in studies reporting positive associations;
- Failure to rule out plausible alternative explanations of the statistically-significant results, including biases, confounding risk factors, and exposure misclassifications;
- Absence of statistically-significant associations between ovarian cancer and using talc-dusted diaphragms or condoms;
- Overall lack of positive exposure-effect relationships;
- Inverse trends for both duration of use and frequency of use in some studies;
- Absence of a plausible biologic mechanism;

- Lack of credible, defensible evidence of carcinogenicity from the results of epidemiological studies of occupational exposures and animal bioassays.

IRRITATION AND SENSITIZATION

Sensitization

Non-Human

Talc was not a sensitizer in female Hartley guinea pigs.[208] Female Hartley guinea pigs (number not stated) received an intradermal injection of 10 mg sterile talc in an emulsion of 0.5 ml sterile saline and 0.5 ml Freund's complete adjuvant; six guinea pigs were dosed in the same manner with 10 mg starch glove powder. (Chemical characterization data were not provided; the talc was British Pharmacopeia-grade). Eleven control animals were injected with the emulsion only. Skin tests were then performed at various intervals by challenging all animals with suspensions starch glove powder in one ear and talc in the other. Slight cutaneous thickening was observed in all control animals 24 h after challenge with both suspensions, and the responses were similar to both talc and the starch. The response to challenge with talc in the talc test group was similar to that seen in the controls. Animals in the starch group had a statistically significantly greater response to the starch challenge compared to controls.

SUMMARY

Talc is a sheet silicate that belongs to the silicate subclass phyllosilicates. In its purest form, it is a mineral that corresponds to the chemical formula for hydrous magnesium silicate; commercially, it contains varying amounts of other minerals naturally found in the ore. Only talc containing no detectable fibrous, asbestos minerals is used in cosmetics, and cosmetic talc must consist of a minimum of 90% hydrated magnesium silicate, with the remainder consisting of naturally associated minerals such as calcite, chlorite, dolomite, kaolin, and magnesite.

In 2012, FDA VCRP data indicated that talc was used in over 2800 cosmetic formulations and, according to concentration of use data received in response to a Council survey, talc is used at up to 100% in cosmetic formulations. Talc is used in almost every category of cosmetic product, and it is used in products that may be applied to baby skin, products that could be incidentally ingested, products used near the eye area or mucous membranes, and in products that are sprayed. The particle size of talc raw material varies widely by product type and by manufacturer.

Talc has many commercial uses and it has pharmaceutical use. It is used as a color additive in drugs and is exempt from certification. Sterile talc is approved as a sclerosing agent. Talc is not allowed for use on the surface of medical gloves. It is used in the production of foods, and it is approved as an indirect food additive as a color.

Syrian golden hamsters received a single 2-h nose-only exposure to talc tested as a commercial baby powder (chemical characteristics unknown), with a median aerodynamic diameter of 6.4-6.9 μm. The biological half-life of the talc deposited in the lungs was 7-10 days. No translocation from the respiratory tract to other tissues was found in this study, and the clearance of talc from the lungs was complete within 4 months after exposure. Following oral administration of [^{3}H]talc to mice, rats, and guinea pigs, most of the radioactivity was excreted in the feces. Wistar rats were used to determine the systemic distribution of talc following intrapleural administration; the study suggested that talc is absorbed very rapidly through the pleura, reaching the systemic circulation with deposition in other organs within 24 h of administration, and that the distribution is not dose-related.

The acute oral LD_{50} of rats was 920 mg/kg in one study and >5000 mg/kg in another. In a study in which mice were placed in a box with circulated baby powder, the mice removed after 30 or 60 min recovered completely and the mice removed after 90 or 120 min died; the chemical composition, amount of powder, and size of the box were not specified. In rats dosed with a single bilateral injection of 100 mg/ml talc into the ovarian bursa and killed 1-18 mos after dosing, one or both ovaries of rats dosed with talc were cystic in appearance at all time periods; the cystic structures were attributed to distention of the bursal sac. Foreign body granulomas, without surrounding inflammation, were seen in the cortical area of five of the injected ovaries, and talc was observed in the granulomas. In rats, a granulomatous reaction in which foreign-body giant cells containing refractile materials was observed without fibrosis at 1 mo and at 3 mos after a single i.p. injection of 50 mg/kg nonfibrous talc. In rats dosed with a single i.p. injection of 0.02, 0.1, or 0.5 g talc in 5 ml normal saline, clusters of foci of inflammatory cells were observed scattered on the surface of the peritoneum and talc particles were seen in the center of each focus.

There were no remarkable results found in studies examining the cellular effect of talc, such as cytotoxicity assays, assays examining the effect of talc on cell viability, or studies on the induction of apoptosis (among others).

Dermal application of talc to shaved rabbit skin for 6 wks resulted in dryness of the skin and skin erosion. Oral administration to rats for 5 days produced minimal toxicity. In inhalation studies, exposure of mice and rats for 4 wks (25 μm particle size) resulted in macrophages in the alveolar space, with more found in the mice than the rats. In rats exposed for 3, 6, or 12 mos, minimal to slight fibrosis resulted. In hamsters, exposure to baby powder (95% talc; 4.9 -6.0 μM) did not result in clini-

cal toxicity, and no trends were observed. Intrapleural administration of talc (25 μm) to rats did not result in mesotheliomas; granulomas at the injection site were common. Infections occurred, but no neoplastic or perineal changes, when talc was instilled intravaginally or perineally in rats. Upon i.v. injection of talc (<5 μm) once weekly for 3 wks, talc was found in the lungs and the liver throughout the study.

Talc is non- or slightly irritating to rabbit eyes. In a female subject that presented with a foreign body sensation and inflammation of the conjunctiva of both eyes, a diagnosis of foreign body granuloma secondary to talc was made.

Application of talc to wounded skin can give rise to scab formation, possible infection, and foreign body granulomas in the dermis.

Talc has a TLV (respirable fraction) of 2 mg/m^3 as a TWA. Human pulmonary effects of talc include diffuse interstitial fibrosis and progressive massive fibrosis (often called complicated pneumoconiosis). In occupational exposure studies, statistically significantly elevated SMRs for silicosis and silico-tuberculosis were observed in an early study of talc miners and millers in the Italian Piedmont region exposed to talc that contained no fibrous material except for tremolite micro-inclusions; SMRs were statistically significantly reduced for malignant neoplasms, including lung, bronchial and tracheal cancers. A follow-up of this group found statistically significant increases in mortality, which were attributed primarily to non-malignant respiratory diseases among the miners. A cohort study of talc miners and millers exposed to talc and magnesite containing trace amounts of quartz, tremolite, and anthophylite found no statistically significant SMRs for all causes, all cancers, or diseases of the circulatory system or respiratory tract. The results of several other epidemiological studies were likely confounded by the presence of up to 3% silica or 6% actinolite in the talc, exposures to high concentrations of silica with or without exposures to fibrous talc (tremolite), or concurrent exposures to radon daughters. A meta-analysis of studies of miners and millers who worked with non-asbestiform talc reported summary SMRs for lung cancer of 0.92 (95% CI: 0.67-1.25) for millers in five countries exposed to high levels of talc without exposure to other occupational carcinogens, and 1.2 (95% CI: 0.86-1.63) for miners in 3 countries exposed to high levels of talc as well as to silica or radon and radon daughters. Studies examining radiological, lung-function and clinical parameters in talc miners and millers and rubber workers found some statistically significant changes.

In exposure-during-cosmetic use studies, the researchers noted that there was a wide variation in talcing times and methods, often by the same volunteer during different applications. Reported talcing times ranged from 17 sec to 31 sec. Endobronchitis and airway stricture was reported in one case in which a subject applied large amounts of talc powder to her face. In another case, a chronic pulmonary granulomatous reaction was reported in a subject who applied "non-powdering talc" to her face for 20 yrs, followed by use of talcum powder 2-3 times a day for a 10-yr period.

Talc administered orally as a suspension in corn oil was not a developmental toxicant in mice (16-1600 mg/kg on days 6-15 of gestation), rats (16-1600 mg/kg on days 6-15 of gestation), hamsters (12-1200 mg/kg on days 6-10 of gestation), or rabbits (9-900 mg/kg on days 6-18 of gestation). No dose response or time-trend pattern was observed in rats that received a single oral dose or once daily dose for 5 days of 30-5000 mg/kg talc.

In vitro, talc was not genotoxic in an UDS assay (10, 20, or 50 μg/cm^2) or a SCE assay (2, 5, 10, and 15 μg/cm^2) in rat pleural mesothelial cells. Talc was not genotoxic in a host-mediated assay in mice dosed by gavage with a single dose or once daily for 5 days with 30, 300, 3000, or 5000 mg/kg talc or cytogenetic assay in rats dosed by gavage once daily for 5 days with 30, 300, 3000 , or 5000 mg/kg talc. Talc was also not genotoxic in a dominant lethal assay in which rats were dosed by gavage with a single dose or once daily for 5 days with 30, 300, 3000, or 5000 mg/kg talc.

In a lifetime inhalation study, a carcinogenic effect was not observed upon exposure of hamsters to a commercial baby powder containing 95% platy talc for 30 or 150 min/day, 5 days/wk. A bioassay using mice and rats was performed by the NTP to determine the carcinogenic potential of non-asbestiform, cosmetic-grade micro-talc following exposure by inhalation, and it was concluded there was *no evidence of carcinogenic activity* in male or female B6C3F1 mice, *some evidence of carcinogenic activity* in male F344/rats, and *clear evidence of carcinogenic activity* in female F344/N rats. The mice were exposed to 6 mg/m^3 (MMAD 3.3 ± 1.9 μm) or 18 mg/m^3 (MMAD 3.6 ± 2.0 μm) talc for 6 h/day, 5 days/wk, for 103-104 wks. The rats were exposed to 6 mg/m^3 (MMAD 2.7 ± 1.9 μm) or 18 mg/m^3 (MMAD 3.2 ± 1.9 μm) talc for 6 h/day, 5 days/wk, for 113 wks (males) or 122 wks (females). Concerns have been raised about this study, including concerns that micronized talc having a significantly smaller particle size distribution than cosmetic talc was used, aerosol concentrations were not properly controlled, proper procedures for dose selection were not followed resulting in the MTD being exceeded at both concentrations tested, and particle overload in the lungs was most likely the cause of the adverse effects reported.

Talc did not induce pleural tumors in rats following intrapleural injection of 20 mg talc (mean size 2.6 ± 2.3 μm). Few tumors developed in rats given weekly i.p. injections of 25 mg talc suspended in 2 ml saline weekly for 4 wks. In mice given an i.p. injection of 20 mg of UV-sterilized commercial talc in 1 ml saline, 12.5% of the animals developed mesothelioma. The researchers also examined the effects of administering 3 mg talc + 3 mg B[a]P in 0.2 ml saline to hamsters in both

studies, concluding that talc + B[a]P had a co-carcinogenic effect; however the Expert Panel noted that appropriate controls were not used.

Results of studies examining particulate migration in the genital tract have been mixed. In one study using monkeys, there was no translocation of bone black from the vagina to the oviducts. However in a human study, researchers concluded that there was evidence of migration of carbon particles to the uterus or the Fallopian tubes and ovaries, although other researchers stated that this finding is misleading because only one radioactive label was used. In a study in rabbits, the number of large starch particles in peritoneal cavity rinsate was greater in test groups that were exposed intravaginally to glove lubricant (i.e., starch) than in controls. In human subjects, it appeared that starch particles migrated to the cervix and uterus.

In studies specific to talc migration, mixed results have also been reported. In rats, talc was found in the ovaries of rats dosed intrauterinally with talc; in rats exposed with a single intravaginal dose, talc was found in the ovaries 4 days after dosing, but not 24 or 48 h after dosing. Talc was not found in the ovaries of rabbits given six daily intravaginal doses, and there was no translocation of talc from the vaginas of monkeys to the ovaries, oviducts, or the body of the uterus. In humans, talc particles were found in 10/13 ovarian tumors and 12/21 cervical tumors; the particles found in the ovarian tumors were generally smaller than those in the cervical tumors, i.e., 1000 Å to 2 μm versus up to 5 μm, respectively. In women with benign ovarian neoplasms, half of whom applied talc to the perineum or underwear, there was no linear relationship between ovarian talc powder burden and exposure. Electron microscopy counts were 0 for about half of the subjects exposed to talc as well as half of the controls; talc was observed with light microscopy in all subjects exposed to talc and 11/12 of the controls.

Numerous epidemiological studies have been performed examining the risk of ovarian cancer following talc exposure. Among the epidemiological investigations reporting statistically-significant associations, the relative risk estimates ranged between 1.0 and 2.0 and were barely statistically significant. Many physiological, sociological, and exposure factors have been linked to ovarian cancer, a number of them with a stronger association than that of hygienic use of cosmetic talc, but causality has not been established for any of them. Most of the epidemiological studies found no trend of increasing ovarian cancer risk with increasing exposure duration or frequency or cumulative exposure, despite a five-fold difference between the lowest and the highest exposure groups. Several of these studies reported an apparent inverse trend. The results of several epidemiological studies suggested that medical procedures expected to prevent the translocation of talc to the ovaries, such as tubal ligation or hysterectomy, reduce the relative risk estimates associated with talc use. Other studies found no difference in relative risk between women who had tubal ligation or hysterectomy and women who did not have these procedures. One study reported inverse exposure-effect trends with duration of talc exposure after adjusting for tubal ligation. The use of talc-dusted condoms or diaphragms (including diaphragms known to have been stored in talc powder), which would clearly result in exposure close to the cervical opening, was not associated with an increased estimate of relative risk of ovarian cancer.

Talc was not a sensitizer in female Hartley guinea pigs.

DISCUSSION

The safety of talc has been the subject of much debate through the years, partly because the relationship between talc and asbestos is commonly misunderstood. Often in early studies, some of the analytical methods used to identify asbestos in talc were not performed and/or interpreted correctly, leading to incorrect conclusions that high levels of asbestos were present in talc. In 1976, the Cosmetic, Toiletry and Fragrance Association (CTFA; now known as the Personal Care Products Council) issued stringent purity standards for talc used in cosmetics, including specifications that talc must contain no detectable fibrous, asbestos mineral; generally-accepted methods for the determination of asbestiform amphibole minerals in cosmetic talc were also identified by the CTFA. Therefore, the Panel evaluated only the safety of talc that does not contain detectable fibrous, asbestos minerals.

During its deliberations, the CIR Expert Panel discussed a 2012 study performed by the FDA in which talc samples and talc-containing products were analyzed for the presence of asbestos. No asbestos was detected in any of the talc samples or the talc-containing products. Additionally, during the Panel's discussion of the FDA study, an industry representative for talc producers assured the Panel that talc is certified to be asbestos-free, and their mines are monitored for asbestos concentrations.

The Panel requested that industry submit additional information describing how they analyze talc to ensure that it is free of asbestiform fibers. Industry should identify the analytical methods used, including the detection limits of these methods, and provide typical, current measurements of impurities in talc used in cosmetic products. This information from representative companies should provide sufficient characterization of the impurities in talc used in current products and, thus, generally document adherence to, or compliance with, the 1976 cosmetics industry specification that the talc used is free of asbestiform fibers. This information will help ensure that current analytical methods and results are reliable, unlike the questionable methods, results, and interpretations of many pre-1976 studies. This is important because many of the persistent concerns

about the possible risks of ovarian and other cancers associated with talc use depend upon assumptions about the impurities in talc, particularly the potential presence of asbestos and other asbestiform fibers.

As evidenced in this safety assessment, numerous studies have been performed to investigate whether or not a causative relationship exists between the cosmetic use of talc in the perineal area and ovarian cancer. The Panel reviewed these studies thoroughly, and determined that they do not support a causal link. The Panel stated that causation would depend on the migration of talc from the perineum to the ovaries. There is no conclusive explanation for the presence of talc in the ovaries reported in some studies. However, the Panel agreed that there is no known physiological mechanism by which talc can plausibly migrate from the perineum to the ovaries. Further, the Panel noted that if typical perineal applications of talc increased the risk of ovarian cancer, then it would be expected to increase the risks of uterine and, especially, cervical cancer as well; the absence of reports of associations between perineal talc use and either uterine or cervical cancer indicates that perineal talc application does not cause ovarian cancer. Additional support for this conclusion comes from, for example, studies demonstrating that the use of talc-dusted condoms or diaphragms, which would clearly result in exposure close to the cervical opening, was generally not associated with increased relative risk estimates for ovarian cancer.

Studies have also examined whether the inhalation of cosmetic-grade talc is associated with respiratory tract cancers. Although an inhalation study performed by the NTP using non-asbestiform, cosmetic-grade talc concluded that there was some evidence of carcinogenic activity in male rats and clear evidence in female rats, the Panel stated that these results were attributable to an artifactual effect caused by particle overload in the lungs of the rats. The talc that was used in this study, i.e., micronized talc at high, saturating concentrations, had particle size distributions much smaller than those of cosmetic-grade talc. The Panel concluded that the use of talc at concentrations up to 35% in spray products, as reported for aerosol make-up bases, or even at 100% in powders, as reported for face powders, would not overwhelm pulmonary clearance mechanisms and would, therefore, not cause pulmonary overload or adverse respiratory effects attributable to cosmetic talc use.

One group of researchers looked at the effect of intratracheal administration of talc plus B[a]P in hamsters, concluding that talc may be co-carcinogenic when administered with B[a]P. The Expert Panel noted the potential for co-carcinogenicity, but determined that the results of these studies were not attributable to a specific effect of talc, appropriate controls were not used, including control animals exposed to B[a]P alone and, thus, the results were not relevant for assessing the safety of the cosmetic use of talc.

Finally, the Panel warned that talc should not to be used on skin where the epidermal barrier is removed or on skin that has 1st degree or greater burn. Case reports were available in which granulomas formed if talc was applied to skin when the epidermal barrier was absent.

CONCLUSION

The CIR Expert Panel concluded that talc is safe in the present practices of use and concentration described in this safety assessment.

TABLES

Table 1. Physical and chemical properties

Property	Description	Reference
physical appearance	essentially white, odorless, fine powder	30
	ranges from snow-white to black, including greenish-gray and shades of green, pink, and red	41
	white, apple-green, gray powder; pearly or greasy luster	209
Mohs' hardness	1	210
	1-1.5 (may be harder when impure)	26,209
crystal system	triclinic	26
morphology	perfect (001) cleavage	26
melting point	900-1000°C	211
	1500°C	29
pH	8.8-9.5	20
	7.7±0.5	42
density	2.7 g/cm^3	212
surface area	<20 m^2/g (B.E.T. method)	213
solubility	insoluble in water, cold acids, or in alkalies; soluble in hot concentrated phosphoric acid	214
brightness (GE)	75-95	20
optical properties		215
n_x	1.539-1.550	
n_z	1.589-1.600	
indices of refraction	α = 1.539 – 1.550	19
	β = 1.589 – 1.594	
	γ = 1.589 – 1.600	

Table 2. Frequency and concentration of use – summary by exposure type and complete table in FDA format

	Number of Uses[43]	Maximum Concentration of Use (%) [44]
Totals*	**2877**	**0.0005-100**
Duration of Use		
Leave-On	*2705*	*0.002-100*
Rinse-Off	*154*	*0.0005-70*
Diluted for (Bath) Use	*18*	*0.001-88*
Presented in complete FDA VCRP format		
Baby Shampoos	NR	7
Baby Lotions, Oils, Powders, Creams	9	99
Bath Oils, Tablets, and Salts	17	1-88
Bubble Baths	NR	0.4-2
Bath Capsules	1	NR
Other Bath Preparations	NR	0.001
Eyebrow Pencil	43	0.01-79
Eyeliner	101	0.1-90
Eye Shadow	869	20-100
Eye Lotion	13	2
Mascara	79	1-50
Other Eye Makeup Preparations	61	2-6
Perfumes	3	2
Fragrance Powders (Dusting and Talcum)	104	15-99
Sachets	3	9
Other Fragrance Preparations	10	3-9
Hair Conditioner	1	0.4
Rinses	NR	0.05
Shampoos	NR	0.04
Tonics, Dressings, and Other Hair Grooming Aids	2	10
Other Hair Preparations	1	NR
Hair Dyes and Colors	NR	0.4-13
Other Hair Coloring Preparations	1	6

Table 2. Frequency and concentration of use – summary by exposure type and complete table in FDA format

	Number of Uses[43]	Maximum Concentration of Use (%) [44]
Blushers	290	48-94
Face Powders	500	20-100
Foundations	201	12-76 (not spray)[45] 1-6 (aerosol spray)
Leg and Body Paints	3	2 (aerosol spray)[45]
Lipstick	54	3-74
Makeup Bases	44	36 (not spray)[45] 35 (aerosol spray)
Rouges	13	NR
Makeup Fixatives	11	10
Other Makeup Preparations	102	0.8-85
Basecoats and Undercoats	5	1-7
Cuticle Softeners	1	0.004-18
Nail Creams and Lotions	NR	2
Nail Polish and Enamel	7	0.002-11
Other Manicuring Preparations	1	35
Dentifrices	1	NR
Other Oral Hygiene Products	NR	11
Bath Soaps and Detergents	51	0.001-70
Deodorant (Underarm)	18	6-85 (not spray)[45] 1-30 (aerosol spray)
Other Personal Cleanliness Products	29	0.03-20
Aftershave Lotion	1	14
Men's Talcum	3	96
Shaving Soap (cakes, sticks, etc)	NR	0.04
Other Shaving Preparations	2	NR
Cleansing	37	0.0005-0.005
Depilatories	4	NR
Face and Neck Creams, Lotions, and Powders (excl. shaving)	32	40 (not spray)[45] 0.4 (spray)
Body and Hand Creams, Lotions, and Powders (excl. shaving)	18	96 (not spray)[45] 0.3 (spray)
Foot Powders and Sprays	9	0.9-97
Moisturizing Creams, Lotions, and Powders	54	3-5
Night Creams, Lotions, and Powders	7	3
Paste Masks (Mud Packs)	28	0.2-18
Skin Fresheners	2	0.002-0.2
Other Skin Care Preparations	25	0.03-20
Suntan Gels, Creams, and Liquids	1	15-41
Indoor Tanning Preparations	5	74
Other Suntan Preparations	NR	3
Summary Information – by Exposure Type		
Eye Area	*1166*	*0.01-100*
Incidental Ingestion	*55*	*3-74*
Incidental Inhalation – Spray	*46*[a]	*0.3-35%*[b 45]
Incidental Inhalation - Powder	*616*	*2-100*
Dermal Contact	*2724*	*0.0005-100*
Deodorants (Underarm)	*18*	*2-75*
Hair – Non-Coloring	*4*	*0.04-10*
Hair –Coloring	*1*	*0.4-13*
Nail	*14*	*0.002-35*
Mucous Membrane	*153*	*0.001-88*
Baby Products	*9*	*7-99*

*The sum of all exposure types may not equal the sum of total uses.

