



Review Section

BIOLOGICAL EFFECTS OF COSMETIC TALC

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Summary—A review of the literature reveals two primary issues: (1) a weak, but not causal, association of hygienic use of cosmetic talc and ovarian cancer; (2) lung changes in animals exposed to talc aerosol concentrations that resulted in lung overload. The evidentiary weight of the most significant of the epidemiological and laboratory studies and their biological significance for human risk assessment are briefly discussed. Publications describing granulomatous lesions attributed to talc on surgical gloves, and consequences of accidental inhalation of baby powder by infants are also reviewed. The literature reviewed does not provide any convincing evidence that pure cosmetic talc, when used as intended, presents a health risk to the human consumer.

Introduction

Hildick-Smith (1976 and 1977) and Lord (1978) have reviewed the older literature relating to talc. Hildick-Smith concluded that the normal use of cosmetic-grade talc does not present a health hazard. In his review of biological effects of talc in laboratory animals, Lord found the mineral to be fibrogenic but he observed that the fibrotic response was a function of the administered dose and 'that there are levels of exposure that are tolerable'. In none of the studies reviewed was there any indication of neoplasia.

A computer search of the literature of the last 15 years provided well over 700 titles/abstracts on various aspects of talc and talc issues. Of these, 137 were selected for review as they describe epidemiological, clinical and relevant animal and *in vitro* studies. Papers on exposures to *industrial* talc, often containing more toxic impurities, such as asbestos fibres, were excluded as irrelevant to the safety of *cosmetic* talc when used as intended. Studies of lesions following intravenous injection of talc by drug addicts were also excluded because of unintended use. The term 'cosmetic talc' in this review refers to talc of high purity as produced by today's responsible manufacturers.

A review of the selected titles reveals two primary issues, namely (1) hygienic use of cosmetic talc and ovarian cancer risk, and (2) health effects of inhaled cosmetic talc. In addition, a number of papers

describe granulomatous lesions attributed to talc on surgical gloves, and consequences of accidental inhalation of baby powder by infants. This review focuses on publications dealing with these and related issues.

Hygienic use of talc and ovarian cancer risk

The Harlow paper

Publication of a paper by Harlow *et al.* (1992) revived concern that chronic talc use in genital hygiene might be associated with an increased risk of epithelial ovarian cancer. That concern was originally raised 21 years earlier in a paper by Henderson *et al.* (1971) on the same subject. Harlow *et al.* (1992) provided the most detailed results to date on the relationship between perineal talc exposure and ovarian cancer. The study is the only one to date designed specifically to address this issue. It is among the largest studies (greatest statistical power) and one of the few to use closely age-matched neighbourhood controls.

The authors interviewed 235 white women diagnosed with epithelial ovarian cancer between 1984 and 1987 in Boston and 239 population-based matched controls. Approximately 50% of cases and 40% of controls used talc on the perineum, undergarments, sanitary napkins or diaphragms. This resulted in a 1.5 odds ratio (OR) for ovarian cancer [95% confidence interval (CI) 1.0–2.1]. Perineal exposure to talc resulted in significantly elevated risks in the subgroups who applied it directly as a body powder (OR 1.7, 95% CI 1.1–2.7), on a daily basis (OR 1.8, 95% CI 1.1–3.0), and for more than 10 years (OR 1.6, 95% CI 1.0–2.7). The greatest risk was

Abbreviations: BAL = bronchoalveolar lavage fluid; CI = confidence interval; NTP = National Toxicology Program; OR = odds ratio; RR = relative risk; SCE = sister chromatid exchange; UDS = unscheduled DNA synthesis.

observed in women with more than 10,000 talc applications during years when they were ovulating and had an intact genital tract (OR 2.8, 95% CI 1.4–5.4); however, this applied to only 14% of the women with ovarian cancer.

The authors acknowledge the inherent limitations of epidemiological studies. In their statistical analyses they adjusted for several confounding variables and conceded the existence of additional but intangible variables. In-person interviews included enquiries into dietary history but it is not clear whether, for example, lactose consumption and coffee consumption were determined and adjusted for; both substances have been associated with a significant increase in the risk of ovarian cancer (Cramer *et al.*, 1989; Whittemore *et al.*, 1988). Except for these two cases, no diligent efforts appear to have been made to identify other confounding variables that could account for increased incidence of ovarian cancer, such as vulvovaginal diseases (e.g. yeast infections and trichomoniasis) and obesity. McGowan *et al.* (1979) reported a higher incidence of rubella infection between the ages of 12 and 18 years in ovarian cancer patients than in controls, but there was a lower frequency of mumps (West, 1966) and of pneumonia and influenza (Joly *et al.*, 1974).