[a] It is not known whether or not the product is a spray.

[b] In 2012, a survey was completed to assess the use of talc in spray products in which companies were asked whether or not they used talc in spray products, and if so, what is the maximum use concentrate of talc in the spray product and in products that are not sprays in the same FDA product category

Table 3. Cellular Effects

Talc/Composition	Particle Size	Test System	Procedure	Results	Reference
talc, non-fibrous	not specified	peritoneal and alveolar macrophages	cytotoxicity assay	low cytotoxicity - cytotoxicity of talc and other dusts was compared to induction of fibrosis following i.p. injection in Wistar rats; there was a good correlation between cytotoxicity of dust to macrophages in vitro and fibrogenicity in vivo	[65]
talc; cosmetic grade (5 samples) 1 sample with 30-35% chlorite 1 sample with 1-3% amphiboles	4 cosmetic-grade samples: 80-91.5% of the respirable dust (1.94-7.36% of the sample) was <7.5 µm; micronized cosmetic talc: 93.5% of the respirable dust (19.46% of the sample) was <7.5 µm; chlorite and amphiboles samples: 3.62 and 9.76% respirable dust, respecttively	unstimulated mouse peritoneal macrophages	cytotoxicity of the 7 talc samples was determined and compared to that of a standard quartz sample and a non-fibrogenic dust (magnetite)	- all 7 talc samples were cytotoxic to macrophages, but far less so that the quartz sample; quartz content of each talc (which ranges from <0.2 – 0.7%) did not seem to affect cytotoxicity - the activity of each of talc sample was similar to that of the others and not related to particle-size distribution - the talc samples induced a statistically significantly greater release of LDH compared to magnetite, and they caused a slightly, but significantly greater release of lysosomal β-glucuronidase than of LDH from the macrophages	[69]
talc, Italian 00000	≤10 µm	rabbit lung fibroblasts	ingestion of talc particles by fibroblasts was determined	- talc was taken up by fibroblasts, and the talc particles were observed in the cells	[70]
talc, Italian	not provided	V79-4 Chinese hamster lung cells; human alveolar Type II lung cells (A549)	cytotoxicity was determined	- 50 µg/ml was not cytotoxic to V79-4 cells - talc inhibited the growth of A549 cells, the inhibitory concentrations and extent of the inhibition were not reported	[68]
talc; composition not provided, but assumed to be cosmetic grade	not provided	OSE2a; GC1a	effect of talc on cell viability; cell cultures were incubated with 0-500 µg/ml talc for 24 – 120 h	- OSE2a cells: cell viability was statistically significantly increased with 5 µg/ml talc at 24 h and statistically significantly decreased at 200 µg/ml after 72 h and at 500 µg/ml after 24 and 72 h - GC1a cells: viability was statistically significantly increased at 5, 20, and 100 µg/ml talc after 72 h and was statistically significantly decreased at 500 µg/ml after 24 h	[67]
as above		OSE2a; GC1a	neoplastic transformation assay	- OSE2a cells: compared to untreated controls, a statistically significant increase in the number of transformed colonies was seen at 5 and 20 µg/ml, but a statistically significant decrease in transformed cells was seen at 100 µg/ml - GC1a cells: 5, 20, and 100 µg/ml talc caused a statistically significant increase in transformed colonies	
as above		OSE2a; GC1a; human PMN	ability to induce ROS	- OSE2a and GC1a cells: initial concentration-dependent decrease in ROS generation (at 24 h); ROS generation then increased in both cell lines, and the increase was statistically significant at 20 µg/ml at 72 and 120 h and at 50 µg/ml at 120 h in the OSE2a cells and at 0.5, 20, and 20 µg/ml at 72 and 120 h and at 5 and 100 µg/ml at 120 h compared to the 24 h value - PMN: a concentration-dependent increase in the induction of ROS, and the increase was statistically significant at 0.5, 5, 20, and 50 µg/ml at 24 h and at 100 and 500 µg/ml at 24 and 72 h; the maximum ROS generation in PMN was seen at 500 µg/ml talc at 24 h, and the increase was 4-fold compared to untreated controls	

Table 3. Cellular Effects

Talc/Composition	Particle Size	Test System	Procedure	Results	Reference
talc, composition not provided	2 µm	PMC; LAC (A549)	cells were exposed to 25, 50, and 75 µg/ml talc suspended in endotoxin-free normal saline for 24, 48,and 72 h to determine the ability to induce apoptosis	- talc induced apoptosis of LAC in a concentration- and time-dependent manner, but talc did not induce apoptosis of PMCs	[71]
talc in endotoxin-free water (assumed to be pharmaceutical-grade)	2.1 µm	PMC	confluent PMCs were exposed to 2-64 µg/cm^2 sterilized talc for 24 h	- PMC viability decreased with increasing talc concentrations; viability with 64 µg/cm^2 was 75% - all concentrations of talc significantly stimulated the release of IL-8 and MCP-1over that of unstimulated cells - talc significantly increased chemotactic activity for neutrophils and monocytes compared to unstimulated cells; the addition of excess IL-8 or MCP-1 antibody decreased chemotaxis, but it did not return entirely to the level of unstimulated cells - talc induced C-X-C and C-C chemokine expression; the transcriptional response of IL-8 and MCP-1 expression was enhanced - talc induced intercellular adhesion molecule-1 (ICAM-1) expression on PMC	[72]
as above			confluent PMC were exposed to 4 µg/cm^2 sterilized talc for 1-72 h; controls were exposed to 4 µg/cm^2 glass microspheres	- talc stimulated production of IL-8 and MCP-1 to a greater degree than did glass beads	
talc in endotoxin-free 0.89% normal saline (4.0 mg/ml) (assumed to be pharmaceutical-grade)	2.1 µm	PMC; MMC	confluent cells were exposed to 0-24 µg/cm^2 sterilized talc in serum-free medium for 72 h; controls were exposed to 4 µg/cm^2 glass microspheres; viability was determined	- PMC viability was 93% with 24 µg/cm^2 talc - MMC viability decreased with increasing concentration of talc; with 24 µg/cm^2 talc, viability ranged from 62-84% depending on the cell line	[73]
as above			confluent cells were exposed to 0-24 µg/cm^2 talc in serum-free media for 24 h; apoptosis was determined TUNEL	- PMC did not show significant apoptosis with varying concentrations - talc induced apoptosis in MMC in a concentration-dependent manner; significance was noted at 6 µg/cm^2, and then plateaued	
as above			PMC/MMC confluent cells were exposed to 4 µg/cm^2 talc for 24-72 h; 6 µg/cm^2 glass microspheres were used as controls; TUNEL and DNA electrophoresis was performed	- apoptosis of PMC cells by talc did not increase with time - talc induced apoptosis in MMC in a time-dependent manner; the increase over time was statistically significant compared to controls - a typical DNA ladder indicative of apoptosis was seen with MMC but not PMC	
talc, non-fibrous; mean surface area – 16.03 m^2/g	1.1 µm	LP9; IOSE	effect on cell viability was determined LP9 cells: changes in gene expression were measured with 15 and 75 µm/cm^2 at 8 h and 15 µm/cm^2 at 24 h IOSE cells: changes in gene expression were measured with 75 µm/cm^2 at 8 and 24 h	- non-toxic to IOSE cells at up to 75 µm^2/cm^2 and to LP9 cells at ≤163 µm^2/cm^2; toxicity seen with ≥243 µm^2/cm^2 - LP9 cells: low conc. of talc increased expression of 1 gene at 8 h and no changes at 24 h, while elevated expression levels of 30 genes were seen at 8 h with high conc. - IOSE: no significant mRNA changes	[74]

Abbreviations: GC1a = normal ovarian granulosa cells; IL-8 = interleukin-8; IOSE = human ovarian epithelial cells; LAC = lung adenocarcinoma cell line; LDH = lactate dehydrogenase; LP9 = human mesothelial LP9/TERT-1 cells; MCP-1 = monocyte chemotactic protein-1; MMC = human malignant mesothelioma cells; OSE2a = normal ovarian epithelial cells; PMC = human pleural mesothelial cells; PMN = polymorphonuclear neutrophils; ROS = reactive oxidative species; TUNEL = terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick end labeling

Table 4. Repeated Dose Toxicity Studies

Talc/Composition	Particle Size	Dose/Conc	Animals; #/grp	Dose Duration	Procedure	Results	Reference
				DERMAL			
commercial talcum powder; composition not provided	not provided	amount applied was not specified	domestic rabbits 5M/5F (test grp) 4M/4F (controls)	1x/day 6wks	- the powder was sprinkled on the shaved skin of the dorsal surface of the body trunk, and then spread evenly over the site - it does not state that the site was wrapped - blood chemistry values were measured at the termination of dosing	- all animals developed skin dryness - signs of skin erosion were observed - no clinical signs were observed - compared to control values: - alanine transaminase, aspartate transaminase, glutamyl transferase, amylase, and potassium ion values were statistically significantly decreased - cholesterol, high density lipoproteins, triglycerides, bilirubin, and glucose values were statistically significantly increased	75
				ORAL			
talc; composition not provided	not provided	29.6% in saline 5000 mg/kg/day	5 rats	5 days	no additional details	minimal signs of toxicity were observed	62
Italian talc, 00000 grade; 92% talc (by wt), 3% chlorite, 1% carbonate minerals; 0.5-1% quartz	25 µm (mean particle size); upper size, 70 µm	100 mg/day in feed	Wistar rats 16M/16F (talc and chrysotile) 8M/8F (controls)	101 days over 5 mos	super-fine chrysotile asbestos (SFA chrysotile)-fed and untreated controls were used; 2 animals/group were killed 3 mos after dosing, all other animals lived until natural death	- talc: mean survival (from start of feeding), 614 days; 1 leiomyosarcoma of the stomach, 2 sarcomas of the uterus - chrysotile: mean survival, 619 days; 1 possible leiomyosarcoma of the stomach, 1 sarcoma of the uterus, 1 lymphosarcoma - controls: mean survival, 641 days; 1 adrenal adenoma	76
				INHALATION			
asbestos-free talc; 19.2-19.4% Mg	MMAD, 2.7 ± 0.1 µm; 79% of the talc by mass had an aerodynamic diameter <5 µm	target: 0, 2, 6, or 18 mg/m^3 actual: 0, 2.2, 5.7, or 20.4 mg/m^3	B6C3F$_1$ mice 10M/10F	4 wks 6 h/day 5 days/wk	- multi-tiered inhalation chambers were used; animals were killed 24 h after the last exposure; lung burdens were measured in half of the animals and the other half were used for microscopic examination - this study was used to determine the exposure concentrations for a 2-yr NTP bioassay	- lung burden averaged 0, 100, 290, and 1020 µg talc/g lung for control, low, mid, and high dose, respectively; lung burdens normalized for lung wt and exposure conc: n/a, 46, 51, and 50 µg talc/g lung/mg/m^3, respectively - no exposure-related abnormalities were seen at necropsy; microscopically, the only exposure-related lesion was a modest, diffuse increase in free macrophages within the alveolar space; the macrophages, which were focally aggregated, contained talc particles	11,77

Table 4. Repeated Dose Toxicity Studies

Talc/Composition	Particle Size	Dose/Conc	Animals; #/grp	Dose Duration	Procedure	Results	Reference
asbestos-free talc; 19.2-19.4% Mg	MMAD, 3.3 ± 0.1µm; 79% of the talc by mass had an aerodynamic diameter <5 µm	target: 0, 2, 6, or 18 mg/m^3 actual: 0, 2.3, 4.3, or 17 mg/m^3	F344/Crl rats 10M/10F	4 wks 6 h/day 5 days/wk	as above - this study was used to determine the exposure concentrations for a lifetime NTP study	- lung burden averaged 3, 70, 170, and 720 µg talc/g lung for control, low, mid, and high dose, respectively; lung burdens normalized for lung wt and exposure conc: n/a, 30, 39, and 42 µg talc/g lung/mg/m3, respectively; normalized low dose value was statistically significantly greater than mid and high dose values - the increase in talc lung burden with exposure concentrations may be attributable to overwhelming the capacity of the respiratory tract to clear particles at 6 and 18 mg/m3 exposures - no exposure-related abnormalities were seen at necropsy; microscopically, the only exposure-related lesion was a modest, diffuse increase in free macrophages within the alveolar space; fewer macrophages were seen in the exposed rats than in the exposed mice; the diffusely scattered macrophages contained talc particles	[11,77]
Italian talc, 00000 grade; 92% talc (by wt), 3% chlorite, 1% carbonate minerals; 0.5-1% quartz	25 µm (mean particle size); upper size, 70 µm	10.8 mg/m^3 (mean) approximately 40% respirable	Wistar rats	7.5 h/day 5 days/wk	animals (6/cage) were exposed to talc dust; SFA chrysotile controls were treated similarly at each time frame; untreated controls were used; some animals were killed 10 days or 1 yr after final exposure, and the remainder lived until natural death	mean fibrosis scoring scale: 1 – nil; 2 – minimal; 4 – slight; 6 – moderate; 8 - severe (for use below)	[76]
		cumulative 3 mos dose=4100 mg/m^{3}h	24M/24F	3 mos	8 animals were killed 10 days and 8 were killed 1 yr after exposure	- mean fibrosis score 10 days/1 yr after talc exposure: 2.2/2.4; chrysotile: 2.8/2.2; controls: 1.8/1.6 - over 50% of the animals were alive at 28 mos	
		cumulative 6 mos dose=8200 mg/m^{3}h	12M/12F	6 mos	6 animals were killed 10 days after and 4 talc and chrysotile animals and 3 control animals were killed 1 yr after exposure	- mean fibrosis score 10 days/1 yr after exposure - talc: 2.7 /3.4; chrysotile: 3.0/3.2; controls: 1.9/1.5 - most test animals died by 28 mos; there were no lung tumors in the talc or control group and 1 adenomatosis in the chrysotile group	
		cumulative 12 mos dose=16,400 mg/m^{3}h	12M/12F	12 mos	6 animals were killed 10 days after exposure and 4 talc and chrysotile animals and 3 control animals were killed 1 yr after exposure	- mean fibrosis score 10 days/1 yr after exposure - talc: 3.4/4.6; chrysotile: 3.2/4.2; controls: 1.3/1.9 - most test animals died by 28 mos; in the lungs, 1 adenoma was found in the talc group; 3 adenomas, 2 adenomatosis, and 1 adenocarcinoma was found in the chrysotile group; there were no lung tumors in the controls	
commercial (talc) baby powder; 95% (w/w) platy talc with trace quantities of carbonates (magnesium and dolomite) and platy chlorite and rutile	MMAD, 4.9 µm	37.1±7.4 µg/l (MTAC) respirable fraction: 9.8± 2.4 µg/l cumulative dose: 3 min: 14.6 mg·h/m^3 30 min: 146 mg·h/m^3 150 min: 732 mg·h/m^3	Syrian golden hamsters, 50M/50F; controls, 25M/25F	30 days 3, 30, or 150 min/day 5 days/wk	single tier exposure; animals lived until natural death	- no statistically significant difference in survival time among groups, but there was a significant difference btwn males and females within grps; no clinical signs of toxicity to talc - the type, incidence, and severity of lesions indicated no trend toward a dose-response and no statistically significant differences between exposed and control groups	[78]

Table 4. Repeated Dose Toxicity Studies

Talc/Composition	Particle Size	Dose/Conc	Animals; #/grp	Dose Duration	Procedure	Results	Reference
talc; "technical" or "pharmaceutical" grade	not provided	30-383 mg/m^3	rats; number not provided	9 mos; 6 h/day, 6 days/wk	details were not provided	None of the animals died as a specific consequence of exposure.	[81]
INTRAPLEURAL							
Italian talc, 00000 grade; 92% talc (by wt), 3% chlorite, 1% carbonate minerals; 0.5-1% quartz	25 µm (mean particle size); upper size, 70 µm	20 mg in physiological saline; 50 mg/ml	Wistar rats 24 M/24 F	until natural death	injection into the right pleural cavity; saline and SFA chrysotile controls were used	- talc: mean survival, 655 days; no mesotheliomas; injection-site granulomas were common; small pulmonary adenoma in one rat, but no other lesions in the lung - saline: mean survival, 691 days; no mesotheliomas - chrysotile: mean survival, 598 days; 18 mesotheli-omas	[76]
INTRAVAGINAL AND PERINEAL							
talc; composition not provided	not provided	100 mg in 0.5 ml saline	Sprague-Dawley rats; 7 F	daily for 3 mos	talc was administered perineally (in aerosol form) or intravaginally; controls were untreated or given intravaginal administration of saline baseline cervicovaginal smears were obtained at study initiation; all animals were killed at study termination	- all animals in both test groups developed infection: intravaginal test group: 5 had vulvovaginitis, 6 had endometritis, 4 had pelvic infection, and 3 had ovary infections (7 ovaries) perineal group: all had vulvovaginitis, 4 had endo-metritis, 5 had pelvic infection, 4 had ovarian infection (8 ovaries), 2 developed salpingitis and tubal inclusion saline controls: 1 had endometritis untreated controls: 2 had vulvovaginitis and endometritis with infection in both ovaries, and 1 of these animals developed salpingitis - no neoplastic change was found	[79]
INTRATRACHEAL							
talc dust from a mill in Vermont; <1% quartz; no fibrous material	MMAD, 7.5 µm; percentage mass <5 µm was 26%	0.15 ml/100 g bw of the dust in 0.9% NaCl containing 13.3 µg/ml rabbit surface active material 0, 0.15, 0.75, or 3.75 mg/100 g bw	hamsters, 6	single exposure	the suspension was instilled intratracheally - dose-response study; results 1 day after exposure -biochemical and cellular indicators of injury in BAL were measured	- no significant effect on macrophage numbers - PMN numbers were elevated - lactate dehydrogenase, peroxidase and albumin levels increased in a dose-dependent manner	[216]
		3.75 mg talc/100 g bw	hamsters, 4 (exposure) or 3 (controls)		- time course experiment; measurements made 1, 4, 7,and 14-days after treatment in broncho-alveolar lavage fluid	- PMN values approached control levels at 4-14 days post-exposure - peroxidase values approached control values by day 7 post-exposure - albumin levels decreased rapidly after exposure - chronic toxic effects on macrophages were observed	

Table 4. Repeated Dose Toxicity Studies

Talc/Composition	Particle Size	Dose/Conc	Animals; #/grp	Dose Duration	Procedure	Results	Reference
				INTRAVENOUS			
approx. 61% SiO_2, 32% MgO, 1% Al_2O_3	<5 µm	25 mg in 0.5 ml physi-ological saline	male guinea pigs, 24 test animals 8 controls	3 doses; given on days 0, 7, and 15	i.v. injection into the thigh vein in the hind leg; 2 test animals and 1 control were killed at 8 different intervals (from 1-150 days) after the last dose	- 8 animals died immediately after the 2nd and 3rd doses - gross observations: no significant abnormalities in the liver; moderate enlargement of the abdominal lymph nodes at study termination; varying degrees of congestion in the lungs developing early and persisting throughout - some particles lodged in the alveolar capillaries of the lung; by day 15, many small focal areas of macrophages and lymphocytes developed near the alveolar capillaries, and an increased density of talc particles was seen - talc particles were observed in the lungs and in the liver throughout the study, and in the abdominal lymph nodes at day 30+; no talc was seen in the tracheobronchial lymph nodes, but a moderate degree of lymphopoiesis was observed at various times	[80]

Abbreviations: BAL = bronchoalveolar lavage fluid; conc = concentration; grp = group; MMAD = mass median aerodynamic diameter; PMN = polymorphonuclear neutrophils

Table 5. Pulmonary effects of occupational exposure

Talc Composition and Particle Size (if given)	Study Population and Location	Timeframe examined	Procedure/Parameters Measured/Limitations	Findings	Reference
			Mining and Milling		
- some chlorite and quartz; very minor to trace amounts of magnesite and dolomite; no amphibole or chrysotile minerals were detected	- 1346 millers, 438 miners, and an equal number of age-matched controls from the town of Alba (>1 yr in job) - mine location: Italy - Germanasca and Chisone Valley (Piedmont)	employees that began work btwn 1921-1950 – followed until 1974	historic prospective study - cumulative exposure for each worker was estimated from the results of successive determinations of air dust content from 1948+ (until retirement or June 30, 1974) - Exposure Levels by distribution of total number of inhaled particles (cumulative exposure for each worker was estimated from the results of successive determinations of air dust content and quantified by calculating an appropriate value of the total amount of inhaled particles during the employment period) <u>Miners</u> level 1: 566 – 1699 mppcf/yr (n=405) level 2: 1700 – 5665 mppcf/yr (n=423) level 3: 5666 – 12,750 mppcf/yr (n=518) <u>Millers</u> level 1: 25 - 41 mppcf/yr (n=163) level 2: 142 - 424 mppcf/yr (n=144) level 3: 425 - 906 mppcf/yr (n=131) <u>Limitation</u> - possible lack of comparability of the occupational and control groups for comparing mortality - smoking status was not known	- by observed vs. expected comparison, the observed overall mortality of miners and millers was significantly lower than expected - there was no relationship found between the ratio of observed to expected deaths and the interval between first exposure and death - among different exposure classes, the ratio did not increase with increasing exposure <u>for miners:</u> **- respiratory disease (all except TB) (SMR = 1.38), silicosis (SMR = 2.01), and silico-TB (SMR = 1.58) were statistically significantly greater than expected** -break-out by exposure showed increasing ratios with increased exposure for these diseases - break-out by interval between first exposure and death showed increasing ratios with increasing latency-yrs for respiratory diseases (all except TB); it was noted that for silicosis with or without TB, the ratios were unchanged over time because of the absence of pneumconiosis in controls, but the number of observed cases showed a constant increase with latency - researchers noted that the trends in dose and latency and the different incidences of silicosis suggests that the inducing factor was silica, not talc -incidence of malignant neoplasms: *- all malignant neoplasms(SMR = 0.77), of the lungs, bronchus and trachea (SMR = 0.46), and of other sites (SMR = 0.58) were statistically significantly lower than expected* - break-out by interval between first exposure and death for all malignant neoplasms and lung cancer showed a decrease with increasing latency - an increasing trend was observed for cancer of the larynx *- CV disease was statistically significantly lower than expected (SMR = 0.75)* <u>for millers:</u> *- CV disease was statistically significantly lower than expected (SMR = 0.78)* - there were no consistent trends observed for any cause of death - break-out by interval between first exposure and death indicated that the ratio of all tumors increased with increasing latency, but the number of observed deaths was still less than expected	[88]

Table 5. Pulmonary effects of occupational exposure

Talc Composition and Particle Size (if given)	Study Population and Location	Timeframe examined	Procedure/Parameters Measured/Limitations	Findings	Reference
- composition as above - dust counts represented particle sizes of 0.5 – 5.0 µm	- 1260 miners and 418 millers in above study	as above	- because of the concern stated above, i.e. the possible lack of comparability of the occupational and control groups for comparing mortality, expected death rates were recalculated using the death rates of the Italian male population as the standard death rate - the mortality patterns for 1946-1974 were examined using the rates relevant to 1951 for the first 5 yrs	Miners **- the observed cause of death for "all causes" (SMR = 1.25); non-malignant respiratory diseases (SMR = 3.29) (primarily pneumoconiosis), and TB (SMR = 1.98) were statistically significantly increased** - there were 58 cases of pneumoconiosis and 13 cases of TB-associated with pneumoconiosis - an increasing trend with increasing exposure was observed for pneumoconiosis and TB - at the highest exposure level, ~20% of total deaths were due to pneumoconiosis, with or without TB - the researchers stated that the high frequency of pneumoconiosis in miners was attributable to the high content of free silica in the air dust, which was as high as 18% in drilling operations	90
				Millers **- the observed cause of death for "all causes" was statistically significantly increased (SMR = 1.2)** - the observed cause of death was increased but NS for non-malignant respiratory diseases (SMR = 1.5) and TB (SMR = 2.0) - there were only 3 cases of pneumoconiosis and 1 case of TB-associated with pneumoconiosis - there was no consistent trend with increased exposure level	
- non-asbestiform talc	- 1795 males; 1244 miners and 551 millers (>1 yr employment) - mine location: Val Chisone, Turin Italy	1946 - 1995	update of study described above - total mortality and selected cause of death; those with a significant increase are given (shown as SMR (95% CI)) - no information was provided on smoking status	Miners **all causes: 1.3 (1.2 – 1.4)** **oral cavity cancers: 6.1 (3.9 – 9.1)** **respiratory tract diseases: 3.1 (2.5 – 3.7)** **digestive tract diseases: 1.4 (1.0 – 1.8)** **cirrhosis: 1.8 (1.3 – 2.5)** **- SMR for lung cancer was not significantly increased; 1.1 (0.7 – 1.5)**	89
				Millers **oral cavity cancers: 3.3 (1.3 – 6.9)** **- SMR for lung cancers was 0.7 (0.3 – 1.2)**	
			- mortality by duration of exposure was examined	- for all miners and millers, no trend in risk with exposure was observed for any of the causes of death **- when miners only were examined, an increasing trend in risk with increasing exposure was observed for non-neoplastic respiratory disease (i.e., silicosis); <10 yrs exposure, the SMR was 2.8 (1.7-4.6); 10-20 yrs exposure, 2.8 (1.7 -4.2); >20 yrs exposure, 3.2 (2.5 – 4.1)**	
			- mortality by time since first exposure (latency) was examined	for all miners and millers, **a direct trend was observed only for non-neoplastic respiratory disease**; at <20 yrs latency, SMR was 1.5 (0.7-2.6); **20-30 yrs, 2.4 (1.5 -3.4); >0 yrs, 2.4, 1.9- 3.0)**	

Table 5. Pulmonary effects of occupational exposure

Talc Composition and Particle Size (if given)	Study Population and Location	Timeframe examined	Procedure/Parameters Measured/Limitations	Findings	Reference
- non-asbestiform talc - trace amounts of quartz, tremolite, and anthophyllite - fibers had been detected near the detection limit for optical microscopy	- 94 miners (>1 yr employment) - 295 millers (>2 yr employment) -mine located in Norway; the mean value for radon daughter exposure was 3.5 pCi/l at the worksite	1935 – 1972 (millers) 1944 – 1972 (miners)	- levels of dust exposure were not registered during the actual period; samples collected from 1980-1982 demonstrated great variability between job category and workplace: mine: 0.94 – 97.35 mg/m^3 mill: 1.4 – 54.1 mg/m^3 Limitations - numbers were too small for further conclusions on cause-specific mortality or to form inferences on particular cancer types	- for combined miners/millers, SMRs were <1 for all causes, all malignant neoplasms, and diseases of the respiratory system - for miners only, obs > exp for number of malignant neoplasms - for combined miners/millers, cancer incidences at all sites, lung, prostate, and intestine, SIRs were <1; SIRs for incidences of kidney, stomach, and bladder cancers were 1.2% (95% CI, 0.1 - 3.4), 1.1 (95% CI, 0.41-2.15), and 2.1 (95% CI, 0.8-4.3) - for miners only, obs > exp for cancer incidence at all sites, stomach, lung, prostate, and other sites - for millers only, obs > exp for cancer incidence of the bladder	[91]
- no asbestos in samples - free silica levels were <0.25% for nearly all bulk talc samples - free silica detectable only in occasional air samples - talc shards and ribbons were seen in talc bulk and airborne dust samples - significant quantities of magnesite, chlorite, and dolomite - traces of calcite, biotite, ankerite, phlogopite	- 225 millers, 163 miners (all males; 47 were included in both groups) (>1 yr employment) - Vermont mines (radon daughter levels ranged from trace quantities to 0.12 working levels; single measurements up to 1.0 working levels have been measured)	1940 – 1975	- U.S. mortality rates were used; data from 1940 – 1967 were obtained and deaths after 1967 were extrapolated - however, because Vermont rates (1949-1975) for non-malignant respiratory diseases and respiratory cancer deaths are greater than U.S. rates, comparisons were made for these causes of deaths with those expected using Vermont rates; cause-specific expected deaths for the study population were obtained by applying death rates, calculated from yearly tallies of deaths and census data, to the person-yrs of observation of the cohort members Limitations - selection bias from radiographic monitoring of talc workers; the bias is most likely small - no data on smoking habits were available	- there were 90 talc-worker deaths observed and 77.32 expected (NS) - for all talc workers, the observed number of deaths for total non-malignant respiratory which was specific for ONMRD ,excluding influenza and pneumonia were statistically significantly increased - 9 of the 11 workers with ONMDR had radiographic reading consistent with pneumoconiosis - the possibility of an interactive effect between cigarette smoking and talc exposure was discussed Miners **- deaths due to respiratory malignant neoplasms were statistically significantly increased** - this increase was also found using Vermont data Millers **- deaths due to total non-malignant respiratory diseases and ONMRD (7 observed/0.89 expected U.S.) were statistically significantly increased** - this increase was also found using Vermont data - the researchers stated that because excess lung cancer mortality was observed for miner and not millers suggests that additional etiologic agents, alone or in combination with talc dust, affects miners	[94]
- milled product is a talc-chlorite mixture - contains 0-3% quartz	- 1070 male workers at a milling site in the French Pyrenees (>1 yr employment) - local (1968+) and national mortality rates were used for comparison	1945-1994	- a nested case-control study protocol was used - two case control studies were set up for each cohort: a lung-cancer study and a study of non-malignant respiratory disease - occupational histories and smoking information was collected by an external interviewer	- the SMR for all causes of death (1968+) was 0.93 - the SMR for non-malignant respiratory diseases was 0.27 - the incidence of pneumoconiosis was 0 - the SMR (obs/exp) for all cancers was 0.73, for stomach cancer was 0.40 (0.38-2.75), and for lung cancer was 1.06 (0.43-2.19)	[95]

Table 5. Pulmonary effects of occupational exposure

Talc Composition and Particle Size (if given)	Study Population and Location	Timeframe examined	Procedure/Parameters Measured/Limitations	Findings	Reference
- milled product is talc-chlorite or talc-dolomite - contains 0.5-4% quartz	- 542 male workers from three mines and their respective mills in the Styrian Alps (>1 yr employment - mortality rates of Styria were used for comparison	1972-1995	- work histories were abstracted from company records; smoking history was obtained from a variety of sources	- the SMR for all causes of death was 0.75 - the SMR for non-malignant respiratory diseases was 1.06 **- the SMR for pneumoconiosis was 5.56 (95% CI; 1.12 – 16.2); 3 cases were observed** - the SMR for all cancers was 1.02, for stomach cancer was 1.18 (0.38-2.75), and for lung cancer was 1.23 (0.76-1.89)	[95]
	- cohort: 40 cases; 39 French and 1 Austrian - 44 controls; 41 French and 3 Austrian		Nested case-control study for respiratory disease	Cumulative exposure to talc (y·mg/m^3): <100; OR = 0.22 100-400; OR = 1.00 400-800; OR = 1.97 ≥800; OR = 2.53 - mortality increased with exposure **all cases: OR = 1.08 (1.02 - 1.16)** pneumoconiosis: OR = 1.17 (0.99 – 1.38) COPD: OR = 1.02 (0.86 – 1.2)	
	- cohort: 30 cases; 23 French and 7 Austrian - 88 controls: 67 French; 21 controls		Nested case control study for lung cancer	Cumulative exposure to talc (y·mg/m^3): <100; OR = 0.86 100-400; OR = 1.07 400-800; OR = 0.60 ≥800; OR = 0.73 - a relationship between mortality and exposure was not observed	
- did not contain tremolite; only amphibole mineral was non-asbestiform actinolite (one bed at ≤6%); ≤42% carbonate minerals, 0.2-1.6% quartz	- workers (number not specified) from a company in Russia that mined, ground, and processed talc; total number of cases not stated (>3 yrs at plant) - the "other population" were matched non-cancer/non-worker deaths from the same town (number not specified)	1949 – 1975	- estimated the death rate by relating the number of deaths from cancer of cases to the number of man-yrs of work for all employees during the same period - the calculated death rates were compared with the analogous death rate for the controls	**- RR of death from tumors of all sites was 5.1 (p < 0.001) for males and 6.4 (p<0.001) and females** **- RR of death from lung cancer was 4.5 (p<0.02) for males** and 9.3 (NS) for females - for lung cancer of male workers compared to controls, the death rate of those <59 yrs old was 2x greater, of those 60-69 yrs old was 6.51x greater, and of those **70+ yrs old was 40.02x greater** **- RR of death from gastric cancer was 3.7 (p<0.02) for males and 6.3 (p<0.05) for females**	[92]

Table 5. Pulmonary effects of occupational exposure

Talc Composition and Particle Size (if given)	Study Population and Location	Timeframe examined	Procedure/Parameters Measured/Limitations	Findings	Reference
- minimal amounts of crystalline silica and asbestiform minerals - contained chlorites and carbonates	- 7 miners/millers - 8 adult age-matched by decade male controls - Vermont mines	4-27 yrs of exposure (timeframe not stated)	- lifetime exposure to talc ranges from 12 – 5930 mppcf - pulmonary tissue from deceased talc workers was examined and compared to pulmonary tissue of controls	- lungs of 4 workers exposed for 4-19 yrs exhibited **focal and diffuse fibrosis with accumulations of talc**, but chest x-rays were negative for pneumoconiosis - lungs of 3 workers exposed for 19, 26, and 27 yrs had **areas of diffuse confluent fibrosis and talc** - 2 workers exposed for 27 yrs had positive chest x-rays; the chest x-ray was not available for the remaining worker - extensive pulmonary fibrosis was found in the patient exposed for 27 yrs (5930 mppcf); large amounts of silicon and aluminum were found in the lungs - the severity of lesions and the concentrations of magnesium and silicon in the lungs compared top controls increased with duration of exposure - circumscribed granulomas were not observed	[96]
- talc was essentially free from silica and asbestos - geometric mean exposure was 1.8 mg/m^3 respirable dust	- 116 miners and millers over the age of 25 in 3 Vermont plants - avg. yrs. employed was 8.5	1975-1976	- exposure levels were >3.0 mg/m^3 respirable dust - a medical history, including questions pertinent to the respiratory system, and smoking history were obtained - pulmonary function tests were performed - an appropriate control group was not available; observed values were compared to predicted values from a standard pop. -chest x-rays were taken in 100 of the subjects <u>Limitations</u> - the follow-up interval is short and the overall range of exposures within the study may be too narrow to detect exposure-related effects in the small study pop. - effects on pulmonary function in non-smokers was not associated with lifetime or current talc exposure after a relatively short avg. yrs. Employed; longer follow-up would be needed before concluding there is no effect of talc on non-smokers at this exposure level	- **observed/predicted FEV_1 (FEV%) and MMEF (MMEF%) were significantly reduced** - yrs of employment and talc-yrs (i.e., lifetime dust exposure) were significantly associated with decreased FEV_1/FVC and MMEF%, but not with FVC% or FEV% - a 43.3% prevalence of any chest x-ray abnormality was observed; with a third being diffuse parenchymal opacities or pleural abnormalities - 12 subjects had small round opacities and 9 had small irregular opacities; there was a statistically significant association with talc-yrs	[101]
- contained talc, chlorite, and a small quantity of dolomite - 0.5-3% free silica (<1% particle size distribution <10 μ) - does not contain asbestos	- 176 millers from Luzenac, France (cross-sectional study)	1978	- cross-sectional study	- 46 workers (27%) had pneumoconiosis - 36 of the cases were slight - 10 of the cases had higher profusion or large opacities - intensity and duration of dust exposure were linked to radiologic signs of pneumoconiosis	[93]

Table 5. Pulmonary effects of occupational exposure

Talc Composition and Particle Size (if given)	Study Population and Location	Timeframe examined	Procedure/Parameters Measured/Limitations	Findings	Reference
	- dust exposed workers - local and national pop. were used as controls	1945-1981	- retrospective study, completed by a prospective study until 1988	- difference in life expectancy of dust-exposed workers compared to the local and national pop. was NS - differences in mortality due to cancer, including lung and digestive system cancers,, were NS - in a cohort or workers deceased between 1970-1981 compared to 97 age-matched controls, the mortality ratio for chronic respiratory diseases was 2.4; a follow-up in 1998 confirmed these results	
	- 39 pneumoconiotic workers; 6 had profusion equal to 2 or 3 - 39 matched for smoking and age non-dust exposed controls		- respiratory function was compared	- VC, TLC, and single breath TCO were statistically significant decreased in pneumoconiotic subjects compared to controls	
	- 8 hospitalized pneumoconiotic workers		- a bronchoalveolar lavage was performed	-hypercellularity was observed, with a significant increase in neutrophilic and eosinophilic PMN leukocytes - numerous talc particles were found in all lavage fluids, including uncoated plate-like particles (0.5 – 40 µm) and atypical ferruginous bodies)	
3 mines - MT: free silica content was below the limit of detection (<0.8%) ; no fibers; NC: 1.5% free silica; acicular particles (aspect ratios 5-100:1 and some diameters <0.1 µm); TX: 2.2% free silica; tremolite and antigorite fibers (0.5-3 µm in length) - geometric mean concentrations of respirable dust in samples (mg/m^3) for miners and millers was 0.66 and 1.1 (MT), 0.45 and 1.56 (TX), 0.14 and 0.26 (NC)	- 177 talc workers from MT, 71 from TX, 51 from NC - since there were no differences among regions by age, smoking, or exposure groups, the populations were combined - were compared to 1140 blue collar workers (males and females from NC in electronics, synthetic textiles, bakeries, and bottling plants)	avg. from 3 plants: 5.5 (TX), 6.6 (MT), and 10.1 (NC) yrs (timeframe not stated)	- cumulative exposure (mg/m^3 x yrs) was 1.21 for MT, 2.64 for TX, and 0.28 for NC - all workers completed a respiratory questionnaire - chest x-rays were taken and sputum was collected Limitations - workers examined were only those currently working - length of the working history was a relatively short time for the development of occupationally-related symptoms - estimating past exposure was a problem	prevalence of dyspnea - 6% in non-smokers, 10% in ex-smokers, 3% in smokers; 5% total (prevalence was increased with age; no demonstrated association with cumulative exposure) prevalence of pleural thickening - 0% in non-smokers; 4% in ex-smokers; 9% in smokers; 5% total (tendency to increase with age; no demonstrated association with cumulative exposure) - cumulative exposure was not significant for any of the lung function tests parameters examined and compared to blue-collar controls - cough: 20.3% of test v. 16.7% controls - phlegm: 20.3% of test v. 17.3% of controls - dyspnea: 5.8% of test v. 7.5% of controls - bilateral pleural thickening: 6.3% of test v. 0.4% of controls mean percent predicted pulmonary function compared to 292 controls FEV_1: 99.7 FVC: 101.0 peak flow: 97.9 FEF_{50}: 94.1 FEF_{75}: 84.5	100

Table 5. Pulmonary effects of occupational exposure

Talc Composition and Particle Size (if given)	Study Population and Location	Timeframe examined	Procedure/Parameters Measured/Limitations	Findings	Reference
- non-asbestiform talc-chlorite mixture	- 398 subjects from talc facilities in the Styrian alps, Austria, and in the French Pyrenees, France - >5 yrs continuous employment btwn 1989-2001	1988-2003	- in the French mill, overall exposure decreased from a geometric mean exposure of 1.95 mg/m^3 (GSD3.9) in 1986 to 0.80 mg/m^3 (GSD 4.3) in 2003; the high GSDs are due to different exposures based on job - in the Austrian mill, the 1988-1995 geometric mean exposure was 0.75 mg/m^3 (GSD 3.67); in 1996, it was 0.30 mg/m^3 (GSD 3.25) - lung function parameters were measured, with the following confounders: pack-yrs; apparatus used to determined respiratory function; gender; gender-specific age and height; medical histories - regression coefficients (95% CI) are presented Limitations - the symptoms questionnaire was only used a mean of two times at the French site and less at the Austrian site - the mean duration of follow-up was <5 yrs	Total cumulative exposure per 10 yrs mg/m^3 FEV_1 (ml): -6.58 (-13.81 to 0.65) FVC (ml): -7.71 (-15.45 to 0.03) FEV_1/FVC (%): 0.000 (-0.090 to 0.090) Cumulative exposure at inclusion per 10 yrs mg/m^3 FEV_1 (ml): -7.26 (-14.65 to 0.13) FVC (ml): -8.47 (-16.38 to -0.57) FEV_1/FVC (%): -0.004 (-0.096 to 0.087) Cumulative exposure since inclusion per 10 yrs mg/m^3 FEV_1 (ml): 7.75 (-25.49 to 40.99) FVC (ml): 10.24 (-28.22 to 48.70) FEV_1/FVC (%): 0.105 (-0.364 to 0.574)	[103]
			- prevalence of self-declared respiratory symptoms, including the following confounders: pack-yrs of cigarettes for chronic bronchitis and usual cough and/or phlegm and age for dyspnea - ORs (95% CI) are presented	Total cumulative exposure per 10 yrs mg/m^3 chronic bronchitis: 1.014 (0.963-1.068) usual cough or phlegm: 1.021 (0.993.-1.050) dyspnea: 1.040 (0.997-1.087) Cumulative exposure at inclusion per 10 yrs mg/m^3 chronic bronchitis: 1.032 (0.985-1.081) usual cough or phlegm: 1.014 (0.983-1.046) dyspnea: 1.031 (0.985-1.080) Cumulative exposure since inclusion per 10 yrs mg/m^3 chronic bronchitis: 0.473 (0.193-1.158) usual cough or phlegm: 1.250 (0.986-1.584) dyspnea: 1.405 (0.870-2.257)	
			radiograph results were examined - ORs (95% CI) are presented - profusion: using the Standard X-rays, the profusion (concentration) of small opacities is classified on a 4-point major category scale (0, 1, 2, or 3), with each major category divided into three, giving 12 ordered subcate-gories of increasing profusion; category 0 refers to the absence of small opacity and category 3 represents the most profuse	Initial cumulative exposure per 10 yrs mg/m^3 **profusion ≥ 0/1: 1.056 (1.031-1.085)** **profusion ≥1/0: 1.060 (1.028-1.095)** pleural abnormalities: 1.036 (0.960-1.119) Cumulative exposure since inclusion per 10 yrs mg/m^3 profusion ≥ 0/1: 0.917 (0.838-1.004) profusion ≥1/0: 0.858 (1.028-1.095) pleural abnormalities: 1.145 (0.980-1.336)	