Harlow *et al.* (1992) mention in one sentence that they used meta-analysis in the statistical evaluation of their epidemiological data. Meta-analysis requires rigid criteria that must be strictly observed to yield meaningful results (Chalmers *et al.*, 1989; Yusuf *et al.*, 1985). Without details on the meta-analytical procedures used by the authors it is not possible to determine whether the use of meta-analysis was appropriate, and if so, whether it was used appropriately.

The sample population in the Harlow study is limited in numbers and restricted to white women in the Boston area. With an overall adjusted OR of 1.5 (CI 1.0–2.1) the results are statistically barely significant. Extrapolating from results in that small, restrictive group to the general population will require caution.

The authors conclude that their "data support the concept that a life-time pattern of perineal talc use may increase the risk for epithelial ovarian cancers", but they do not claim to have established a cause-effect relationship.

Related literature

Harlow *et al.* (1992) cite a number of literature references on talc translocation and putative association between hygienic use of talc and ovarian cancer. These references contribute to the ambiguity of the database as some of them suggest translocation or support an association whereas others do not; again, others suggest alternative explanations for greater-than-average incidences of ovarian cancer. For example, Cramer *et al.* (1989) suggested that lactose consumption might be a dietary risk factor

and transferase a genetic risk factor. Whittemore *et al.* (1988) observed in a well-designed study (188 cases, 539 controls) that the ovarian cancer risk in women who had consumed coffee for more than 40 years was 3.4 times that of women who had never regularly consumed coffee. This relationship is more robust ($P = 0.01$) than the marginal significance of the relationship with perineal talc use [relative risk (RR) = 1.40, $P = 0.06$].

A causal relationship between talc and ovarian cancer requires that talc particles, administered to the perineum or to the vagina, can translocate to the ovaries. Whether or not inanimate particles without locomotion of their own can do this without assistance has been the subject of a number of investigations in humans and animals. Results have been inconsistent and ambiguous. For a discussion of relevant findings published before 1986, reference is made to Wehner *et al.* (1986).

Henderson *et al.* (1986) observed talc particles in the ovaries of all eight ex-breeder rats after *intrauterine* deposition of a talc suspension. Following *intravaginal* deposition of talc suspension, talc particles were found in the ovaries of only two of six ex-breeder rats. Retrograde flow of menstrual products into the peritoneal cavity through the oviducts is well known; therefore, translocation to the ovaries of talc particles deposited in the uterus in 250 μ l saline, perhaps aided by the hydrostatic pressure of the saline solution during and after deposition, is not surprising. Yet in two of six rats the inanimate talc particles managed to cross the cervical barrier and reach the ovaries, perhaps also aided by hydrostatic pressure during deposition. Henderson *et al.* (1986) express a guarded opinion on the association of talc with cancer, stating that "carcinogenic activity of talc has not been established although its ubiquitous presence in the environment and its elemental similarity to asbestos has brought it under suspicion". Elemental similarity, of course, does not necessarily mean similarity in biological effects. It is well known that differences in physical properties, such as shape and surface characteristics, between elementally similar substances are responsible for significant differences in their biological effects. The pharmacological action of certain elementally and structurally identical agents (isomers) depends on whether they are dextrorotatory or levorotatory.

A remarkably large number of talc particles were found by Henderson *et al.* (1979) in human ovarian tissue, namely from 6900 to 55,100 particles/g wet weight tissue in three normal ovaries, from 17,400 to 24,300 in three cystic ovaries, and from 6400 to 24,300 in three ovarian adenocarcinomas. In another reference (Henderson *et al.*, 1978), 2×10^5 particles/mm³ are reported from oxygen incineration studies of human ovarian tissue.

Talc particles in human and animal tissues can be identified by X-ray fluorescence and X-ray diffraction

(Wehner *et al.*, 1977c) and by neutron activation of talc before animal exposure and subsequent γ -ray analysis of animal tissues for at least two suitable radionuclides (Wehner *et al.*, 1986 and 1977b). The neutron activation technique eliminates contamination problems during sample collection and processing.

Talc particles found, for example, on ovarian tissue might be contaminants deposited during sample collection and processing. For talc particles in ovarian tissue, contamination during sample collection and processing can be ruled out.