Table 5. Pulmonary effects of occupational exposure

Talc Composition and Particle Size (if given)	Study Population and Location	Timeframe examined	Procedure/Parameters Measured/Limitations	Findings	Reference
the talc ore contained chlorite, aluminum, some dolomite (<3%), some quartz (<3%), and traces of calcite, apatite, pyrite, and mica - amphiboles were not been detected	- 166 millers (158 M/8 F) from a talc-producing factory in SW France	workers employed 1989-1990	- geometric mean exposure at the time of the study was 1.87 mg/m^3 (GSD, 2.5 mg/m^3) - each subject was given a standardized questionnaire and questioned about smoking and occupational history during their annual medical check-up - a chest radiograph that had been taken between 1982-1987 was reviewed - 139 subjects had a second radiograph in 1992 - the prevalence of self-reported symptoms (as %) according to cumulative exposure were determined Limitations - less than optimal quality of the spirometric tests that led to the exclusion of 30 subjects	<u><20 y mg/m^3 (n=46)</u> chronic bronchitis: 0% chronic cough or phlegm: 8.7% dyspnea: 4.4% wheeze: 4.4% <u>20-50 y mg/m^3 (n=25)</u> chronic bronchitis: 4% chronic cough or phlegm: 20% dyspnea: 8% wheeze: 4% <u>50-150 y mg/m^3 (n=54)</u> chronic bronchitis: 13% chronic cough or phlegm: 35.7% dyspnea: 17% wheeze: 3.7% <u>>150 y mg/m^3 (n=41)</u> chronic bronchitis: 2% chronic cough or phlegm: 14.6% dyspnea: 14.6% wheeze: 0%	[102]
			- standardized functional variables according to cumulative exposure were determined	<u><20 y mg/m^3 (as mean (SD)) (n=36)</u> FVC: 1.33 (1.28) FEV: 1.22 (1.21) FEV/FVC: 0.25 (0.70) MMEF: 0.66 (1.58) <u>20-50 y mg/m^3 (n=20)</u> FVC: 0.82 (1.04) FEV: 0.77 (1.22) FEV/FVC: 0.27 (0.79) MMEF: 0.36 (1.41) <u>50-150 y mg/m^3 (n=44)</u> FVC: 1.10 (1.07) FEV: 0.74 (1.17) FEV/FVC: -0.04 (0.80) MMEF: -0.19 (1.15) <u>>150 y mg/m^3 (as mean (SD)) (n=36)</u> FVC: 0.65 (1.03) FEV: 0.50 (1.06) FEV/FVC: 0.24 (0.75) MMEF: -0.06 (1.12)	

Table 5. Pulmonary effects of occupational exposure

Talc Composition and Particle Size (if given)	Study Population and Location	Timeframe examined	Procedure/Parameters Measured/Limitations	Findings	Reference
			- radiological opacities at the first radiograph - given in terms of cumulative exposure to talc	<u>any opacity including 0/1</u> coefficient: 0.33 OR (95% CI): **1.39 (1.06-1.84)** <u>any opacity excluding 0/1</u> coefficient: 0.97 OR: **2.65 (1.25-5.64)** - 4 pleural abnormalities were reported at the first reading - the prevalence of small opacities was higher in the second radiograph, with 11 new opacities compatible with pneumoconiosis (1/0 or above)	
Plant Workers					
Rubber Workers					
non-fibrous talc; <2 fibers/cc - <1% free silica - avg dust concentrations ranged from 0.47 – 3.55 mg/m^3, with most jobs exposed to <1 mg/m^3	- 80 talc workers (15.9 yrs avg. length of employment) and 189 non-exposed rubber workers (13.4 yrs avg. length of employment) (average talc exposure, i.e. "dust yrs", was 9 yrs) - plant location not specified	1972-1974	- subjects were asked about medical, occupational, smoking, and respiratory histories - pulmonary function tests were performed - exposure to talc was evaluated by respirable mass sampling - 28 workers were studied for acute change in $FEV_{1.0}$ and FVC for one shift - pulmonary function changes related to talc exposure were measured in white workers >24 yrs old -chest x-rays were taken in most exposed workers	- there were no significant differences between exposed and non-exposed workers in age, smoking, or socioeconomic or ethnic factors - statistically significant increases in cough for 3 mos and phlegm for 3 mos (chronic bronchitis symptoms) and wheezing most days and nights (an obstructive respiratory disease symptom) were observed in exposed workers; none of the workers had dyspnea - talc had no acute effect on ventilatory capacity - talc workers had lower (NS) FVC standardized flow rates and a lower ratio of $FEV_{1.0}$ to FVC; the flow rate/FVC at 12.5% FVC was statistically significantly decreased in exposed workers -for workers of >10 yrs, residual $FEV_{1.0}$ was statistically significantly decreased in exposed workers - none of the chest x-rays were definitely consistent with classical talc pneumoconiosis	[99]

Table 5. Pulmonary effects of occupational exposure

Talc Composition and Particle Size (if given)	Study Population and Location	Timeframe examined	Procedure/Parameters Measured/Limitations	Findings	Reference
			Pottery Plant Workers		
non-fibrous talc	- white men from 3 ceramic plumbing fixture plants (>1 yr employment)	employed during 1939-1966	- workers were exposed to both silica and talc - mortality from 1940-1980 was examined <u>Limitations</u> - information on smoking patterns was not available	- with high silica/non-fibrous talc exposure, there was a statistically significant increase in SMR for lung cancer (SMR=2.54) and non-malignant disease mortality (SMR=2.20) - with high silica/no talc exposure, the increase was only seen for non-malignant respiratory disease (SMR=2.64) - **with non-fibrous talc, SMRs for lung cancer were statistically significant increased with 5-14 and 15+ yrs duration of exposure and -14 and 15+ yrs since first talc exposure** - SMRs for non-malignant respiratory diseases were statistically significant increased with <5, but not 5-14 or 15+ yrs duration of exposure and with 5-14, but not >15, yrs since first talc exposure - **the researchers postulated that non-fibrous talc was related to excess lung cancer, and that it was possible that silica might act as a co-factor or promoting agent**	[97,98]

Abbreviations: CI = confidence interval; CV = cardiovascular; exp = expected; FEF = forced expiratory flow; FEV = forced expiratory volume; FVC = forced vital capacity; GI = gastrointestinal; GSD – geometric standard deviation; MMEF = maximum mid-expiratory flow; NS = non-statistically significant; obs = observed; ONMRD = other non-malignant respiratory disease; OR = odds ratio; PMN = polymorphonuclear cells; pop. = population; RR = relative risk; SD = standard deviation; SIR = standardized incidence ration; SMR = standardized mortality ratio; TB = tuberculosis; TCO = transfer factor for carbon monoxide; VC = vital capacity

Bolded text was used to highlight statistically significant increases
Italicized text was used to highlight statistically significant decreases

Table 6. Exposure During Cosmetic Talc Use

Study Population	Test Article	Measurement Device	Study Conditions	Procedure	Respirable Amount	Other Results	Reference
infant exposure simulation; number not given	commercial talcum powder (composition not defined)	gravimetric dust sampler	simulated	- powder was dusted into a shallow tray from a height of 7-13 cm - the air inlets of the sampler were placed where the baby's nose would be, as well as 40 cm above the tray (representing mother's exposure); the dust concentration was similar for the mother and the infant	0.10 mg/min/m^3	10 s dusting period: total median dust concentration - 0.243 mppcf 65 s settling period: median dust concentration - 0.124 mppcf median exposure/application: 0.1752 mppcf-min median weekly exposure (5 applications/day): 0.102 mppcf-h	[57]
48 infants	commercial talcum powder (composition not defined)	10 mm nylon cyclone	actual	-mothers diapered infants, applying powder in their usual method -the cyclone inlet was held next to the baby's head, approx. 4" above the change mat - procedure was repeated 3x in succession and the mean of the 3 runs was used; was performed over two 4-day periods	0.19 ± 0.084 mg/m^3	avg. use/exposure: 0.88 g exposure time: 0.52 min TWA: 0.095 ± 0.039 mg·min/m^3	[104]
adults, 23 males and 21 females	commercial talcum powder (composition not defined)	10 mm nylon cyclone	actual	- subjects applied powder in their usual manner in an anteroom - a headband with an attached 10-mm cyclone positioned at the level of the nose was worn - performed over two 4-day periods	2.03 ± 1.49 mg/m^3	avg. use/exposure: 8.84 g exposure time: 1.23 min TWA: 1.727 mg·min/m^3	
infant simulation; 4 subjects	baby powder with: - Chinese talc - Italian 00000 grade talc (cosmetic talcs; both perfumed and unperfumed; Chinese and Italian perfumed talc contained 0.045 and 0.2% perfume, respectively)	for respirable dust: cyclone elutriator/filter head system with 25-mm diameter filter; allowed sampling of all particles <1 µm, 50% of 5-µm particles, and no 7-µm particles for total dust: cyclone removed and open filter holder with a 37 mm filter	simulated	- in a 3.7 x 2.8 m room, adult subjects used a doll to simulate powdering during diapering - the sample collection unit was on a table next to the doll's head -the "doll's nose" was approx. 15-30 cm from the sampling point - sampling time was 5 min -2 trials at 1 h intervals	Chinese, perfumed: <0.1-0.9 mg/m^3 unperfumed: <0.1-0.9 mg/m^3 Italian, perfumed: <0.1-0.3 mg/m^3 unperfumed: <0.1-0.5 mg/m^3	- there were no major differences among concentrations of respirable dust - mean concentration of respirable talc (for Chinese and Italian perfumed and unperfumed talcs) – 0.21 mg/m^3 - respirable talc accumulated during 4 samplings: 0.005-0.3 mg/m^3 - no evidence that perfume affected amount of respirable talc - mean talcing time: 19-21 s	[51]
4 female subjects	loose face powder: - Chinese talc - Italian 00000 grade talc - Italian micronized-grade talc (cosmetic talcs; all unperfumed)	as above	actual	- in a 2 x 1 m room, subjects applied powder in their normal manner (a small window was open during application) - the application puff was only dipped once in the powder - the subject's nose was approx.. 15 cm from the sampling point - sampling time was 5 min - 2 trials at1- h intervals	Chinese: <0.1-1.1 mg/m^3 Italian: <0.1-0.8 mg/m^3 Italian, micronized: <0.3-1.7 mg/m^3	with the exception of micronized talc, there were no major differences among concentrations of respirable dust - mean concentration of respirable talc (for Chinese and Italian perfumed and unperfumed talcs) – 0.48 mg/m^3 - respirable talc accumulated during 4 samplings: 0.1-0.4 mg/m^3 - no evidence that perfume affected amount of respirable talc - mean talcing time: 17-19 s	

Table 6. Exposure During Cosmetic Talc Use

Study Population	Test Article	Measurement Device	Study Conditions	Procedure	Respirable Amount	Other Results	Reference
4 female subjects	adult dusting powder: - Chinese talc - Italian 00000 grade talc (both perfumed and unperfumed) - Italian micronized-grade talc, unperfumed (cosmetic talc)	as above	actual	- in a 2.3x 2 m room, subjects applied powder in their normal manner - the subject's nose was approx.. 30-90 cm from the sampling point - one experiment with unperfumed Italian talc was performed at >90% humidity - sampling time was 5 min - particle size analysis was performed for unperfumed Italian 00000 and micronized talc - 2 trials at 1 h intervals	Chinese, perfumed: 0.3-2.6 mg/m^3 unperfumed: 0.5-1.8 mg/m^3 Italian, perfumed: 0.4-1.7 mg/m^3 unperfumed: 0.5-2.6 mg/m^3 high humidity: 0.2-0.8 mg/m^3 Italian, micronized: 0.6-3.3 mg/m^3	-with the exception of micronized talc, there were no major differences among concentrations of respirable dust - mean concentration of respirable talc (for Chinese and Italian perfumed and unperfumed talcs) – 1.13 mg/m^3 - mean concentrations of micronized talc were 1.9 mg/m^3 - respirable talc accumulated during 4 samplings: 0.3-2.5 mg/m^3 - total talc with cyclone removed: Italian 00000 unperfumed, 2.7-4.8 mg/m^3; Italian micronized, 0.2-1.5 mg/m^3 - total talc with cyclone removed: Italian 00000 unperfumed, 2.7-4.8 mg/m^3; Italian micronized, 0.2-1.5 mg/m^3 - total talc with open filter: Italian 00000 unperfumed, 8-27 mg/m^3; Italian micronized, 10-17 mg/m^3 - detectable background levels of respirable talc were found only with micronized talc (0.6-1.6 mg/m^3) and Italian talc (<0.1-1.0 mg/m^3) at high humidity - no evidence that perfume affected amount of respirable talc - particle size analysis demonstrated that most particles were between 1 and 8 μm - mean talcing time: 27-31 s	
adult consumers and miners	consumer – cosmetic talc; miner – talc dust	not stated	actual	comparison between adult consumer's 1 min daily exposure and a miner's 8 h daily exposure		-consumers: weekly exposure resulting from use lasting 10 s, with 65 s settling time, would be 0.102 mppcf-h of talc dust/wk -miners: assuming a max. daily exposure of 20 mppcf talc dust, weekly exposure would be 890 mppcf-h -exposure of miners about 8000 x greater than that of consumers (calculations were not provided)	[57]

Table 7. Lung Talc Burden in Mice [11]

	Male		Female	
Evaluation	**6 mg/m^3**	**18 mg/m^3**	**6 mg/m^3**	**18 mg/m^3**
	Normalized to Control Lung Weight (mg talc/g control lung)			
6 mos	0.415 0.114 (2)	1.41 ± 0.29 (4)	0.524 ± 0.056 (4)	1.35 ± 0.24 (4)
12 mos	1.084 ± 0.130 (4)	9.00 ± 1.45* (4)	0.707 ± 0.170 (4)	6.17 ± 1.39* (4)
18 mos	0.426 ± 0.040 (2)	8.36 (n=1; no std. dev. calc.)	1.387 ± 0.178** (4)	7.83 ± 1.36* (3)
24 mos	2.973 ± 0.762* (8)	19.73 ± 4.03** (6)	2.667 ± 0.720** (6)	20.05 ± 0.98** (5)
	Normalized to Exposure Concentration (mg talc/g control lung per mg talc/m^3)			
6 mos	0.069 ± 0.019 (2)	0.078 ± 0.016 (4)	0.087 ± 0.009 (4)	0.075 ± 0.013 (4)
12 mos	0.181 ± 0.022 (4)	0.500 ± 0.081$^{\#}$ (4)	0.118 ± 0.028 (4)	0.343 ± 0.077$^{\#}$ (4)
18 mos	0.071 ± 0.007 (2)	0.464 (n=1; no std. dev. calc.)	0.231 ± 0.030 (4)	0.435 ± 0.075 (3)
24 mos	0.496 ± 0.127 (8)	1.096 ± 0.224$^{\#}$ (6)	0.445 ± 0.120 (6)	1.114 ± 0.055$^{\#}$ (5)

(n) number of animals examined for lung talc burden
* significantly different ($p \leq 0.05$) from 6 mos group
** significantly different ($p \leq 0.01$) from 6 mos group
$^{\#}$ significantly different ($p \leq 0.05$) from 6 mg/m^3 group

Table 8. Lung Talc Burden in Rats [11]

	Male		Female	
Interim Evaluation	**6 mg/m^3**	**18 mg/m^3**	**6 mg/m^3**	**18 mg/m^3**
	Normalized to Control Lung Weight (mg talc/g control lung)			
6 mos	2.63 ± 0.24 (3)	10.83 ± 0.23 (3)	2.43 ± 0.19 (3)	8.34 ± 0.12 (3)
11 mos	4.38 ± 0.59* (3)	20.96 ± 2.04* (3)	4.71 ± 0.26* (3)	14.16 ± 3.36 (3)
18 mos	7.31 ± 0.71** (3)	27.57 ± 0.91* (3)	7.66 ± 0.34** (2)	24.33 ± 0.63* (3)
24 mos	10.45 ± 1.26** (6)	24.15 ± 3.41* (9)	9.10 ± 0.88** (2)	29.40 ± 2.40** (3)
	Normalized to Exposure Concentration (mg talc/g control lung per mg talc/m^3)			
6 mos	0.439 ± 0.040 (3)	0.602 ± 0.013$^{\#}$ (3)	0.406 ± 0.032 (3)	0.464 ± 0.007$^{\#}$ (3)
11 mos	0.731 ± 0.098 (3)	1.165 ± 0.113$^{\#}$ (3)	0.785 ± 0.043 (3)	0.787 ± 0.187 (3)
18 mos	1.22 ± 0.12 (3)	1.53 ± 0.05 (3)	1.28 ± 0.06 (2)	1.35 ± ± 0.04 (3)
24 mos	1.74 ± 0.21 (6)	1.34 ± 0.19 (9)	1.52 ± 0.15 (2)	1.63 ± 0.13 (3)

(n) number of animals examined for lung talc burden
* significantly different ($p \leq 0.05$) from 6 mos group
** significantly different ($p \leq 0.01$) from 6 mos group
$^{\#}$ significantly different ($p \leq 0.05$) from 6 mg/m^3 group

Table 9. Epidemiological Studies Evaluating Talc Exposure and Ovarian and Endometrial Cancer Risk

Talc/Composition	Population/ Geographical Area	Study/ Diagnosis Yrs	Study Description and Limitations	Findings	OR or RR (95% C.I.)	Reference
OVARIAN CANCER						
PERSONAL USE						
PROSPECTIVE STUDY						
talc; purity and composition not specified	- 307 registered nurses in 11 states with epithelial ovarian cancer (out of 31,789 subjects of 121,700 total pop. that reported using talc) (Nurses' Health Study)	1982 - 1996	- subjects answered questionnaires every 2 yrs from 1976-1996, subjects were questioned about talc use in 1982 - risk was age-adjusted and multivariate for age, parity, OC use, BMI, tubal ligation history, smoking status, and PMH use - women who did not respond to the questions on talc use in 1982 and who reported a diagnosis of cancer before 1982 were excluded Limitations - question of talc use was ever/never only; did not determine the age at which use began or the duration - this also may have contributed to a higher prevalence of use compared to other studies - were unable to assess the potential effect of talc use prior to first pregnancy - follow-up period may have been inadequate if latency is >15 yrs - question about tubal ligation was asked as a component of contraceptive use, so not all women may have responded	Ever/never perineal use of talc 58.3%of cases never used perineal talc - 41.7% of cases ever had perineal use of talc (age) (multivariate) Frequency of perineal talc use - 60.6%of cases never used talc on perineum - 14% of cases used talc on perineum <1x/wk (age) (multivariate) - 9.8% of cases used talc on perineum 1-6 x/wk (age) (multivariate) - 15.6% of cases used talc on perineum daily (age) (multivariate) Talc use on sanitary napkins - 78.8%of cases never used talc on sanitary napkins - 11.7% of cases used talc on sanitary napkins (age) (multivariate) Talc use perineally and/or on sanitary napkins - 58.3%of cases did not use talc perineally or on sanitary napkins - 33.6% of cases talc on perineum or sanitary napkins (age) (multivariate) - 8.1% of cases talc on perineum and sanitary napkins (age) (multivariate)	**RR** 1.0 1.05 (0.84-1.32) 1.09 (0.86-1.0) 1.0 1.1 (0.79-1.53) 1.14 (0.81-1.59) 0.95 (0.65-1.4) 0.99 (0.67-1.46) 1.09 (0.79-1.49) 1.12 (0.82-1.55) 1.0 0.89 (0.62-1.29) 0.89 (0.61-1.28) 1.0 1.11 (0.87-1.41) 1.15 (0.9-1.46) 0.89 (0.58-1.35) 0.9 (0.59-1.37)	[148]
			- the tumors were stratified by histological subtype - risk was adjusted for age or for age, parity, OC use, and tubal ligation, and sometimes for BMI (multivariate)	All serous cancers (185 total) - 54.6% never used talc perineally - 45.4% ever used talc perineally (age) (multivariate) Serous invasive cancers (160 total) - 52.5 % never used use talc perineally - 47.5% ever used talc perineally (age) (multivariate) Endometroid cancers (42 total) - 61.9% never used use talc perineally - 38.1% ever used talc perineally (age) (multivariate) Mucinous cancers (50 total) - 60% never used use talc perineally - 40% ever used talc perineally (age) (multivariate)	**RR** 1.0 1.23 (0.02 – 1.64) 1.26 (0.94 – 1.69) 1.0 1.33 (0.98 – 1.82) **1.40 (1.02 – 1.91)** 1.0 0.91 (0.49 – 1.69) 0.91 (0.49 – 1.87) 1.0 0.98 (0.56 – 1.73) 0.93 (0.53 – 1.66)	

Table 9. Epidemiological Studies Evaluating Talc Exposure and Ovarian and Endometrial Cancer Risk

Talc/Composition	Population/ Geographical Area	Study/ Diagnosis Yrs	Study Description and Limitations	Findings	OR or RR (95% C.I.)	Reference
			HOSPITAL-BASED CASES/HOSPITAL-BASED CONTROLS			
talc; purity and composition not specified	- 135 women in the Washington, D.C. area with epithelial ovarian cancer (hospital-based) - 171 hospital controls	1974-1977	- subjects were asked questions about reproductive and sexual history, medical history, drug use, other exposures, and talc use Limitation - a potential bias is that talc exposure was not a major focus of the study during questioning	Ever/never talc use - 45.9% of cases and 35.7% of controls had no exposure to talc - 49.7% of cases and 58.5% of controls had exposure to talc Use with diaphragm - 18.5% of cases and 24% of controls reported diaphragm use with talc - 10.4% of cases and 6.4% of controls reported diaphragm use with no talc Areas of application of talc - 57% of cases and 49.1% of controls reported no body talc use - 40% of cases and 45.6% of controls reported some body talc use - 27.4% of cases and 33.3% of controls reported all-over use of talc - 5.2% of cases and 1.8% of controls reported genital use of talc	**RR** 1 0.7 (0.4 - 1.1) 0.8 (0.4 - 1.4) 1.6 (0.7-3.7) 1.0 0.8 (0.5 - 1.2) 0.7 (0.4 - 1.2) 2.5 (0.7 - 10.0)	152
talc; purity and composition not specified	- 235 females in London and Oxford, England with epithelial ovarian cancer (from 15 hospitals) - 451 age-matched hospital controls	Oct 1978 – Feb 1983	- subjects were asked about talc reproductive and sexual history, contraceptive use, breastfeeding, talc usage, hysterectomy, HRT - all risk estimates were adjusted for age and social class; some were adjusted for parity	Frequency of talc usage never: 37.3% of cases; 39.5% of controls rarely: 2.6% of cases; 3.5% of controls monthly: 3.0% of cases; 5.3% of controls weekly: 24.3% of cases; 17% of controls daily: 30.2% of cases; 30.8% of controls - no consistent trend of increase risk with increasing frequency of talc (χ^2 (trend) = 3.80; p = 0.05)	**RR** 1.0 0.9 (0.3-2.4) 0.7 (0.3-1.8) 2.0 (0.3-3.4; p=0.07) 1.3 (0.8-1.9)	139
talc; purity and composition not specified	- 77 patient at Johns Hopkins Hospital in Baltimore, MD with epithelial ovarian cancer - 46 age-race matched hospital controls	1981-1985	- subjects questioned about presence and length of genital fiber and respiratory fiber exposure (in this study, fiber exposure was defined as exposure to asbestos, talc, and fiberglass), reproductive factors, estrogen use, family history of cancer, and contraceptive use; information on previous abdominal and gynecological operations was ascertained - potential confounders: obesity, socioeconomic status, religion, reproductive status, live births >2, OC use; confounders added dependent on effect on OR	Areas of application of talc - 88% of cases and 87% of controls reported genital fiber use - 28.9% of cases and 18.6% of controls reported genital bath talc exposure - 61.8% of cases and 55.8% of controls reported application of bath talc to body (risk adjusted for # of live births) - 50.7% of cases and 54.5% of controls reported cosmetic face powder use (risk adjusted years of education) Use of talc on sanitary napkins or on diaphragm - 61.8% of cases and 55.8% of controls reported talc use on sanitary napkins (risk adjusted for highest wt 1 yr prior to diagnosis) - 18.9% of cases and 11.4% of controls reported powder on diaphragm (risk adjusted for # of live births and yrs of education)	**OR** 1.0 (0.2-4.0) 1.7 (0.7 - 3.9) 1.6 (0.6 – 2.7) 1.1 (0.4 – 2.7) **4.8 (1.3 – 17.8)** 3.0 (0.8 – 10.8)	164

Table 9. Epidemiological Studies Evaluating Talc Exposure and Ovarian and Endometrial Cancer Risk

Talc/Composition	Population/ Geographical Area	Study/ Diagnosis Yrs	Study Description and Limitations	Findings	OR or RR (95% C.I.)	Reference
talc; purity and composition not specified	- 499 patients at Roswell Park Cancer Institute, Buffalo, NY, with epithelial ovarian cancer - 755 age-at-diagnosis matched hospital controls - numbers were adjusted based on answers to questionnaires (i.e., if the subject did not respond to talc use or recall the duration of use)	Oct 1982 – Oct 1995	- information on parity, menstrual history, use of exogenous hormones, contraceptive history, talc use, and personal hygiene was obtained and subjects were questioned about medical, social, family, dietary, and occupational histories - risk was adjusted for OC use, smoking history, family history of epithelial ovarian cancer, age at menarche, menopausal status, income, education, geographic location, history of tubal ligation and/or hysterectomy Limitations - ascertainment and recall bias likely - subjects were asked whether condoms or diaphragms were used for contraception, but did not ask about frequency or duration or diaphragm storage in talc	Areas of application of talc - 52.2% of cases and 55.1% of controls never used talc - 34.0% of cases and 32.2% of controls reported talc use in the genital or thigh area - 2.8% of cases and 2.9% of controls reported talc use on sanitary napkins - 11.0% of cases and 9.8% of controls reported talc use in genital or thigh area and on sanitary napkins Duration of talc use - 56% of cases and 58.4% of controls had no talc use - 9.1% of cases and 9.3% of controls used talc for 1-9 yrs - 11.4% of cases and 7.6% of controls used talc for 10-19 yrs 23.5% of cases and 24.6% of controls used talc for ≥20 yrs	**OR** 1.0 1.0 (0.8 - 1.3) 0.9 (0.4 – 2.0) 1.1 (0.7 – 1.7) 1.0 0.9 (0.6 – 1.5) 1.4 (0.9 – 2.2) 0.9 (0.6 – 1.2)	[170]
HOSPITAL-BASED CASES/POPULATION-BASED CONTROLS						
talc; purity and composition not specified	- 215 white females in the Greater Boston area with epithelial ovarian cancer (from 12 hospitals) - 215 matched pop. controls	Nov 1978 – Sept 1981	- exposure to talc by way of contraceptive practices, operations, or perineal hygiene was reviewed for each subject and control -risk was adjusted for parity and menopausal status	- 42.8% of cases and 28.4% of controls had any perineal exposure as a dusting powder on the perineum or on sanitary napkins; adjusted RR was compared to subjects with neither exposure - 27.9% of cases and 22.3% of controls had used talc for dusting the perineum or sanitary napkins, but not both - 14.9% of cases and 6% of controls had exposure through both dusting the perineum and sanitary napkins; RR was compared to subjects with neither exposure	**OR** **1.92 (1.27-2.89**; p<0.003) 1.55 (p=0.06) 3.28 (p<0.001; (1.68-6.42)	[143]
talc, purity and composition not specified; often reported as 'baby powder"	- 235 white women in Boston with epithelial ovarian cancer (from 10 hospitals) - 239 age- and residence-matched pop. controls	July 1984-Sept 1987	- subjects were asked questions about demographic and occupational, medical and reproductive, and dietary histories, cigarette smoking, and hygienic practices, including use of douches, type of sanitary protection, and perineal exposure to talc - use of talc on areas other than the perineum were considered non-exposed - risk was adjusted for parity, education, marital status, religion, use of sanitary napkins, douching, age, and wt	Ever/never perineal use of talc - 51.5% of cases and 60.7% of controls reported no genital talc application - 48.5% of cases and 39.3% of controls reported perineal talc exposure Use on sanitary napkins, underwear, and/or diaphragm - 3.8% of cases and 5.0% of controls reported talc use on sanitary napkins and/or underwear - 8.5% of cases and 8.8% of controls reported exposure with diaphragm use or from their partner in combination with sanitary napkins and/or underwear - 36.2% of cases and 25.5% of controls reported exposure by dusting powder to the perineum in combination with sanitary napkins and/or underwear	**OR** 1.0 1.5 (1.0 – 2.1) 1.1 (0.4 – 2.8) 1.2 (0.6 – 2.4) **1.7 (1.1 – 2.7)**	[151]
				Frequency of talc application - 13.6% of cases and 11.7% of controls reported <5 appl/mo -10.2% of cases and 10.5% of controls reported 5-29 appl/mo - 24.7% of cases and 16.7% of controls reported ≥30 appl/mo	1.5 (0.8 – 2.7) 1.2 (0.6 – 2.2) **1.8 (1.1 – 3.0)**	

Table 9. Epidemiological Studies Evaluating Talc Exposure and Ovarian and Endometrial Cancer Risk

Talc/Composition	Population/ Geographical Area	Study/ Diagnosis Yrs	Study Description and Limitations	Findings	OR or RR (95% C.I.)	Reference
				Duration of use of talc		
				-6.0% of cases and 6.3% of controls reported <10 yrs talc use	1.2 (0.5 – 2.6)	
				-20.9% of cases and 16.3% of controls reported 10-29 yrs talc use	1.6 (1.0 – 2.7)	
				- 21.7% of cases and 16.3% of controls reported ≥30 yrs talc use	1.6 (1.0 – 2.7)	
				Number of lifetime applications		
				- 8.1% of cases and 7.9% of controls reported <1000 lifetime applications	1.3 (0.7 – 2.7)	
				- 24.3% of cases and 19.2% of controls reported 1000-10,000 lifetime applications	1.5 (0.9 – 2.4)	
				- 16.2% of cases and 12.1% of controls reported >10,000 lifetime applications	1.8 (1.0 – 3.0)	
				Age at first use of talc		
				- 28.1% of cases and 20.9% of controls were <20 yrs old	**1.7 (1.1 – 2.7)**	
				-11.5% of cases and 10.9% of controls were 20-25 yrs old	1.2 (0.6 – 2.2)	
				- 8.9% of cases and 7.5% of controls were >25 yrs old	1.6 (0.8 – 3.2)	
				Years since last talc use		
				- 20.4% of cases and 11.3% of controls used talc within the last 6 mos	**2.3 (1.3 – 4.0)**	
				-15.3% of cases and 16.3% of controls last used talc 6 mos-10 yrs ago	1.1 (0.7 – 1.9)	
				- 12.8% of cases and 11.7% of controls last used talc 10 or more yrs ago	1.4 (0.8 – 2.6)	
			-era of use was examined; restricted to women that were older than 10 yrs in 1960 - same adjustments listed previously were made	Era of talc use - 12.3% of cases and 12.6% of controls used talc after 1960 - 31.9% of cases and 23.9% of controls used talc before 1960	 1.1 (0.6 – 2.1) **1.7 (1.1 – 2.7)**	
			-brand of powder used was examined; if more than one brand was used, the brand used most frequently and for the longest time was counted - same adjustments listed previously were made	Brand/type of talc used - 38.7% of cases and 30.1% of controls used brand or generic baby powder - 6.8% of cases and 7.2% of controls used deodorizing or other scented powders	 **1.6 (1.1 – 2.5)** 1.2 (0.6 – 2.5)	
talc; purity and composition not specified	- 767 women from the Delaware Valley area of PA, NJ, and DE with epithelial ovarian cancer (from 39 hospitals) - 1367 age- and geography-matched pop. controls	1994-1998	- subjects were asked questions about sexual, menstrual, obstetric, and breast-feeding histories, history of medical condition that may be related to pelvic inflammation, OC use, tubal ligation, hysterectomy, ovarian operations, and talc exposure - risk was adjusted for age, parity, race, familial history of ovarian cancer, OC use, tubal ligation, hysterectomy, and breast-feeding Limitations - low participation rate among cases and controls - potential recall bias	Risk based on area of talc application - 45.5% of cases and 53.3% of controls did not use talc - 21% of cases and 16% of controls applied talc to the genital/rectal area - 10% of cases and 6.9% of controls applied talc to sanitary napkins - 9% of cases and 7.3% of controls applied talc to underwear - 1.3% of cases and 2.4% of controls applied talc to diaphragm/ cervical cap - 7.3% of cases and 9.2% of controls reported talc exposure via a male partner - 43.7% of cases and 37.5% of controls applied talc to feet	**OR** 1.0 **1.5 (1.1-2.0)** **1.6 (1.1-2.3)** **1.7 (1.2-2.4)** 0.6 (0.3-1.2) 1.0 (0.7-1.4) **1.4 (1.1-1.6)**	[162]

Table 9. Epidemiological Studies Evaluating Talc Exposure and Ovarian and Endometrial Cancer Risk

Talc/Composition	Population/ Geographical Area	Study/ Diagnosis Yrs	Study Description and Limitations	Findings	OR or RR (95% C.I.)	Reference
				Risk based on length of application to genital/rectal area/ feet		
				- 52.3% of cases and 59.9% of controls reported no use	1.0	
				- 2.2% of cases and 1.2% of controls reported talc use of <1 yr	2.0 (1.0-4.0)	
				- 10% of cases and 7.4% of controls reported talc use of 1-4 yrs	**1.6 (1.1-2.3)**	
				- 5.2% of cases and 4.3% of controls reported talc use of 5-9 yrs	1.2 (0.8-1.9)	
				- 30.4% of cases and 27.1% of controls reported talc use of <1 yr	1.2 (1.0-1.5)	
talc; purity and composition not specified	- 170 French-Canadian women in Montreal with primary ovarian carcinomas or borderline tumors (from 2 hospitals); - 111 of the cases were sporadic; 58 cases were familial - 170 age- and ethnic group-matched pop. controls	1995-1996	- subjects were asked questions about reproductive factors; familial history of cancer; medical history, including use of hormone replacement therapy, use of OCs, tubal ligation, and hysterectomy; smoking, alcohol, and education; perineal talc use - study was comparing the risk factors between familial and sporadic ovarian cancer	- 10.6% of cases and 4.7% of controls reported perineal use of talc - 9.91% of the sporadic cases and 12.1% of the familial cases reported perineal use of talc	p= 0.064 p= 0.79 (sporadic v. familial)	[149]
	- 153/170 of the cases and 152/170 controls from above - 101 of the cases were sporadic, 51 of the cases were familial		- multivariate analysis was performed with 153 cases and 152 controls		**RR**	
				- perineal use of talc by cases vs. controls	2.49 (0.94-6.58; P=0.066)	
				- perineal talc use by sporadic cases	2.45 (0.85-7.07; P=0.098)	
				- perineal talc use by familial cases	3.25 (0.83-12.4; P=0.084)	
			HOSPITAL-BASED CASES/HOSPITAL- and POPULATION-BASED CONTROLS			
talcum powder; purity and composition not specified	- 188 women from northern California with primary epithelial cancer (from 7 hospitals) - 280 matched hospital controls - 259 matched pop. controls	Jan 1983 – Dec 1985	- the researchers stated that RR associated with talc use, tubal ligation, and hysterectomy were similar when cases were compared to both control groups; therefore the control groups were combined - risk was adjusted for parity Limitations - failure to interview all eligible ovarian cancer patients and a completely random sample of controls - cofounding by differential talc use among women with characteristics predictive of ovarian cancer (unlikely) - random error in reported talc use	Type of talc exposure	**OR**	[169]
				- 40% of cases and 43% of controls reported no talc use	1.0	
				- 12% of cases and 10% of controls reported talc exposure on the perineum only	1.45 (0.81-2.6)	
				- 3% of cases and 5% of controls reported talc exposure on sanitary pads only	0.62 (0.21-1.80)	
				- 5% of cases and 4% of controls reported talc exposure with diaphragm use only	1.60 (0.63-3.58)	
				- 36% of cases and 31% of controls reported talc exposure by two of the three use types	1.36 (0.91-2.04)	
				- 1% of cases and 2% of controls reported talc exposure by all three use types	0.35 (0.04-2.94)	
			- risk was also examined based on duration of use of talcum powder; talc use after tubal ligation or hysterectomy was excluded - risk was adjusted for parity	Duration of talc use		
				- 55% of cases and 59% of controls did not report yrs of talc use	1.0	
				- 18% of cases and 13% of controls reported talc exposure of 1-9 yrs	1.60 (1.00-2.57; p=0.05)	
				- 27% of cases and 27% of controls reported talc exposure of 10+ yrs	1.11 (0.82-1.96; p=0.61)	
				- 23% of cases and 19% of controls reported 20+ talc applications/mo	1.45 (0.94-2.22)	
				-overall trend for 30 uses/mo	1.30 (0.88-1.92)	

Table 9. Epidemiological Studies Evaluating Talc Exposure and Ovarian and Endometrial Cancer Risk

Talc/Composition	Population/ Geographical Area	Study/ Diagnosis Yrs	Study Description and Limitations	Findings	OR or RR (95% C.I.)	Reference
			POPULATION-BASED CASES/POPULATION-BASED CONTROLS			
talc (as baby powder) deodorizing powders that contain other substances in addition to talc	- 116 white women of western Washington state with borderline ovarian tumors (from the Seattle-Puget Sound Cancer Surveillance System) - 158 white age- and residence-matched controls	1980-1985	- subjects were asked questions about reproductive and sexual history, medical history, and perineal exposure to talc - risk was adjusted for age, parity, and use of oral contraceptives Limitations - only 30% of potentially eligible cases and controls participated	Types of exposure to talc - 57.8% of cases and 59.5% of controls reported no perineal exposure to powder - 42.2% of cases and 40.5% of controls reported any perineal exposure to powder - 6.9% of cases and 13.3% of controls reported powder exposure by diaphragm storage only - 9.5% of cases and 17.1% of controls reported powder exposure by diaphragm storage or by other methods - 20.7% of cases and 19.0% of controls reported powder exposure following bathing only - 29.3% of cases and 23.4% of controls reported powder exposure following bathing or by other methods - 6.0% of cases and 2.5% of controls reported powder exposure by use on sanitary napkins only - 12.1% of cases and 6.3% of controls reported powder exposure by use on sanitary napkins or by other methods - 6.0% of cases and 23.4% of controls reported after bathing and on sanitary napkins	**RR** 1 1.1 (0.7-2.1) 0.5 (0.2-1.4) 0.5 (0.2-1.3) 1.2 (0.6-2.6) 1.3 (0.8-2.7) 2.2 (0.8-19.8) 1.9 (0.9-6.9) 2.2 (0.8-18.8)	150
			-	Type of powder used (i.e., baby, deodorizing, or cornstarch) - 15.5% of cases and 19.6% of controls reported baby powder only - 19.0% of cases and 21.5% of controls reported baby powder only or combined use - 11.2% of cases and 12.0% of controls reported talc, unspecified (no combined use) - 3.4% of cases and 4.4% of controls reported cornstarch only - 8.6% of cases and 23.4% of controls reported deodorizing powder only - 12.1% of cases and 4.4% of controls reported deodorizing powder only or combined use	0.8 (0.4-1.9) 0.9 (0.5-2.0) 1.0 (0.4-2.4) 0.8 (0.2-3.8) **3.5 (1.2-28.7)** **2.8 (1.1-11.7)**	
				Route of talc exposure and type of powder used - any powder use after bathing - 8.6% of cases and 3.8% of controls reported any use of deodorizing powder -20.7% of cases and 20.3% of controls reported no use of deodorizing powder - any powder use on sanitary napkins - 6.9% of cases and 23.4% of controls reported any use of deodorizing powder -5.2% of cases and 3.8% of controls reported no use of deodorizing powder	3.1 (0.8-10.9) 1.1 (0.5-2.4) 2.6 (0.9-22.4) 1.5 (0.4-6.5)	

Table 9. Epidemiological Studies Evaluating Talc Exposure and Ovarian and Endometrial Cancer Risk