Wehner *et al.* (1985 and 1986) investigated talc translocation in Cynomolgus monkeys (*Macaca fascicularis*). The female of this species resembles the human female closer than any other animal model in the physiological and anatomical parameters of interest. The authors deposited a suspension of neutron-activated talc in the posterior fornix of the vagina on 30 consecutive work days (45 calendar days), that is, through at least one menstrual cycle (Wehner *et al.*, 1986). 2 days after the 30th talc application the animals were killed. The following samples underwent γ -ray analysis: vagina with the cervix of the uterus; uterus; the entire oviduct in three sections; ovaries; and peritoneal lavage fluid. Only the vagina-with-cervix samples—the site of deposition—contained varying quantities of talc. No talc was detected in any of the other samples. The detection limit of the neutron activation/ γ -ray analysis technique under the described experimental conditions was approximately 0.5 μ g talc (Wehner *et al.*, 1986) or about 1/230,000–1/245,000 of the estimated talc deposition in the posterior vaginal fornix (Wehner *et al.*, 1985).

Harlow and Weiss (1989) interviewed 116 patients with borderline ovarian tumours on their use of hygienic powders and found 'no appreciably altered risk' in the use of baby powder or cornstarch. However, the unspecified smaller number among those women who use deodorizing powders alone or in combination with other talc-containing powders had a 2.8-fold higher risk than 158 women without perineal exposure to powder. In the light of this newly discovered confounding variable, Harlow and Weiss recommend that the specific type(s) of powder used should be identified in future studies on hygienic powder use and ovarian tumours.

Cramer *et al.* (1982) observed a statistically significant ($P < 0.003$) relationship between epithelial ovarian cancer and talc used for dusting the perineum or sanitary napkins in 215 women. However, Cramer *et al.* (1982) found no relationship between ovarian cancer and talc exposure from dusting condoms or diaphragms, even though talc, in the latter applications, is deposited close to the cervical os. Hartge *et al.* (1983) made a similar observation from their epidemiological study. Their data indicate that the use of talc on a diaphragm did not appear to increase risk and that there was no overall association

between talc use and risk of ovarian cancer although a small group of women who specifically reported 'genital use' of talc showed an unspecified excess relative risk.

Mostafa *et al.* (1985) observed in 175 grossly normal, surgically removed human ovaries a 9% incidence of magnesium silicate granulomas and an additional 9% incidence of histological changes very similar to these granulomas.

Booth *et al.* (1989) reported an association between infertility as well as late onset of menopause and increased risk of ovarian cancer. In their opinion, the evidence linking talc with ovarian cancer was controversial, and they stated that more studies are needed to clarify this issue.

The association between 'fibre' exposure and ovarian cancer has been described by Rosenblatt *et al.* (1992). Cases were ascertained between 1981 and 1985. The authors define fibre exposure "as exposure to asbestos, talc (which may contain asbestos), and fiberglass". The authors observed elevated, but statistically not significant, risks with the use of condoms, powdered diaphragms and genital bath-talc. The risk for use of talc on sanitary napkins was significantly greater than unity (RR = 4.8; 95% CI = 1.3–18.0). The authors conclude that "The results of our study and others suggest that genital fiber exposure may be associated with an adverse effect ... but further study is needed to determine if this relationship is causal in nature."

Tzonou *et al.* (1993) examined the use of analgesics, tranquilizers and perineal talc application as risk factors for ovarian cancer in 189 cases and 200 controls. Talc use was determined on a no/yes basis without attempts to quantify application. The authors adjusted for a number of confounding variables, among them age, years of schooling, body weight, age at menarche, menopausal status, parity (nulliparous/parous, parous age at first birth, smoking (non-smoker/ever smoker), consumption of alcohol (glasses/day) and coffee (cups/day). There was a marginally significant inverse association with an apparent dose-response trend between frequency of analgesics use and ovarian cancer, and a highly significant dose-dependent positive relation between hair dyeing and ovarian cancer. As to talc, the authors state, "although the number of talc users is in general small and the respective confidence interval fairly large, there is clearly no evidence of an increased risk associated with perineal application of talc."

Chen *et al.* (1992) investigated risk factors for epithelial ovarian cancer in Beijing in 112 cases and 224 age-matched community controls. Among a number of other risk factors, the authors reported in their abstract an elevated risk in women with a history of long-term (>3 months) application of talc-containing dusting powder to the lower abdomen and perineum (RR 3.9, 95% CI 0.9–10.63).

Examination of the full paper reveals that these figures are based on seven (!) cases and five (!) controls.

Kupryjanczyk (1989) described multiple talc granulomas, inclusion cysts and adhesions in close proximity to an adenomatoid tumour of the left ovary of a 41-year-old patient. She suggests that talc crystals, as well as repair and inflammatory processes, should be taken into account as initiating factors in the development of ovarian adenomatoid tumours in susceptible patients.