Talc/Composition	Population/ Geographical Area	Study/ Diagnosis Yrs	Study Description and Limitations	Findings	OR or RR (95% C.I.)	Reference
talc-containing dusting powder; purity and composition not specified	- 112 females in Beijing, China with epithelial ovarian cancer (from Beijing Cancer Registry) - 224 age-matched community controls	1984-1986	- subjects were asked questions about menstrual, obstetric, marital, medical, and familial histories - risk was adjusted for education and parity -risk with occupational exposure was also determined Limitations - some ovarian cancer patients may not have been ascertained for the study - high rate of loss due to deaths could reflect on survival and on risk - exclusion of controls with current health problems	Types of talc exposure - 93.8% of cases and 97.8% of controls reported no use of dusting powder - 6.3% of cases and 2.2% of controls reported dusting powder use on the lower abdomen and perineum - number of cases and controls exposed occupationally to talc (occupation was not specified)	**RR** 1.0 3.9 (0.9-10.6) 0.9 (0.3-2.9)	[141]
5 categories of powder: talcum, cornstarch, baby, deodorant, and scented body/bath	- 313 white women in western WA (pop.-based) with epithelial ovarian cancer - 422 white age- and geography-matched pop. controls	Jan 1986 – Dec 1988	- subjects were questioned about genital powder exposure, demographic characteristics, reproductive, medical, and smoking histories, and birth control methods - risk was adjusted for age; further adjustment for education, income, marital status, BMI, OC use, or parity did not alter the estimated RRs Limitations - a sizeable number of eligible women, particularly those with ovarian cancer, did not participate - difficult to ascertain whether perineal powder application correctly estimates actual exposure to particles - direct comparison with other studies is limited because of differences in definitions, groupings, and analysis of genital powder use - insufficient information to address influence of condom use on risk	Ever/never genital use of talc - 49.2% of cases and 60.7% of controls reported no lifetime genital powder application - 50.8% of cases and 39.3% of controls reported any lifetime genital powder application	**OR** 1.0 **1.5 (1.1 - 2.0)**	[142]
				Exclusive use of powder - 17.6% of cases and 11.4% of controls reported perineal dusting only - 7.0% of cases and 8.3% of controls reported diaphragm storage in powder only - 3.8% of cases and 2.4% of controls reported powder on sanitary napkins only - 5.8% of cases and 6.6% of controls reported genital deodorant spray only	**1.8 (1.2 – 2.9)** 0.8 (0.4 – 1.4) 1.5 (0.6 – 3.6) 1.5 (0.8 – 3.0)	
			- risk was adjusted for age and other methods of genital powder application	Any perineal dusting and CLE (days) - 30.4% of cases and 20.6% of controls reported any dusting - 6.4% of cases and 5.2% of controls reported ≤2000 days CLE - 7.7% of cases and 6.2% of controls reported 2001-5000 CLE - 6.7% of cases and 5.2% of controls reported 5001-10,000 CLE - 8.9%of cases and 4.0% of controls reported >10,000 CLE	1.8 (0.9 – 3.5) 1.6 (0.9 – 2.9) 1.2 (0.6 – 2.4) 1.8 (0.9 – 3.4)	

Table 9. Epidemiological Studies Evaluating Talc Exposure and Ovarian and Endometrial Cancer Risk

Talc/Composition	Population/ Geographical Area	Study/ Diagnosis Yrs	Study Description and Limitations	Findings	OR or RR (95% C.I.)	Reference
			- risk was adjusted for age and other methods of genital powder application	Any diaphragm storage in powder CLE (mos) - 14.7% of cases and 12.1% of controls reported diaphragm storage in powder - 7.7% of cases and 6.2% of controls reported ≤60 mos CLE - 4.8% of cases and 4.7% of controls reported >60 mos CLE	 1.0 (0.6 – 1.6) 1.1 (0.6 – 1.9) 0.8 (0.4 - 1.7)	
			- risk was adjusted for age and other methods of genital powder application (none/any)	Any powder on sanitary napkins and CLE (mos) and applications - 12.1% of cases and 9.5% of controls reported any powder on sanitary napkins - 8.0% of cases and 5.0% of controls reported ≤120 mos CLE - 3.8% of cases and 4.5% of controls reported >120 mos CLE - 7.3% of cases and 4.5% of controls reported ≤1000 lifetime applications - 4.5% of cases and 5.0% of controls reported >1000 lifetime applications	 0.9 (0.5 – 1.5) 1.3 (0.7 – 2.4) 0.5 (0.2 – 1.1) 1.3 (0.7 – 2.5) 0.6 (0.3 – 1.2)	
			- risk was adjusted for age and other methods of genital powder application	Any genital deodorant spray and CLE (mos) and applications - 12.8% of cases and 9.5% of controls reported any genital deodorant spray - 7.7% of cases and 7.4% of controls reported ≤12 mos CLE - 4.8% of cases and 2.1% of controls reported >12 mos CLE - 9.3% of cases and 8.1% of controls reported ≤500 lifetime applications - 3.2% of cases and 1.4% of controls reported >500 lifetime applications	 **1.9 (1.1 – 3.1)** 1.5 (0.9 – 2.8) **2.7 (1.1 – 6.6**; p < 0.05) 1.7 (1.0 – 2.9) 2.6 (0.9 – 7.6; p < 0.05)	
			- risk was adjusted for age	Exclusive use by powder type - 5.1% of cases and 3.8% of controls used talcum powder only - 9.9% of cases and 8.5% of controls used baby powder only - 1.6% of cases and 2.6% of controls used cornstarch only - 2.9% of cases and 2.4% of controls used deodorizing powder only - 8.6% of cases and 5.9% of controls used bath/body powder only	 1.2 (0.6 – 2.5) 1.4 (0.8 – 2.4) 0.9 (0.3 – 2.9) 1.0 (0.4 – 2.6) 1.6 (0.9 – 3.0)	
			- risk was adjusted for age and use of other types of powders (yes/no)	Use of any powder type -10.5% of cases and 5.5% of controls reported any talcum powder -16.6% of cases and 14.5% of controls reported any baby powder -2.6% of cases and 3.8% of controls reported any cornstarch -7.7% of cases and 5.7% of controls reported any deodorizing powder -16.6% of cases and 10.2% of controls reported any bath/body powder	 1.6 (0.9 – 2.8) 1.1 (0.7 – 1.8) 0.8 (0.3 – 2.0) 1.1 (0.6 – 2.0) 1.5 (0.9 – 2.4)	

Table 9. Epidemiological Studies Evaluating Talc Exposure and Ovarian and Endometrial Cancer Risk

Talc/Composition	Population/ Geographical Area	Study/ Diagnosis Yrs	Study Description and Limitations	Findings	OR or RR (95% C.I.)	Reference
			- the tumors were stratified by histological subtype - risk was adjusted for age		**RR**	
				Controls (422 total) 60.7% never used powder perineally 39.3% ever used powder perineally	1.0	
				All serous tumors (131 total) - 45.8% never used powder perineally - 54.2% ever used powder perineally	**1.7 (1.1 – 2.5)**	
				Serous tumors (43 total) - 67.4 % never used use powder perineally - 32.6% ever used powder perineally	0.7 (0.4 – 1.4)	
				Endometroid tumors (36 total) - 52.8% never used use powder perineally - 47.2% ever used powder perineally	1.2 (0.6 – 2.3)	
				Other tumors (103 total); (17 clear cell; 3 undiffentiated; 83 unclassified adenocarcinomas or unspecified carcinomas) - 44.7% never used powder perineally - 55.3% ever used powder perineally	**1.8 (1.1 – 2.8)**	
talc; purity and composition not specified	- 189 women in Greater Athens with epithelial ovarian tumors (2 hospitals) - 200 hospital visitor controls	June 1989-Mar 1991	- the women were asked about smoking; alcohol and coffee consumption; reproductive history; frequency of use of analgesics, tranquilizers, or hypnotics; hair dyes; talc in the perineal region; hair dyes - multiple regression adjusted for age, yrs of schooling, body wt prior to onset, age at menarche, parity, menopausal status, age at first birth and at menopause, smoking, coffee drinking, alcohol consumption, hair dyeing, talc application, use of analgesics, and tranquilizers/hypnotics, and for mutual confounders Limitations - moderate study size - possibility of selection bias - possibility of information bias	- 3.1% of cases and 3.5% of controls reported talc application in the perineum - a crude RR, age-adjusted RR, and multiple regression RR were determined	**OR** 0.90 (crude; 0.30-2.74) 0.86 (age-adjusted; 0.27-2.68) 1.05 (multiple regression; 0.28-3.98)	167
talc, purity and composition not specified, and cornstarch	- 450 women from Toronto and Ontario, Canada with epithelial ovarian cancer (pop.-based) - 564 age-matched pop.-based controls	Nov 1989 – Oct 1992	- subjects were questioned about medical and reproductive histories, menstrual characteristics, pregnancies, hormone and contraceptive use, and talc (and cornstarch) usage, type, and exposure - risk was adjusted for age, OC use, parity, breast-feeding, tubal ligation, hysterectomy, and family history of ovarian or breast cancer	Powder type exposures - 44%of cases and 35.6% of controls reported any talc exposure - 0.44% of cases and 0.85% of controls reported any cornstarch exposure - 0.89%of cases and 1.24% of controls reported cornstarch/talc exposure - 11.3% of cases and 8.7% of controls reported talc exposure via sanitary napkins 38.2% of cases and 10.5% of controls reported talc exposure after bathing	**OR** **1.42 (1.08 – 1.86)** 0.31 (0.06 – 1.66) 0.68 (0.18 – 2.33) 1.26 (0.81 – 1.96) 1.31 (1.0 – 1.73)	140

Table 9. Epidemiological Studies Evaluating Talc Exposure and Ovarian and Endometrial Cancer Risk

Talc/Composition	Population/ Geographical Area	Study/ Diagnosis Yrs	Study Description and Limitations	Findings	OR or RR (95% C.I.)	Reference
			- risk was adjusted as above	Frequency (per mo) of after-bath talc use - mean uses/mo after-bath talc was 14.6 for cases and 17.2 for controls - 16.9% of cases and 10.5% of controls reported <10 uses/mo after-bath talc - 12.8% of cases and 11.3% of controls reported 10-25 uses/mo after-bath talc - 9.1% of cases and 10.6% of controls reported >25 uses/mo after-bath talc	0.89 (0.74 – 1.07) **1.84 (1.24 – 2.73)** 1.13 (0.74 – 1.72) 0.95 (0.61 – 1.49)	
			- it was assumed the regular after-bath talc use commenced at age 20 - risk was adjusted as above	Duration of after-bath talc use - mean yrs after-bath talc use was 32.9 yrs for cases and 35.4 yrs for controls - 13.3% of cases and 9.2% of controls reported <30 yrs after-bath talc use - 15.8% of cases and 11.9% of controls reported 30-40 yrs after-bath talc use - 9.1% of cases and 11.3% of controls reported >40 yrs after-bath talc use	1.09 (0.98 – 1.21) **1.7 (1.09 - 2.64)** 1.44 (0.96 – 2.15) 0.87 (0.54 – 1.38)	
			- risk was adjusted as above	After-bath talc use pre/post 1970 - case mean was 26.4 yrs and control mean was 24.9 yrs after-bath talc use before 1970 - case mean was 6.5 yrs and control mean was 10.4 yrs after-bath talc use after 1970	1.09 (0.98 – 1.22) 1.1 (0.89 – 1.35)	
talc; purity and composition not specified	- 200 women in Israel with primary invasive (164) or borderline (36) epithelial ovarian cancer (Israel Cancer Registry) - 408 geography-matched pop. controls	Jan 1990 – Sept 1993	- subjects were asked questions about obstetric and gynecologic history, including infertility and treatment, smoking, education, and talc usage Limitations - no access to medical records to verify information - possibility of recall bias - possibility that results were confounded by a specific cause of infertility	- 89.0% of cases and 94.4% of controls reported never-seldom use of talc **- 10.5% of cases and 5.6% of controls reported moderate-a lot use of talc (P= 0.04)**	not given	[166]
talc; purity and composition not specified	- 824 women in Queensland, New South Wales, and Victoria, Australia with epithelial ovarian cancer (gynecological-oncology registries) - 860 age- and geography-matched pop. controls	Aug 1990 – Dec 1993	- subjects were asked questions about education and ethnicity, and obstetric, marital, occupational, medical, and familial histories, childhood mumps history, and use of talc - risk was adjusted for parity Limitations - potential selection bias	- 56.7% of cases and 52.0% of controls used talc around the abdomen/perineum	**OR** **1.27 (1.04-1.54)**	[163]

Table 9. Epidemiological Studies Evaluating Talc Exposure and Ovarian and Endometrial Cancer Risk

Talc/Composition	Population/ Geographical Area	Study/ Diagnosis Yrs	Study Description and Limitations	Findings	OR or RR (95% C.I.)	Reference
talc, baby powder, deodorizing powders; purity and composition not specified	- 563 women in eastern MA and NH with epithelial ovarian cancer (pop.-based) - 523 age-matched pop. controls - (Phase I of the New England Case Control [NECC] study)	May 1992 – March 1997	- subjects were asked questions about demographics, reproductive and menstrual history, medical history, personal habits, and whether talc-, baby-, or deodorizing powders were dusted or sprayed regularly and age at 1st use, type of powder, applications/mo, and total yrs of use -risk was adjusted for age, study center, tubal ligation, BMI, parity, OC use, and family history of breast/ ovarian cancer Limitations - possible recall bias - potential bias from confounding	Exposure to talc - 55.4% of cases and 63.9% of controls reported no personal use of talc - 17.6% of cases and 18.0% of controls reported use of talc in non-genital areas - 12.6% of cases and 9.8% of controls reported exposure through dusting of the perineum - 3.6% of cases and 2.3% of controls reported exposure through dusting sanitary napkins - 1.4% of cases and 1.2% of controls reported exposure through dusting underwear - 9.4% of cases and 5.0% of controls reported multiple uses in the genital area	**OR** 1.0 1.08 (0.77–1.50) 1.45 (0.97-2.18) 1.45 (0.68-3.09) 1.21 (0.40-3.64) **2.15 (1.30-3.57)**	[145]
			- risk adjusted as above	Eve/never genital talc use - 73% of cases and 81.8% of controls reported no genital talc use - 27.0% of cases and 18.2% of controls reported any genital use	 1.0 **1.60 (1.18-2.15)**	
			-risk was adjusted for age, study center, tubal ligation, and use of other powders	Type of powder used - 26.4% of cases and 17.6% of controls reported use of talc - 0.2% of cases and 0.6% of controls reported use of cornstarch	 **1.69 (1.26-2.27)** 0.31 (0.03-3.01)	
			- subjects with no personal use were asked about use by husband - risk was adjusted as above	No personal use/use of talc by husband - 87.6% of cases and 92% of controls reported no husband talc use - 12.4% of cases and 8.0% of controls reported husbands did use talc	1 .0 1.52 (0.92-2.52)	
			-risk was adjusted for age, study center, tubal ligation, BMI, parity, OC use, and family history of breast/ ovarian cancer	Frequency of use per month for total of all uses in the genital area - 11.5% of cases and 5.4% of controls reported ≤30 uses/mo - 10.6% of cases and 9.8% of controls reported 30-39 uses/mo - 9.8% of cases and 2.9% of controls reported 40+ uses/mo	**2.21 (1.37-3.56)** 1.17 (0.78-1.76) 1.57 (0.80-3.10)	
			- risk was adjusted as above	Duration of talc use -9.9% of cases and 5.9% of controls reported <20 yrs talc use -5.8% of cases and 5.0% of controls reported 20-30 yrs talc use - 10.6% of cases and 7.1% of controls reported ≥30 yrs talc use - p-value for linear trend, excluding non-genital exposure - p-value for linear trend, including non-genital exposure	 **1.86 (1.16-3.00)** 1.33 (0.76-2.30) 1.44 (0.91-2.26) p = 0.477 p = 0.062	
			- same adjustments listed previously were made	Total applications - 9.2% of cases and 5.2% of controls applied talc <3000 x - 6.5% of cases and 5.4% of controls applied talc 3000 – 10,000 x - 6.5% of cases and 3.8% of controls applied talc >10,000 x - p-value for linear trend, excluding non-genital exposure - p-value for linear trend, including non-genital exposure	 **1.84 (1.12-3.30)** 1.43 (0.84-2.41) 1.43 (0.92-2.22) 0.164 0.472	

Table 9. Epidemiological Studies Evaluating Talc Exposure and Ovarian and Endometrial Cancer Risk

Talc/Composition	Population/ Geographical Area	Study/ Diagnosis Yrs	Study Description and Limitations	Findings	OR or RR (95% C.I.)	Reference
			- same adjustments listed previously were made	Age at first use of talc - 17.4% of cases and 12.8% of controls were <20 yrs old -6.5% of cases and 3.4% of controls were 20-25 yrs old - 2.3% of cases and 1.7% of controls were >25 yrs old - p-value for linear trend including non-exposed subjects	 **1.46 (1.03-2.07)** **1.87 (1.03-3.39)** 1.54 (0.64-3.72) p=0.504	
			- the tumors were stratified by histological subtype - risk was adjusted for age, BMI, primary relevance with breast or ovarian cancer, parity, OC use, tubal ligation, and study center		**OR**	
				Controls (523 total) - 81.8% never used talc perineally - 18.2% ever used talc perineally	1.0	
				Serous borderline tumors (86 total) - 73.3% never used talc perineally - 26.7% ever used talc perineally	1.38 (0.82 – 2.31)	
				Serous invasive tumors (229 total) - 68.6 % never used use talc perineally - 31.4% ever used talc perineally	**1.70 (1.22 – 2.39)**	
				Mucinous tumors (83 total) - 80.7% never used talc perineally - 19.3% ever used talc perineally	0.79 (0.44 – 1.40)	
				Endometroid/clear cell tumors (130 total) - 76.2% never used use talc perineally - 23.8% ever used talc perineally	1.04 (0.67 – 1.61)	
				Undifferentiated tumors (35 total) - 71.4% never used use talc perineally - 28.6% ever used talc perineally	1.44 (0.67 – 3.08)	
talc; purity and composition not specified	- 668 women in eastern MA and NH with invasive ovarian cancer (pop.-based) - 721 age-matched pop. controls - (Phase 2 of the NECC)	July 1998 – July 2003	- risk for ovarian cancer with talc use was determined -risk was adjusted for age, study center, parity, non-White race, and Jewish religion Limitations - exposure information was collected by self-report, introducing the possibility of misclassification - inability to directly compare anti-MUC1 antibody levels in cases and controls to calculate an OR	Talc use - 47.8% of cases and 47.6% of controls reported no talc use - 32.0% of cases and 28.2% of controls reported genital use of talc - 20.2% of cases and 24.1% of controls reported body use of talc only	**OR** 1.0 1.16 (0.90 – 1.49; P=0.25) 0.87 (0.66 - 1.15; P=0.33)	[146]

Table 9. Epidemiological Studies Evaluating Talc Exposure and Ovarian and Endometrial Cancer Risk

Talc/Composition	Population/ Geographical Area	Study/ Diagnosis Yrs	Study Description and Limitations	Findings	OR or RR (95% C.I.)	Reference
talc; purity and composition not specified	-210 women with ovarian cancer - 600 birth-, DNA type-,and menopausal status-matched controls (these are subjects included in the Nurses' Health Study that provided blood or buccal samples)	1989-2004	- examined whether an association between genital talc exposure and ovarian cancer risk is modified by variants of the *NAT2* and *GSTM1* genes and the *GSTT1* gene - subjects were asked about application of talcum, baby or deodorizing powder to the perineal area or sanitary napkins - risk with regular talc use and frequency of genital talc use was determined -risk was adjusted for the matching factors, duration of oral contraceptive use, parity, tubal ligation, BMI, and duration of PMH use Limitations - inability to detect interactions with certain combi-nations of genes and for specific histologic subtypes - loss of some detail due to the use of common expo-sure and covariate definitions (particularly for the NECC)	total epithelial cancer (210 cases; 600 controls) - 40% of cases and 39% of controls reported any history of genital talc use - 70.8% of cases and 76% of controls reported no regular genital talc use (1x/wk or more) - 29.2% of cases and 24% of controls reported regular genital talc use Frequency of genital talc use - 61.5% of cases and 64.6% of controls reported no frequency of genital talc use - 9.2% of cases and 11.4% of control reported use <1 x/wk - 11.3% of cases and 11.2% of controls reported use 1-6 x/wk - 18% of cases and 13% of controls reported daily genital talc use - P_{trend} for frequency of genital talc use	**OR** p= 0.79 1.0 1.24 (0.83 – 1.83; p = 0.15) 1.0 0.98 (0.54 – 1.79) 1.01 (0.57 – 1.79) 1.44 (0.88 – 2.37; p = 0.08) 0.18	[147]
				serous invasive ovarian cancer (93 cases; 263 controls) - 68.2% of cases and 73.8% of controls reported no regular genital talc use - 31.8% of cases and 26.3% of controls reported regular genital talc use Frequency of genital talc use - 61.4% of cases and 62.9% of controls reported no frequency of genital talc use - 6.8% of cases and 10.8% of control reported use <1 x/wk - 13.6% of cases and 10.4% of controls reported use 1-6 x/wk - 18.2% of cases and 15.8% of controls reported daily use - P_{trend} for frequency of genital talc use	1.0 1.48 (0.82-2.68) 1.0 0.79 (0.29-2.11) 1.64 (0.71-3.79) 1.34(0.65-2.76) 0.29	
	- 1175 women from MA and NH with epithelial ovarian cancer - 1202 age- and state-matched pop. controls - (pooled data from subjects in Phase I and Phase 2 of the NECC that provided a blood specimen)	May 1992 – July 2003	- subjects were asked about use of talcum, baby or deodorizing powder, type of use of the powder, fre-quency of use, number of years of use, brand used -risk was adjusted for the matching factors, duration of OC use, parity, tubal ligation, BMI, and duration of PMH use - risk with regular talc use and frequency of genital talc use was determined - risk was adjusted for age, study center, duration of OC use, parity, tubal ligation, BMI, duration of PMH use	total epithelial cancer (1175 cases; 1202 controls) - 29% of cases and 24% of controls reported any history of genital talc use - 73.2% of cases and 79.7% of controls reported no regular genital talc use (1x/wk or more) - 26.8% of cases and 20.3% of controls reported regular genital talc use Frequency of genital talc use - 70.9% of cases and 76.3% of controls reported no frequency of genital talc use - 2.3% of cases and 3.4% of control reported use <1 x/wk - 10.5% of cases and 8.0% of controls reported use 1-6 x/wk - 16.3% of cases and 12.3% of controls reported daily genital talc use - P_{trend} for frequency of genital talc use	**p = 0.003** 1.0 **1.40 (1.15 – 1.70**; **p < 0.001)** 1.0 0.72 (0.43 – 1.19) 1.33 (1.00 – 1.79) **1.41 (1.10 – 1.79**; **p = 0.006)** **0.002**	