In their paper on the aetiology of ovarian cancer, Baylis *et al.* (1986) conclude, "It certainly cannot be said at present that talc causes ovarian cancer." However, because the cause of ovarian cancer is unknown, and because of the "unexpected and unwarranted" presence of talc in ovarian cancer tissue and talc's "chemical similarity with asbestos", the authors are pursuing further investigations.

In their review paper on the epidemiology of ovarian cancer, Greene *et al.* (1984) summarize the role of talc and asbestos as follows: "while the above observations [reviewer's comment: referring to some of the publications reviewed here] are provocative, a conclusive role for talc or asbestos or both in the genesis of human ovarian cancer has yet to be demonstrated in either cohort or case-control studies."

There are other papers in which an association between hygienic talc application and ovarian cancer is mentioned. Most are reviews, referring to the literature reviewed here. None provide new information on the talc/ovarian cancer issue.

Hamilton *et al.* (1984) injected 100 μ l saline containing 10 mg talc into ovaries of rats and observed no evidence of neoplasia.

In their review, Longo and Young (1979) point out that "epidemiological data could be interpreted as showing that the risk of developing cancer from an occupational talc exposure was due to contaminating asbestos." This could equally apply to chronic exposure from hygienic use of talc. The authors support this view by subsequently stating "... consumer talc products marketed before 1973 were variably contaminated by asbestos", and, later, "... data collected on populations exposed before 1976 may reflect the hazard of contaminating asbestos rather than talc. Unfortunately, adherence to the revised Cosmetic, Toiletry and Fragrance Association guidelines is voluntary ... so that, even now [1979; year added], commercial talcs are not certain to be asbestos-free." Cralley *et al.* (1968) found fibre contents ranging from 8 to 30% in cosmetic talc products available at the time of their investigation.

In considering mechanisms that might be involved in ovarian carcinogenesis, Venter (1981) points to the extremely high concentrations of gonadotrophins and potent steroids in the follicular fluid that is released monthly into the pelvic cavity by the rupture of the ovarian follicles. The concentration of these

chemicals correlates with the mitotic and biosynthetic activities of granulosa cells, of which approximately 50 million accumulate in a follicle during the follicular phase with about 6.5 ml of antral fluid before the follicle is transformed into a corpus luteum. Given the fact that oestrogens cause proliferation of certain cells, Venter proposes the hypothesis that the antral fluid could act as an ovarian cancer promoter. Dietl *et al.* (1986) emphasize that the ovarian surface epithelium is a dynamic tissue with distinct morphological differentiations: it may proliferate inwards and form crypts and inclusion cysts or it may develop superficial papillary excrescences. In addition, constant metaplastic changes may take place in various parts of the müllerian epithelium. These growth processes appear to be influenced by endogenous and exogenous factors. It is conceivable that these factors, in combination with the physiological, biochemical and morphological characteristics of the ovarian tissue, can induce neoplastic lesions in the ovarian surface epithelium. The repeated breaks in the epithelium that occur during ovulation apparently increase the risk of developing neoplasia.

Biological effects of inhaled talc

The literature search revealed that publications on biological effects of inhaled cosmetic talc are sparse and basically fall into two categories: (1) findings in animal studies; (2) accidental inhalation of large quantities of talc by infants and small children.

Talc pneumoconioses in adults

Feigin (1989) distinguished between three forms of pulmonary disease caused by talc inhalation, namely (1) talcosilicosis, (2) talcoasbestosis and (3) pure talcosis. Feigin writes: "Talcosilicosis is produced by exposure to talc usually from Italy but also from California associated with silica and other non-asbestiform minerals. ... The clinical and radiographic manifestations resemble those of silicosis. ... The only documented difference between silicosis and talcosilicosis is the presence of talc, as demonstrated histologically. No other differences have been described. The radiographic changes are indistinguishable from those of silicosis." Talcoasbestosis is caused by inhalation of talc containing asbestiform fibres, such as tremolite and anthophyllite, as mined, for example, in upper New York state. On pure talcosis, Feigin writes: "Symptoms and pulmonary function test results consistent with restrictive pulmonary disease are well documented in pure talcosis; airway obstruction may also occur. The clinical form of the disease has most often been documented in miners and other workers involved in the obtaining and processing of pure talc. It has also been documented in people exposed to cosmetics, but only when the exposure was very heavy and prolonged".