Table 9. Epidemiological Studies Evaluating Talc Exposure and Ovarian and Endometrial Cancer Risk

Talc/Composition	Population/ Geographical Area	Study/ Diagnosis Yrs	Study Description and Limitations	Findings	OR or RR (95% C.I.)	Reference
				serous invasive ovarian cancer (450 cases; 1202 controls)		
				- 69.0% of cases and 79.7% of controls reported no regular genital talc use	1.0	
				- 31.0% of cases and 20.3% of controls reported genital talc use	**1.62 (1.26-2.09)**	
				- 66.6% of cases and 76.3% of controls reported no frequency of genital talc use	1.0	
				- 2.4% of cases and 3.4% of control reported use <1 x/wk	0.65 (0.32-1.33)	
				- 12.5% of cases and 8.0% of controls reported use 1-6 x/wk	**1.56 (1.08-2.26)**	
				- 18.5% of cases and 12.3% of controls reported daily use	**1.61 (1.18-2.20)**	
				- P_{trend} for frequency of genital talc use	**< 0.001**	
	- pooled analysis of the NECC study (Phase 1 and Phase 2 combined) and the 210 cases and 600 controls from the Nurses' Health Study (presented above)		- the researchers analyzed the interactions between talc use and genes in detoxification pathways	total epithelial cancer		
				- no regular genital talc use (1x/wk or more)	1.0	
				- any reported regular genital talc use	1.36 (1.13 – 1.63)	
				Frequency of genital talc use		
				- no frequency of genital talc use	1.0	
				- reported use <1 x/wk	0.82 (0.55 – 1.20)	
				- reported use 1-6 x/wk	1.26 (0.97 – 1.63)	
				- reported daily genital talc use	**1.41 (1.14 – 1.76)**	
				- P_{trend} for frequency of genital talc use	**<0.001**	
				serous invasive ovarian cancer		
				- reported no regular genital talc use	1.0	
				- reported any genital talc use	**1.60 (1.26 – 2.02)**	
				- no frequency of genital talc use	1.0	
				- 2 reported use <1 x/wk	0.70 (0.39 – 1.24)	
				- reported use 1-6 x/wk	**1.12 – 2.21)**	
				- reported daily use	**1.56 (1.17 – 2.08)**	
				- P_{trend} for frequency of genital talc use	**<0.001**	
				- there was no clear evidence of an interaction with *GSTM1* alone or *NAT2*		

Table 9. Epidemiological Studies Evaluating Talc Exposure and Ovarian and Endometrial Cancer Risk

Talc/Composition	Population/ Geographical Area	Study/ Diagnosis Yrs	Study Description and Limitations	Findings	OR or RR (95% C.I.)	Reference
talc; purity and composition not specified	"average risk" women from the 3 phases without hysterectomy or family history of cancer - 1098 women with invasive ovarian cancer (pop.-based) - 1363 age-matched pop. controls that were >40 yrs old (includes women from NECC phases 1 and 2, and the 897 Phase 3 cases and 857 Phase3 controls)	1992-2008 (all 3 phases) (Phase 3: 2003-2008)	- Phase 1[145] and Phase 2[146] described previously - reviewed relative risk for "average risk" women (excluded women at high risk for breast or ovarian cancer) **Limitations** - use of case-control data to develop the scoring system because of: - potential for recall bias - potential for selection bias - the calculation of only RR and not absolute risk	Long-term use of talc - 84.9% of cases and 88.8% of controls reported no long-term (10+ yr) talc use - 15.1% of cases and 11.2% of controls reported long-term talc use	**OR** 1.0 **1.42 (1.12 – 1.81**; P = 0.004)	[168]
talc; purity and composition not specified	- 609 women from Los Angeles county with ovarian cancer (pop. based) - 688 race/ethnicity- and age-matched controls	1998-2002	- subjects were asked questions about medical, gynecological, reproductive, and lifestyle histories, family history of breast or ovarian cancer, OC use; tubal ligation or hysterectomy; use of NSAIDs, and talc use - risk was adjusted for race, age, education, tubal ligation, cancer history, menopausal status, OC use, parity	Use of talc - 60% of cases and 68.2% of controls never used talc - 40% of cases and 31.8% of controls ever used talc - 18.5% of case and 15% of control talc users used talc in non-perineal area - 21.5% of case and 16.9% of control talc users used talc in perineal area	**RR** 1.0 **1.48 (1.15 – 1.91)** **1.43 (1.03 – 1.98)** **1.53 (1.13 – 2.09)**	[171]
				Frequency and duration of talc use - 5.8% of cases and 4.5% of controls used talc for ≤20 yrs and ≤10x/mo - 3.8% of cases and 4.4% of controls used talc for ≤20 yrs and >10 - ≤30x/mo - 3.5% of cases and 3.1% of controls used talc for ≤20 yrs and ≥30x/mo - 7.4% of cases and 7.1% of controls used talc for >20 yrs and ≤10x/mo - 8.4% of cases and 6.3% of controls used talc for >20 yrs and >10 - ≤30x/mo - 11.1% of cases and 6.5% of controls used talc for≥20 yrs and ≥30x/mo	 1.36 (0.79 – 2.32) 1.16 (0.63 – 2.12) 1.23 (0.63 – 2.41) 1.27 (0.80 – 2.01) 1.57 (0.99 – 2.50) **2.08 (1.34 – 3.23)**	
				Total number of talc uses - 8.1% of cases and 7.6% of controls used talc ≤5200 x - 7.6% of cases and 6.8% of controls used talc >5200- ≤15,600 x - 10.4% of cases and 8.9% of controls used talc >15,600- ≤52,000 x - 13.9% of cases and 8.6% of controls used talc >52,000 x	 1.2 (0.77 – 1.88) 1.38 (0.87 – 2.20) 1.34 (0.89 – 2.02) **1.99 (1.34 – 2.96)**	

Table 9. Epidemiological Studies Evaluating Talc Exposure and Ovarian and Endometrial Cancer Risk

Talc/Composition	Population/ Geographical Area	Study/ Diagnosis Yrs	Study Description and Limitations	Findings	OR or RR (95% C.I.)	Reference
			- examined risk based on total number of talc uses before/after 1975	Before 1975		
				- 4.0% of cases and 5.1% of controls used talc ≤5200 x	0.84 (0.47 – 1.51)	
				- 4.8% of cases and 4.2% of controls used talc >5200- ≤15,600 x	1.41 (0.79 – 2.53)	
				- 8.1% of cases and 6.5% of controls used talc >15,600- ≤52,000 x	1.45 (0.91 – 2.31)	
				- 13.6% of cases and 8.4% of controls used talc >52,000 x	**1.93 (1.29 – 2.88)**	
				After 1975		
				- 4.1% of cases and 2.5% of controls used talc ≤5200 x	1.95 (0.98 – 3.89)	
				- 2.8% of cases and 2.6% of controls used talc >5200- ≤15,600 x	1.17 (0.56 – 2.48)	
				- 2.6% of cases and 2.5% of controls used talc >15,600	0.98 (0.45 – 2.13)	
talc; purity and composition not specified	- 83 African-American and 550 white women from 48 counties of NC with epithelial ovarian cancer - 134 African-American and 533 white age-, race/ethnicity-, and geographical region-matched controls	1999-2008	- examined risk factors in African-American vs. white women, including use of talc -risk was adjusted for age Limitations - relatively small sample size of African-American women - modest sample size precluded conducting analyses within subgroups - participation bias	African-American women	**OR**	160
				- 54.2% of cases and 56.0%of controls reported no talc use	1.0	
				- 45.8% of cases and 44.0% of controls reported any talc use	1.19 (0.68 – 2.09)	
				White women		
				- 59.6% of cases and 61.0%of controls reported no talc use	1.0	
				- 40.4% of cases and 39.0% of controls reported any talc use	1.04 (0.82 – 1.33)	
talc; purity and composition not specified	- 256 women from 22 central CA counties with epithelial ovarian cancer (pop.-based) - 1122 age- and ethnicity-matched controls	2000-2001	- subjects were asked questions on menstrual, reproductive, gynecological, surgical, and family cancer histories, use of exogenous hormones - examined risk with talc use based on frequency, duration, and cumulative use and timing of use - numbers were adjusted based on available data - risk was adjusted for age, race/ethnicity, OC use, and breastfeeding Limitations - relatively small sample size - low response fraction - possible recall bias - inability to exclude use during non-ovulatory periods or and post-tubal ligation or hysterectomy - inability to differentiate among formulations used	Ever/never use of talc	**OR**	159
				- 57.4% of cases and 62.9% of controls never used talc	1.0	
				- 42.6% of cases and 37.1% of controls ever used talc	**1.37 (1.02 – 1.85)**	
				Frequency of use		
				- 13.4% of cases and 12.5% of controls used talc rarely to several times/mo	1.34 (0.87 – 2.08)	
				- 12.4% of cases and 13.2%of controls used talc 1-3x/wk	1.16 (0.74 – 1.81)	
				- 16.5% of cases and 11.1% of controls used talc 4-7x/wk	**1.74 (1.14 – 2.64)**	
				- P_{trend}	**0.015**	
				Duration of use		
				- 7.4% of cases and 9.2% of controls used talc for ≤3 yrs	1.01 (0.58 – 1.76)	
				- 13.2% of cases and 9.1% of controls used talc for 4-12 yrs	**1.86 (1.16 – 2.98)**	
				- 11.9% of cases and 9.4% of controls used talc for 13-30 yrs	1.45 (0.90 – 2.32)	
				- 8.6% of cases and 8.1% of controls used talc for >30 yrs	1.22 (0.72 – 2.08)	
				- P_{trend}	**0.045**	
				Cumulative use (frequency x duration)		
				- 7.4% of cases and 8.8% of controls were in the 1st quartile (lowest exposure)	1.03 (0.59 – 1.80)	
				- 11.5% of cases and 8.8% of controls were in 2nd quartile	**1.81 (1.10 – 2.97)**	
				- 14.0% of cases and 9.9% of controls were in 3rd quartile	**1.74 (1.11 – 2.73)**	
				- 8.2% of cases and 8.1%of controls were in 4th quartile (highest exposure)	1.06 (0.62 – 1.83)	
				- P_{trend}	0.051	

Table 9. Epidemiological Studies Evaluating Talc Exposure and Ovarian and Endometrial Cancer Risk

Talc/Composition	Population/ Geographical Area	Study/ Diagnosis Yrs	Study Description and Limitations	Findings	OR or RR (95% C.I.)	Reference
				Year of first use		
				- 21.5% of cases and 19.4% of controls before /during 1975	1.22 (0.84 – 1.77)	
				- 19.4% of cases and 15.0% of controls after 1975	**1.92 (1.27 – 2.91)**	
				Age at first use		
				- 12.4% of cases and 16.0% of controls were <20 yrs old	0.95 (0.61 – 1.48)	
				- 10.7% of cases and 5.8% of controls were 20-24 yrs old	**2.41 (1.43 – 4.09)**	
				- 17.8% of cases and 12.6% of controls were ≥25 yrs old	**1.80 (1.19 – 2.73)**	
				First use before or after first birth		
				- 18.8% of cases and 23.8% of controls prior to first birth	0.98 (0.64 – 1.48)	
				- 22.0% of cases and 10.6% of controls after first birth	**2.51 (1.63 – 3.87)**	
				Yrs since last use		
				- 13.2% of cases and 12.5%of controls are current users	1.27 (0.81 – 1.98)	
				- 11.2% of cases and 5.8% of controls used talc 1-2 yrs ago	**2.40 (1.43 – 4.05)**	
				- 8.3% of cases and 7.8% of controls used talc 3-20 yrs ago	1.57 (0.90 – 2.73)	
				- 8.3%of cases and 8.3% of controls used talc >20 yrs ago	1.13 (0.66 – 1.94)	
talc; purity and composition not specified	- 1576 women from Australia with epithelial ovarian cancer - 1509 age- and state-of-residence-matched pop. controls	Jan 2002 – Sept 2005	- subjects were asked questions about medical and surgical and family cancer histories, lifestyle habits, reproductive factors, hysterectomy/tubal ligation, and talc use - risk was adjusted for age, education, parity, and OC use Limitations - low response rate for controls, which could result in selection bias - medical histories were self-reported	- 54% of cases and 57% of controls reported never using talc in the perineal region - 46% of cases and 43% of controls reported ever using talc in the perineal region Duration of use (with no ligation/hysterectomy) - 13% of cases and 13% of controls reported 0-10 yrs talc use - 14% of cases and 15% of controls reported >10-25 yrs talc use - 19% of cases and 16% of controls reported >25 yrs talc use - P_{trend}	**OR** 1.0 **1.17 (1.01 – 1.36)** 1.13 (0.90 – 1.41) 1.08 (0.87 – 1.34) **1.29 (1.04 – 1.58)** **0.021**	158
talc; purity and composition not specified	- 230 women with serous ovarian tumors and 133 women with benign mucinous tumors in Australia - 752 pop. controls	2002 - 2005	- examined the association between use of talc and the risk of benign mucinous and serous ovarian tumors- - risk was adjusted for age, state of residence, education, parity, hormonal contraceptive use, hysterectomy, and smoking status - **OR for each factor examined is presented in the order mucinous, serous, combined**	- 56% of mucinous cases, 55% of serous cases, and 56% of controls reported no talc use in the perineal region - 44% of mucinous cases, 45% of serous cases, and 44% of controls reported talc use in the perineal region Amount of talc used in the perineal region - 11% of mucinous cases, 6% of serous cases, and 10% of controls reported minimal talc use in the perineal region - 14% of mucinous cases, 9% of serous cases, and 11% of controls reported moderate talc use in the perineal region - 18% of mucinous cases, 27% of serous cases, and 21% of controls reported substantial talc use in the perineal region	**OR** 1.0 1.19 (0.80 – 1.76) 1.04 (0.75 – 1.43) 1.10 (0.84 – 1.45) 1.02 (0.53 – 1.98) 0.70 (0.37 – 1.30) 0.85 (0.52 – 1.38) 1.57 (0.87 – 2.84) 0.85 (0.49 – 1.48) 1.05 (0.68 – 1.64) 0.98 (0.58 – 1.66) 1.21 (0.82 – 1.79) 1.16 (0.83 – 1.62)	154

Table 9. Epidemiological Studies Evaluating Talc Exposure and Ovarian and Endometrial Cancer Risk

Talc/Composition	Population/ Geographical Area	Study/ Diagnosis Yrs	Study Description and Limitations	Findings	OR or RR (95% C.I.)	Reference
				P_{trend} for:		
				mucinous tumors	0.9	
				serous tumors	0.2	
				combined	0.3	
dusting powder, many contain talc	- 812 women from 13 counties in western WA state with epithelial ovarian cancer (pop.-based) - 1313 age-matched pop. controls	Jan 2002 – Dec 2005	- subjects were asked questions about lifestyle, medical, reproductive, and contraceptive histories, use of contraceptive and menopausal hormone preparations, and genital powder exposure - risk was adjusted for age, year of diagnosis, residence, parity, and hormonal contraception - subjects were asked to report the types of powder(s) used after bathing, including talcum, baby, cornstarch, deodorant, body/bath, and other or unknown		**OR**	[165]
				- 86.2% of cases and 88.5% of control reported never using powder after bathing	1.0	
				- 13.8% of cases and 11.5% of controls reported use of powder after bathing	1.27 (0.97 – 1.66)	
				- 93.2% of cases and 91.7% of controls did not use powder on sanitary napkins	1.0	
				- 6.8% of cases and 8.3% of controls used powder on sanitary napkins	0.82 (0.58 – 1.16)	
				- 77.7% of cases and 72.6% of controls (that were diaphragm users) did not use powder on diaphragms	1.0	
				- 22.3% of cases and 27.4% of controls (that were diaphragm users) used powder on diaphragms	0.72 (0.48 – 1.10)	
				- 89.6% of cases and 90.5% of controls did not use vaginal deodorant spray	1.0	
				- 10.4% of cases and 9.5% of controls used vaginal deodorant spray	1.15 (0.85 – 1.56)	
			- risk was evaluated based on duration, frequency, and timing of use - risk was adjusted as above	- 86.2% of cases and 88.5% of controls never used powder	1.0	
				Duration of use		
				- 4.1% of cases and 2.9% of controls used powder for 1-9.9 yrs	1.39 (0.85 – 2.28)	
				- 3.6% of cases and 2.7% of controls used powder for 10-19.9 yrs	1.46 (0.87 – 2.45)	
				- 3.7% of cases and 3.0% of controls used powder for 20-34.9 yrs	1.28 (0.78 – 2.10)	
				- 2.3% of cases and 2.9% of controls used powder 35+ yrs	0.91 (0.51 – 1.62)	
				Lifetime number of applications		
				- 3.2% of cases and 2.7% of controls reported 1-1599 applications of powder	1.21 (0.71 – 2.06)	
				- 5.6% of cases and 2.8% of controls reported 1600-4799 applications of powder	**2.08 (1.32 – 3.27)**	
				- 2.5% of cases and 3.0% of controls reported 4800-9999 applications of powder	0.87 (0.50 – 1.53)	
				- 2.2% of cases and 2.8% of controls reported 10,000+ applications of powder	0.87 (0.48 – 1.57)	
				Age at first use		
				- 1.5% of cases and 2.1% of controls were <15 yrs old	0.74 (0.37 – 1.50)	
				- 3.3% of cases and 2.7% of controls were 15-20 yrs old	1.20 (0.71 – 2.03)	
				- 3.9% of cases and 3.3% of controls were 20-30 yrs old	1.25 (0.77 – 2.03)	
				- 5.1% of cases and 3.4% of controls were 30+ yrs old	**1.69 (1.08 – 2.64)**	

Table 9. Epidemiological Studies Evaluating Talc Exposure and Ovarian and Endometrial Cancer Risk

Talc/Composition	Population/ Geographical Area	Study/ Diagnosis Yrs	Study Description and Limitations	Findings	OR or RR (95% C.I.)	Reference
				Time since first use		
				- 5.2% of cases and 3.1% of controls reported ≤25 yrs	**1.77 (1.12 – 2.78)**	
				- 4.7% of cases and 3.1% of controls reported 25-38 yrs	1.46 (0.91 – 2.32)	
				- 2.0% of cases and 2.6% of controls reported 38-45 yrs	0.87 (0.47 – 1.61)	
				- 2.0% of cases and 2.7% of controls reported 45+ yrs	0.82 (0.44 – 1.52)	
				Age at last use		
				- 3.1% of cases and 2.5% of controls were <35 yrs old	1.14 (0.66 – 1.97)	
				- 4.3% of cases and 3.0% of controls were 35-50 yrs old	1.42 (0.88 – 2.31)	
				- 3.1% of cases and 2.7% of controls were 50-60 yrs old	1.25 (0.73 – 2.13)	
				- 3.2% of cases and 3.3% of controls were 60+ yrs old	1.21 (0.72 – 2.05)	
				Time since last use		
				- 6.4% of cases and 5.3% of controls are current users	1.30 (0.89 – 1.91)	
				- 3.2% of cases and 2.0% of controls reported ≤12 yrs	1.74 (0.98 – 3.10)	
				- 1.7% of cases and 2.16% of controls reported 13-23 yrs	0.85 (0.44 – 1.66)	
				- 2.3% of cases and 2.1% of controls reported 24+ yrs	1.13 (0.61 – 2.08)	
				Calendar year of first use		
				- 2.3% of cases and 3.0% of controls reported ≤1959	0.86 (0.48 – 1.53)	
				- 3.0% of cases and 2.9% of controls reported 1960-1969	1.10 (0.65 – 1.89)	
				- 3.2% of cases and 2.9% of controls reported 1970-1979	1.12 (0.66 – 1.89)	
				- 5.3% of cases and 2.7% of controls reported 1980+	**2.03 (1.28 – 3.24)**	
talc; purity and composition not specified	- 902 women from Western PA, Eastern OH, and Western NY in the HOPE study with primary epithelial ovarian, peritoneal, or Fallopian tube cancer - 1802 age group- and geography-matched controls	2003 - 2008	- subjects were asked about reproductive, gynecological, and medical histories, lifestyle, family medical history, whether they ever sought medical attention for fertility issues, use of fertility drugs - risk was adjusted for race, education, geographical site, BMI, family breast and ovarian cancer history, tubal ligation, OC use, number of live births, breast-feeding, age at menarche, menopausal status, perineal talc use, and HRT use Limitation - inability to identify infertile women that never sought medical attention - reliance on self-reported fertility drug use	Ever/never use of talc - 72.4% of cases and 79.1% of controls reported never using talc in the perineal region - 27.6% of cases and 20.9% of controls reported ever using talc in the perineal region	**OR** 1.0 **1.40 (1.16 – 1.69)**	156
EFFECT OF TUBAL LIGATION OR HYSTERECTOMY ON RISK						
HOSPITAL-BASED CASES/HOSPITAL-BASED CONTROLS						
talc; purity and composition not specified	- 211/499 patients at Roswell Park Cancer Institute with epithelial ovarian cancer had tubal ligation or hysterectomy - 261/755 age at diagnosis-matched hospital controls had tubal ligation or hysterectomy	Oct 1982 – Oct 1995	- described previously		**OR**	170
				- 48.2% of cases and 42% of controls used talc and did not have tubal ligation or hysterectomy	1.2 (0.8 – 1.6)	
				- 47.4% of cases and 49.8% of controls used talc and had tubal ligation	0.8 (0.5 – 1.2)	
				- 52% of cases and 60% of controls used talc and had a hysterectomy	0.9 (0.4 – 2.2)	

Table 9. Epidemiological Studies Evaluating Talc Exposure and Ovarian and Endometrial Cancer Risk

Talc/Composition	Population/ Geographical Area	Study/ Diagnosis Yrs	Study Description and Limitations	Findings	OR or RR (95% C.I.)	Reference
	- 135 cases had undergone tubal ligation or hysterectomy within 5 yrs of the diagnosis			- risk excluding these cases	0.9 (0.4 – 2.2)	
			HOSPITAL-BASED CASES/HOSPITAL- and POPULATION-BASED CONTROLS			
talcum powder; purity and composition not specified	- 188 women from northern California with primary epithelial cancer (from 7 hospitals) - 280 matched hospital controls - 259 matched pop. controls	Jan 1983 – Dec 1985	- described previously	- 48% of cases and 54% of controls did not use talc - 52% of cases and 46% of controls used talc - 37% of cases and 34% of controls did not use talc and had no ligation or hysterectomy - 38% of cases and 28% of controls used talc and had no ligation or hysterectomy - 11% of cases and 20% of controls did not use talc and had ligation or hysterectomy	**OR** 1.0 1.37 (0.97-1.96) 1.0 1.33 (0.58-2.01) *0.50 (0.29 – 0.88; p<0.01)*	[169]
			POPULATION-BASED CASES/POPULATION-BASED CONTROLS			
talc; purity and composition not specified	- 450 women in the Boston area with epithelial ovarian cancer - 454 pop. matched controls (study group combined [143] and [151]	Nov 1978 – Sept 1987	- described previously	- 86.6% of cases and 87.7% of controls had no ligation or hysterectomy were talc users - 13.4% of cases and 12.3% of controls had tubal ligation or hysterectomy and were talc users - 90.0% of cases and 84% of controls had no ligation or hysterectomy were non-talc users - 10% of cases and 16% of controls had tubal ligation or hysterectomy and were non-talc users	**OR** 1 1.1 (0.6-2.1) 1 *0.6 (0.4-1.0; P=0.04*)	[144]
talc; purity and composition not specified	- 307 registered nurses in 11 states with epithelial ovarian (Nurses' Health Study; described previously)	1982 - 1996	-described previously	- risk of ever talc users that had tubal ligation compared to never talc users - risk for ever talc use when excluding those with history of tubal ligation or hysterectomy	**RR** 0.97 (0.71-1.32) 1.15 (0.89-1.49)	[148]
talc, purity and composition not specified	- 450 women from Toronto and Ontario, Canada with epithelial ovarian cancer (pop.-based) - 564 age-matched pop.-based controls	Nov 1989 – Oct 1992	- study was described previously - risk with yrs of after-bath talc use and tubal ligation/hysterectomy was examined - risk was adjusted as described previously	case mean was 28.4 yrs and control mean was 26.9 yrs of after-bath talc use before ligation/hysterectomy - case mean was 4.5 yrs and control mean was 8.5 yrs of after-bath talc use after ligation/hysterectomy	**OR** 1.11 (0.99 – 1.24) 1.03 (0.82 – 1.29)	[140]
talc; purity and composition not specified	- 256 women from 22 central CA counties with epithelial ovarian cancer (pop.-based) - 1122 age- and ethnicity-matched controls	2000-2001	- study was described previously - risk of talc use and hysterectomy or tubal ligation was examined - risk was adjusted as described previously	Tubal Ligation - 57.4% of cases and 65.8% of controls did not have tubal ligation and never used talc - 42.6% of cases and 34.2% of controls did not have tubal ligation and ever used talc - 56.9% of cases and 54.9% of controls did have tubal ligation and never used talc - 43.1% of cases and 45.1% of controls did have tubal ligation and ever used talc	**OR** 1.0 **1.54 (1.10 – 2.16)** 1.0 0.88 (0.46 – 1.68)	[159]

Table 9. Epidemiological Studies Evaluating Talc Exposure and Ovarian and Endometrial Cancer Risk

Talc/Composition	Population/ Geographical Area	Study/ Diagnosis Yrs	Study Description and Limitations	Findings	OR or RR (95% C.I.)	Reference
				Hysterectomy - 59.5% of cases and 63.7% of controls did not have a hysterectomy and never used talc - 40.5% of cases and 36.3% of controls did not a hysterectomy and ever used talc - 50.0%% of cases and 58.8% of controls did have a hysterectomy and never used talc - 50.0% of cases and 41.2% of controls did have a hysterectomy and ever used talc	1.0 1.33 (0.95 – 1.87) 1.0 1.79 (0.91 – 3.52)	
talc; purity and composition not specified	- 1576 women from Australia with epithelial ovarian cancer - 1509 age- and state of residence-matched pop. controls	Jan 2002 – Sept 2005	- study was described previously - risk was examined with number of years talc use post-hysterectomy or tubal ligation	- 88% cases and 88% controls reported no talc use post-surgery - 3% of cases and 3% of controls reported 0-10 yrs talc use - 6% of cases and 6% of controls reported >10-25 yrs talc use - 3% of cases and 3% of controls reported >25 yrs talc use - trend	**OR** 1.0 1.08 (0.71 – 1.62) 1.14 (0.82 – 1.57) 1.00 (0.64 – 1.51) P = 0.61	158
OCCUPATIONAL EXPOSURE AND RISK						
talc used as a coating agent for paper; purity and composition not specified; workers may also have been exposed to asbestos and/or other dusts	- 46 female pulp and paper workers from 10 mills in Norway with epithelial ovarian cancer - 179 age-matched controls identified by incidence density sampling	1953 – 1999 (mostly from 1980+)	-risk estimates specific to mill, work department, agent, and time period - indicators of occupational exposure included duration of employment, time since 1st exposure to diagnosis, and year of 1st exposure - subjects were asked about occupational history, possible household asbestos exposure, fertility pattern, age at menarche and menopause, OC use, family cancer history, and other personal factors Limitations - there were many missing values for the question on hygienic talc use	- 50% of cases and 52% of controls reported never being exposed to talc - 50% of cases and 48% of controls reported ever being exposed to talc	**OR** 1.0 1.10 (0.56 – 2.18)	157
talc; purity and composition not specified	- 275 women in the Washington, D.C. area with epithelial ovarian cancer (hospital-based) - 316 hospital age- and race-matched controls	1978-1981	- RR of ovarian cancer was determined according to length of occupational exposure to talc within various occupations - exposure = # of yrs in the job assigned probabilities of definite, probable, and possible exposure - risk was adjusted for employment, race, age, parity, and gynecologic surgery Limitation - no information was available on individual exposure characteristics, leading to the assumption that it was homogenous within job title	- 95.7% of cases and 90.2% of controls were not exposed - 1.8% of cases and 3.5% of controls were exposed for <5 yrs - 0.7% of cases and 2.5% of controls were exposed for 5-9 yrs - 1.8% of cases and 3.8% of controls were exposed for 10+ yrs	**RR** 1.0 0.5 (0.1 – 1.4) 0.3 (0.1 – 1.4) 0.5 (0.2 – 1.5)	153

Table 9. Epidemiological Studies Evaluating Talc Exposure and Ovarian and Endometrial Cancer Risk

Talc/Composition	Population/ Geographical Area	Study/ Diagnosis Yrs	Study Description and Limitations	Findings	OR or RR (95% C.I.)	Reference
			ENDOMETRIAL CANCER			
talc; purity and composition not specified	- 599 women from the Nurses' Health Study with invasive endometrial adenocarcinoma	1982-2004	- described previously - risk was assessed among all women - risk was adjusted for age, parity age at last birth, menarche, and menopause, OC and PMH use, BMI, smoking, diabetes, menopausal status, and family history of uterine cancer Limitations - single assessment of talc use (ever/never) - did not assess duration of talc use	Use of talc - 55.8% of cases reported never using talc perineally - 44.2% of cases reported ever using talc perineally - 66.3% of cases reported no regular perineal use of talc (1+/wk) - 33.7% of cases reported regular perineal use of talc	**IRR** 1.0 1.13 (0.96 – 1.33) 1.0 1.17 (0.99 – 1.40)	[155]
			- risk assessed in premenopausal women (70 cases [11.7% of all women] were premenopausal) - risk was adjusted for age, parity, age at last birth, age at menarche, OC use, BMI, smoking, diabetes, and family history of uterine cancer	Talc use in premenopausal women - 67.1% of cases reported never using talc perineally - 32.9% of cases reported ever using talc perineally - 75.7% of cases reported no regular perineal use of talc (1+/wk) - 24.3% of cases reported regular perineal use of talc	 1.0 0.69 (0.40 – 1.19) 1.0 0.77 (0.42 – 1.39)	
			- risk was assessed among post-menopausal women (529 cases [88.3% of all women] were post-menopausal) - risk estimate was multivariate (as for all women) or adjusted by age	Talc use in post-menopausal women - 54.3% of cases reported never using talc perineally - 45.7% of cases reported ever using talc perineally - 65% of cases reported no regular perineal use of talc (1+/wk) - 35% of cases reported regular perineal use of talc	Multivariate 1.0 **1.21 (1.02 – 1.44)** 1.0 **1.24 (1.03 – 1.48)**	
				as above	Age-Adjusted 1.0 **1.38 (1.16 – 1.64)** 1.0 **1.40 ((1.17 – 1.68)**	
			- risk in post-menopausal women based on frequency of use and application to sanitary napkins -risk was adjusted multivariate (as above) or by age	Frequency of Use 10.8% of cases reported perineal use of talc <1x/wk 16.4% of cases reported perineal use of talc 1-6x/wk 18.5% of cases reported daily use of talc	Multivariate 1.09 (0.81 – 1.45) 1.28 (1.00 – 1.63) 1.24 (0.98 – 1.56)	
				as above	Age-Adjusted 1.22 (0.91 – 1.62) **1.40 (1.10 – 1.79)** **1.49 (1.18 – 1.87)**	
				Sanitary napkin talc use - 85.7% of cases never used talc on sanitary napkins - 14.3% of controls used talc on sanitary napkins	Multivariate 1.0 0.98 (0.75 – 1.27)	
				as above	Age-Adjusted 1.0 1.04 (0.80 – 1.35)	

Table 9. Epidemiological Studies Evaluating Talc Exposure and Ovarian and Endometrial Cancer Risk

Talc/Composition	Population/ Geographical Area	Study/ Diagnosis Yrs	Study Description and Limitations	Findings	OR or RR (95% C.I.)	Reference
talc; purity and composition not specified	- 1399 women in Australia with primary endometrial cancer (pop. based) - 740 controls	July 2005-Dec 2007	- subjects were asked about medical, hormonal, and reproductive histories, other potential risk factors, and talc use - risk was adjusted for age, age at menarche, parity, pregnancies, OC use, hormone replacement therapy, BMI, and smoking status Limitation - non-participation, in that those who did not participate may have more advanced disease - non-differential misclassification of talc use - residual confounding may have distorted the results	Use of talc - 40.7% of cases and 41.5% of controls never used talc - 59.3% of cases and 58.5% of controls ever perineal talc use - 71.9% of cases and 70.4% of controls reported ever upper body use Frequency of any perineal talc use - 5.1% of cases and 7.1% of controls reported infrequent use -9.1% of cases and 8.5% of controls reported use a few times/mo - 11% of cases and 7.1% of controls reported use a few times/wk - 33.3% of cases and 35% of controls reported daily use - P_{trend} (including non-talc users)	**OR** 1.0 0.88 (0.68 – 1.14) 0.9 (0.71 – 1.14) 0.68 (0.40 – 1.15) 0.88 (0.56- 1.41) 1.32 (0.82 – 1.11) 0.82 (0.61 – 1.14) 0.44	[161]
				Duration of any perineal talc use - 19% of cases and 16% of controls reported 1-20 yrs use - 15.6% of cases and 11.2% of controls reported 21-40 yrs use - 18.2% of cases and 18.8% of controls reported 41-60 yrs use - 5% of cases and 11.2% of controls reported 61-80 yrs use - P_{trend} (including non-talc users)	1.21 (0.84 – 1.75) 1.1 (0.73 – 1.65) 0.82 (0.57 – 1.17) 0.25 (0.15 – 0.43) *<0.001*	
				Frequency of any upper body talc use - 4.4% of cases and 6.6% of controls reported infrequent use - 6.9% of cases and 9.1% of controls reported use a few times/mo - 15.4% of cases and 10.1% of controls reported use a few times/wk - 45.1% of cases and 44.3% of controls reported daily use - trend (including non-talc users)	0.57 (0.35 – 0.93) 0.58 (0.38 – 0.89) **1.45 (1.01 – 2.09)** 0.9 (0.70 – 1.16)	
				Duration of any upper body talc use - 20.7% of cases and 19.4% of controls reported 1-20 yrs use - 16.9% of cases and 12.8% of controls reported 21-40 yrs use - 23.6% of cases and 22.6% of controls reported 41-60 yrs use - 9.3% of cases and 14% of controls reported 61-80 yrs use -P_{trend} (including non-talc users)	1.16 (0.85 – 1.58) 1.12 (0.79 – 1.59) 0.86 (0.64 – 1.17) 0.41 (0.28 – 0.61) *0.001*	
			- risk was evaluated using a "composite" variable that multiplied frequency of talc use by years of use to assess lifetime exposure -resulting values were categorized as low (<5 yrs); moderate (5-20 yrs); high (20-40 yrs); very high use (40+ yrs)	Perineal talc use - 16.6% of cases and 15.6% of controls had low lifetime use - 12% of cases and 11.4% of controls had moderate lifetime use - 11.2% of cases and 8.6% of controls had high lifetime use -17.2% of cases and 20.9% of controls had very high lifetime use - P_{trend} (including non-talc users)	0.95 (0.65 – 1.37) 1.0 (0.66 – 1.54) 1.01 (0.64 – 1.60) 0.67 (0.47 – 0.96) 0.07	
				Upper body talc use - 13.5% of cases and 17% of controls had low lifetime use - 14.7% of cases and 13% of controls had moderate lifetime use - 16.5% of cases and 12.6% of controls had high lifetime use -25.8% of cases and 25.9% of controls had very high lifetime use - P_{trend} (including non-talc users)	0.72 (0.52 – 1.01) 1.25 (0.87 – 1.78) 1.07 (0.75 – 1.52) 0.8 (0.59 – 1.07) 0.49	

Abbreviations: BMI = body mass index; C.I. = confidence interval; CLE = cumulative lifetime exposure; HOPE = Hormone and Ovarian Cancer Prediction; HRT = hormone replacement therapy; IRR = incidence rate ratios; NECC – New England Case Control; NSAID = non-steroidal anti-inflammatory drug; OC = oral contraceptive; OR = odds ratio; PMH = postmenopausal hormone; pop. = population; RR = relative risk

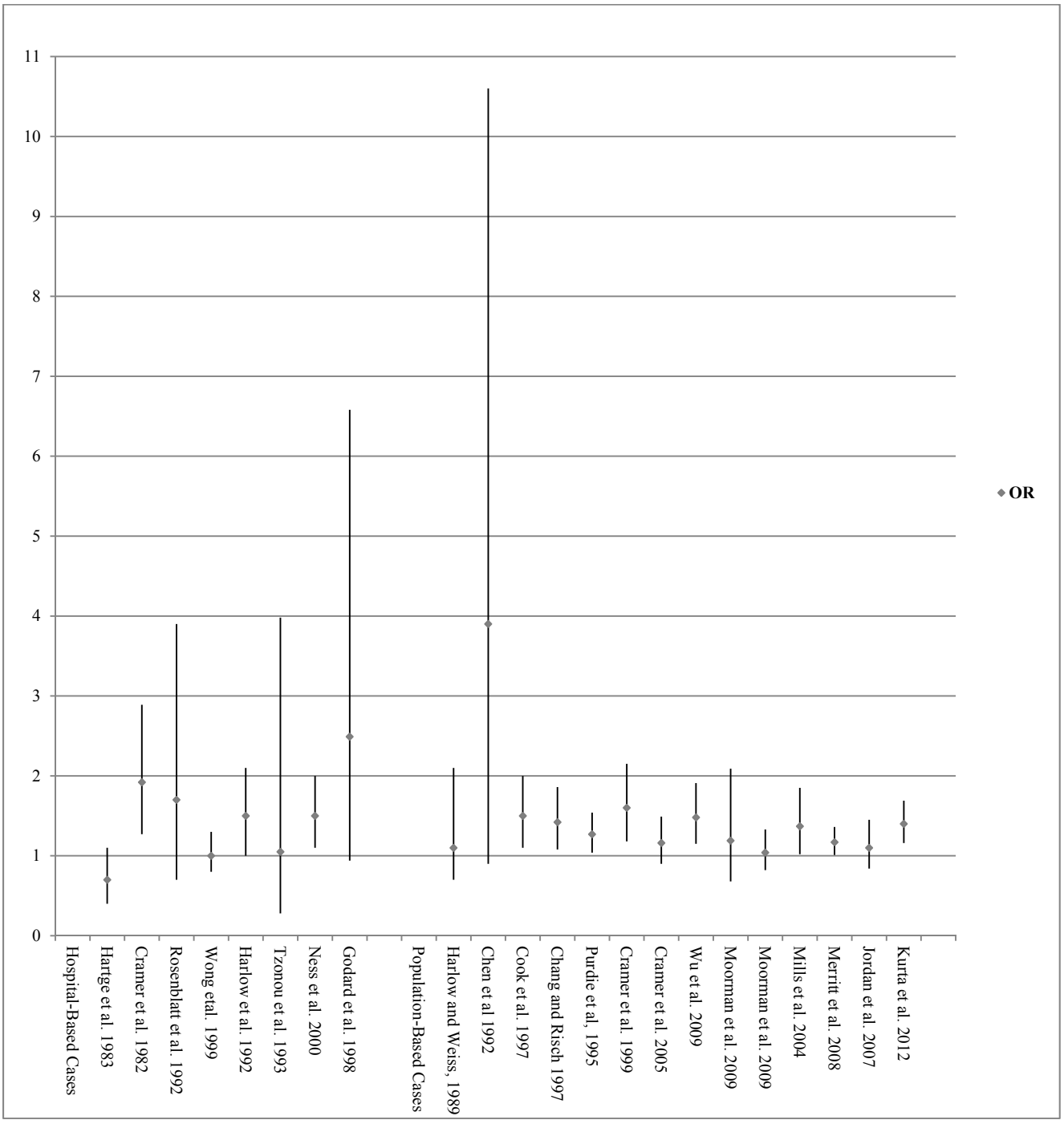
Bolded text was used to highlight statistically significant increases
Italicized text was used to highlight statistically significant decreases

Table 10. Summary of case-control studies evaluating ovarian cancer risk for "ever" use of talc in the perineal area

# Case subject	*# Control subjects*	*Study Years*	*P/H cases*	*OR or RR*	*95% C.I.*	*Reference*
			HOSPITAL-BASED CASES			
135	171	1974-1977	H	0.7	0.4 – 1.1	[152]
215	215	1978-1981	H	**1.92**	**1.27 – 2.89**	[143]
77	46	1981-1985	H	1.7	0.7 - 3.9	[164]
499	755	1982-1995	H	1.0	0.8 – 1.3	[170]
235	239	1984-1987	H	1.5	1.0 – 2.1	[151]
189	200	1989-1991	H	1.05	0.28 – 3.98	[167]
767	1367	1994-1998	H	**1.5**	**1.1 – 2.0**	[162]
153	101	1995-1996	H	2.49	0.94 – 6.58	[149]
			POPULATION-BASED CASES			
116	158	1980-1985	P	1.1	0.7 – 2.1	[150]
112	224	1984-1986	P	3.9	0.9 – 10.6	[141]
313	422	1986-1988	P	**1.5**	**1.1 – 2.0**	[142]
450	564	1989-1992	P	**1.42**	**1.08 – 1.86**	[140]
824	860	1990-1993	P	**1.27**	**1.04 – 1.54**	[163]
563	523	1992-1997	P	**1.60**	**1.18 – 2.15**	[145]
668	721	1998-2003	P	1.16	0.90 – 1.49	[146]
609	688	1998-2002	P	**1.48**	**1.15 – 1.91**	[171]
83	134	1998-2008	P	1.19	0.68 – 2.09	[160]
550	553	1998-2008	P	1.04	0.82 – 1.33	[160]
256	1122	2000-2001	P	**1.37**	**1.02 – 1.85**	[159]
1576	1509	2002-2005	P	**1.17**	**1.01 – 1.36**	[158]
363	752	2002-2005	P	1.10	0.84 – 1.45	[154]
902	1802	2003-2008	P	**1.40**	**1.16 – 1.69**	[156]

CHARTS

Chart 1. Odds ratio and confidence intervals in case-control studies evaluating ovarian cancer risk for "ever" use of talc in the perineal area



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