This reviewer could find only two literature references on talcosis in consumers. Wells *et al.* (1979)

describe a case of talcosis due to talc abuse, initially suspected to be tuberculosis, in a 41-year-old housewife. On direct questioning the patient admitted to very heavy (at least once a day) use of talc powder over her whole body in an unventilated room for many years. The other reference is to a paper by Tukiainen *et al.* (1984) who describe two cases. One of them involved an elderly female smoker of 20 years with a history of several operations. When she presented years later with non-productive cough, dyspnoea, tachycardia and low-grade fever, talcosis was considered a possibility on account of her 10-year use of talcum powder two or three times a day in an unventilated room. The authors eventually diagnosed chronic sarcoidosis with talc deposition in the lungs. The other case was an elderly female smoker of 30 years who had been occupationally exposed to industrial talc from 1958 to 1968.

Scatarige and Stitik (1988) reviewed the literature on the induction of thoracic malignancies in inorganic dust pneumoconiosis. They concluded that "talc pneumoconiosis does not appear to be associated with an increased risk of lung carcinoma or mesothelioma, and animal studies have failed to convincingly demonstrate the carcinogenicity of talc."

Accidental inhalation of large quantities of talc by infants

A number of reports describe consequences of accidental inhalation of large quantities of baby talc powder by infants. Although the cases do not constitute talc use as intended, they are nevertheless included in this review for the sake of completeness as they present a form of—albeit accidental—talc inhalation.

Brouillette and Weber (1978) describe the case of a prematurely born 1-month-old girl, presented at a hospital in cardiac arrest. She was covered with talc powder which had been poured into her mouth and nose by her 3-year-old brother. Following appropriate treatment of her severe pneumonia, she was discharged after 12 days of hospitalization without apparent consequences. The authors refer in their paper to at least 24 previous cases of massive talc powder inhalation by infants. Most of the children were older than 6 months, and those old enough to play with the powder container were considered at risk. The mortality in these cases was 20%.

Mofenson *et al.* (1981) point out the potential hazard of careless use of baby powder. They reviewed the experience of the Poison Control Center at the Nassau County Medical Center, New York, with baby powder inhalation in children less than 5 years of age, in whom most of the incidents occur. Of approximately 4300 calls in a 6-month period, 40 concerned baby powder inhalation. Symptoms included cough in 14 children, dyspnoea in five, sneezing in five, vomiting in six, and cyanosis in one.

McCormick *et al.* (1982) describe the hazards associated with diaper (nappy) changing, based on statistics from the Massachusetts Poison Control System. Of 138 cases of exposure to various 'poisons' during diaper change in a 3-month period, powders accounted for 47%. Symptoms such as coughing, wheezing and shortness of breath were described as mild, occurring most often with powders.

Motomatsu *et al.* (1979) report the clinical case of two baby girls who died following accidental inhalation of baby powder and unsuccessful treatment. "In order to investigate the harm of baby powder," the authors placed eight mice in a box, the bottom of which was covered with baby powder which was then "blown up" with compressed air. Neither aerosol characterization nor other measurements or experimental data are provided by the authors. Four mice, removed from exposure after 30 and 60 min, "recovered completely". Two other mice, removed after 90 min exposure, died within 6 hours and the last two mice died after 2 hours of exposure. Histopathological findings include haemorrhage, oedema and desquamation of bronchial epithelium.

Pfenninger and D'Apuzzo (1977) describe two cases of powder inhalation. One was a 7.5-month-old girl who had inhaled Fissan baby powder containing talc, zinc oxide and other unspecified substances. The patient responded only slowly to treatment and required 19 days of hospitalization but eventually recovered fully. The second case involved a 13-month-old boy who had inhaled Merfen powder containing talc and borate of phenylmercury. The patient responded well to treatment and recovered completely within 4 days.

De La Rocha and Brown (1989) report a case of baby powder inhalation followed by adult respiratory distress syndrome in a 16-month-old girl who recovered fully after 20 days of hospitalization.

Gutermuth *et al.* (1980) describe accidental talc inhalation and treatment in an 11-month-old female infant and in a 21-month-old boy. The first patient recovered after a 16-day hospital stay, the second one after a 13-day hospital stay.

Mussi *et al.* (1979) report a fatal case of powder inhalation in a 14-month-old girl. After a characteristic fairly asymptomatic initial period—in this case 12 hours—the girl did not respond to treatment and died 41 hours after the accident.

Swanson-Bicarman *et al.* (1991) report the case of a 10-month-old boy who was hospitalized for 16 days following massive talc inhalation. The patient had recovered completely by the time of his discharge.

Butenandt *et al.* (1981) treated a 9-month-old male infant who had accidentally inhaled several grams of Penanten powder which contained 96% talc. Prompt bronchial lavage plus appropriate treatment resulted in an asymptomatic status after only 4 days of hospitalization.

Cotton and Davidson (1985) describe the case of a prematurely born 4-month-old male infant with a tracheotomy tube in place to maintain airway patency. During diaper change at home, baby powder was spilled accidentally and apparently blocked the infant's airway. At arrival in the hospital the boy was in cardiac arrest. He was resuscitated but died the following day.

Pairaudeau *et al.* (1991) report respiratory arrest in a 12-week-old boy, following a talc spill on his face during diaper change. He recovered during several days of hospitalization and treatment.

Cruthirds *et al.* (1977) diagnosed progressive diffuse pulmonary fibrosis (talc pneumoconiosis) in a 10-year-old girl who had inhaled a considerable quantity of baby powder at 2 years of age at which time hospitalization was not thought indicated.

Articles by Rumack (1982), Hayden and Sproul (1984), Wagner and Hindi-Alexander (1984) and Hollinger (1990) are mainly brief reviews which do not contribute new scientific information above and beyond the papers reviewed in this report.

Animal studies

Wehner *et al.* (1977c) exposed hamsters to a respirable talc aerosol concentration of approximately 8 mg/m^3 for 3, 30, or 150 minutes/day, 5 days/week for 30 days, or for 30 or 150 minutes/day either until they died naturally or for a maximum of 300 days. The hamsters received cumulative exposures ranging from about 15 to more than 6000 mg/hr/m^3 . Estimates based on a pulmonary deposition and clearance study with neutron-activated talc (Wehner *et al.*, 1977b) indicate that $0.05\text{--}6 \mu\text{g}$ talc, depending on the length of exposure, was deposited in the hamster lungs at each exposure. Estimates based on infant-dusting experiments (J. N. Sivertson, personal communication, 1976) show that the weekly hamster exposures, expressed in mg/hr/m^3 , exceeded the average weekly infant exposures by some 30 to 1700 times, depending on the hamster exposure group. At death, the lungs, trachea, larynx, liver, one kidney, stomach, uterus, one ovary, or one testis, and all tissues showing gross lesions were collected for histopathological examination. The talc exposures did not affect body weight, survival or the type, incidence or degree of histopathological changes in the exposed groups compared with sham-exposed controls.

Wehner *et al.* (1977b) determined pulmonary deposition, translocation and clearance of inhaled talc in hamsters by a single 2-hour nose-only exposure to neutron-activated talc and subsequent serial killing. Lungs, liver, kidneys, ovaries, skinned carcass and 2-day and 4-day excreta were subjected to γ -ray analysis. The isotope ^{60}Co was used to estimate talc quantities in the samples; the isotope ^{45}Sc was used to check the validity of ^{60}Co as a tracer for talc. From 20 to $80 \mu\text{g}$ talc (approx. 6–8% of the quantity inhaled) was deposited in the deep lung with

a biological half-life of 7–10 days. Alveolar clearance was essentially complete 4 months after exposure. No translocation of talc to liver, kidneys, ovaries or other parts of the body was found.

To validate the interpretation of the pulmonary deposition, translocation and clearance data (Wehner *et al.*, 1977b), Wilkerson *et al.* (1977) investigated whether radionuclides leached from the neutron-activated talc in serum and in dilute hydrochloric acid. Leaching was negligible in both liquids, but somewhat higher in dilute hydrochloric acid than in serum.

A gavage study with neutron-activated talc showed that talc absorption in the gastro-intestinal tract of hamsters is also negligible (Wehner *et al.*, 1977a).

In 1992, the National Toxicology Program (NTP, 1992) prepared for public review and comment a draft technical report on a comprehensive chronic inhalation study conducted at the Lovelace Biomedical and Environmental Research Institute. The study, designed to investigate toxicology and carcinogenesis of talc in rats and mice, followed the standard NTP experimental protocol for chronic inhalation studies. F344/N rats and B6C3F₁ mice were exposed for 6 hours/day, 5 days/week to an intended talc aerosol concentration of 0, 6 or 18 mg/m^3 . In rats, the exposures resulted in impaired respiratory function; increased lung weights; inflammatory, reparative and proliferative processes in the lungs; hyperplasia of alveolar epithelium; interstitial fibrosis; accumulation of macrophages in lymphoid tissue and regional lymph nodes; and occasionally squamous metaplasia. Incidence and severity of these changes generally were a function of dose. The incidences of alveolar/bronchiolar adenomas and carcinomas were significantly higher in female rats (but not in males) of the 18 mg/m^3 exposure group than in the controls. A significantly increased incidence of pheochromocytomas of the adrenal medulla in talc-exposed rats of both sexes cannot be explained, as there is no known mechanism by which talc particles deposited in the lungs can affect the adrenal medulla, with the possible exception of a stress-related effect owing to a high pulmonary particle load. In mice, the talc exposures produced chronic inflammation and macrophage accumulation in the lungs, but no hyperplasia, metaplasia or interstitial fibrosis, and no pulmonary neoplasms.

As a relatively recent, comprehensive study that yielded interesting—even puzzling—results, the Lovelace study deserves special comment. Although it was generally well conducted, the study has flaws that can interfere with the interpretation of its results. Inclusion of negative and positive dust control groups would have allowed unambiguous determination of relative toxicity/carcinogenicity of inhaled talc. As it is, the question remains whether the observed pulmonary lesions and other changes in the talc-exposed rodents of the Lovelace study are

talc-specific or a non-specific foreign-body (dust) reaction that is to be expected as a consequence of inhalation exposures at concentrations that result in lung overload.

The investigators were unable to maintain target aerosol concentrations for the 18 mg/m³ rat exposure group during 19 of the 113–122 weeks of exposure. For 7 of these weeks the rats were exposed to approximately twice the intended aerosol concentration. Even the two intended exposure concentrations led to an impairment of lung clearance mechanisms; both of them, therefore, meet the criteria for a maximum tolerated dose or maximum functionally tolerated dose. On the basis of present knowledge and standards for conducting chronic inhalation studies to investigate carcinogenicity, the chosen talc aerosol concentrations in the Lovelace study were too high. The carcinogenic response observed in female rats of the high-dose exposure group might therefore be attributable to a secondary effect of carcinogenesis, based on a high particle load in the lung (lung overload condition). The Lovelace study can be considered irrelevant for assessing the pulmonary oncogenicity of inhaled talc in humans and the authors of the NTP draft report do not imply any such relevance. Talc aerosol doses received by users of cosmetic talc are several orders of magnitude lower (Aylott *et al.*, 1979; Russell *et al.*, 1979) with no danger of reaching a lung overload condition. The increased incidence of pheochromocytomas in male and female rats at the high talc exposure concentration remains a perplexing phenomenon that needs to be independently confirmed. Its relevance for humans is questionable, last but not least, again because of the excessive amount of talc accumulating in the rat lungs and the possibility of subsequent stress-related effect. Background incidences of pheochromocytomas in control rats were already rather high, and no significant increase was observed in the low exposure groups, although these groups also clearly showed symptoms of lung particle overload with impairment of alveolar macrophage clearance function.

The benign pulmonary lesions in the talc-exposed animals generally were those typically observed in inhalation exposures of laboratory rodents to high concentrations of a variety of dusts. There was a significant incidence of bronchiolar/alveolar adenomas and carcinomas in the female rat group exposed to 18 mg/m³, but not in the males, and not in mice of either sex. The biological significance of this observation remains uncertain.

Pickrell *et al.* (1989) investigated the relationship between the inhalation exposure concentration of talc and the resulting lung burdens and histological lesions. Rats were exposed to 0, 2.3, 4.3 and 17 mg talc/m³ for 6 hours/day, 5 days/week, for 4 weeks. Lung burdens were 0, 0.07, 0.17 and 0.72 mg talc/g lung, respectively. Mice were exposed to 0, 2.2, 5.7 or 20.4 mg talc/m³, which resulted in lung burdens of

0, 0.10, 0.29 and 1.0 mg talc/g lung. Histological changes consisted of a modest increase in talc-containing free macrophages within alveolar spaces in both rat and mouse groups exposed to the highest concentration of talc.

Wagner *et al.* (1977) exposed groups of rats to mean respirable concentrations of 11 mg SFA chrysotile or Italian talc/m³, 7.5 hours/day, 5 days/week, for 3, 6 or 12 months, respectively. Some rats were killed 10 days after termination of exposures, others after one year. Minimal to slight fibrosis as a function of exposure duration occurred in the dust-exposed rats.

In vitro studies

Beck *et al.* (1987) investigated the toxicity of quartz- and asbestos-free talc and of granite (12% quartz), collected from worksites, in hamsters that received the dusts by intratracheal instillation. Dose-response (0.15, 0.75 and 3.75 mg/100 g body weight) and time-course (1–14 days) studies were conducted in bronchoalveolar lavage fluid (BAL). One day after exposure, both talc and granite caused elevated enzyme levels, pulmonary oedema, and increased cell numbers in BAL. Macrophage phagocytosis was inhibited. Response levels were either between 'nontoxic' iron oxide and toxic alpha-quartz or comparable with alpha-quartz. The response to granite dust decreased fairly rapidly as a function of time, but talc exposure resulted in longer elevated enzyme levels and decreased macrophage phagocytosis. The authors conclude that, given similar mass deposition in the lungs, talc causes more lung injury than granite.

Endo-Capron *et al.* (1993) studied genotoxicity of three talc samples in rat pleural mesothelial cells, using genotoxicity assays for unscheduled DNA synthesis (UDS) and sister chromatid exchanges (SCEs). Attapulgit and anatase served as negative controls, chrysotile and crocidolite as positive controls. The positive asbestos controls enhanced UDS or SCEs in treated cultures compared with untreated control cultures, but the talc samples and the negative controls did not.

Davies *et al.* (1983) tested the cytotoxicity of seven specimens of high-purity talc dust in mouse peritoneal macrophages. All samples consistently showed moderate macrophage cytotoxicity, suggesting that they would be fibrogenic *in vivo*.

Talc granulomas from powdered surgical gloves

Talc powder is fibrogenic when administered by various routes to many species of animals (Lord, 1978). When introduced into open wounds it may induce talc granulomas. This phenomenon is used therapeutically in pleurodesis, the deliberate production of adhesions between the parietal and visceral pleura by (usually surgical) deposition of talc or kaolin to treat recurrent pneumothorax. Chappell

et al. (1979) published a survey of the long-term effects of talc and kaolin pleurodesis. There was no increased incidence of lung cancer and no case of mesothelioma in 199 traceable patients who underwent pleurodesis 14 to 40 years previously. Weissberg and Kaufman (1986) successfully used talc for pleurodesis in the treatment of resistant empyema in five patients who completely recovered from empyema with no undesirable side-effects. However, in the vast majority of cases, talc granulomas are undesirable effects of wound contamination with talc, usually from surgical gloves.

Sparrow and Hallam (1991) implicate talc powder in the aetiology of an appreciable number of umbilical granulomas excised from infants and young children. In view of these cases and with reference to the sometimes disastrous consequences of accidental inhalation of baby powder by infants, the authors strongly discourage the routine use of talc powder in the care of infants.

Healey and McDonald (1977) observed a talc granuloma in the right hemiscrotum of a 3-year-old boy who had undergone a right hydrocelectomy 3 months previously. The authors state that the interval for granuloma formation following contamination is extremely variable, ranging from 2 weeks to 45 years, with an average of 2 months after surgery. The extent of granuloma formation depends mainly on the dose and antigenicity of the contaminant and on host response.

Pratt *et al.* (1985) consistently found birefringent particles, which they identified as talc, in the subserosal stroma of hernia sacs. Cellular response was remarkably mild, perhaps owing to the small particle size (about 10 μm) compared with about 50 μm of particles in talc granulomas. The authors further hypothesize that the particles were ingested with medication or food and reached the peritoneal cavity by migration through the intact intestinal wall.

Al-Sheikhli (1978) observed talc powder in granulomas of the vocal cords of a 16-year-old girl and suspects as the cause accidental talc contamination of an endotracheal tube with which she was intubated 4 months previously.

Simsek *et al.* (1992) report a case of severe obstruction of the urinary tract due to a talc granuloma in a 70-year-old male patient 7 years after a suprapubic transvesical prostatectomy.

Pelling and Evans (1986) experimentally tested in rats long-term peritoneal tissue response to mould-release agents and lubricant powder used on surgical gloves. Intraperitoneal implantation of talc produced significantly more adhesions and more severe, persistent, granulomatous reaction than starch powder and calcium carbonate.

Sheikh *et al.* (1984) describe tissue reactions to talc and Keoflo (low cross-linked cornstarch) which they tested as contaminants on the surface of surgical sutures or as pellets implanted in the abdominal muscle of rats. Keoflo caused a strong acute

inflammatory reaction which, together with the starch, had essentially disappeared by the fourth week, leaving minimal lesions and scar formation. By contrast, the implanted talc initially induced only mild to moderate acute inflammation followed by chronic inflammatory response, and granuloma formation by the third day. The results suggest that low cross-linked cornstarch is a bioabsorbable substance, whereas talc is not. The authors therefore conclude that low cross-linked cornstarch "is a safe material for use as surgical glove powder", a conclusion not supported by findings of cornstarch-induced lesions reported independently by several other investigators (see below). Kaiser *et al.* (1982) reported similar results with intraperitoneal tests in rats.

Talc may contaminate surgical gloves as a mould-release agent during the manufacturing process or it may be deliberately added as a lubricant for easier donning. In a letter to the editor, Henderson and Griffiths (1979) state: "The large number of talc particles observed on certain American-produced surgeons' gloves, on occasions in excess of 6×10^7 particles/cm², would suggest that it is this material that is being employed as the releasing dusting powder in the molding process." Tolbert and Brown (1980) and Khan *et al.* (1983) point out that removal of talc particles from gloves is difficult using recommended washing and wiping procedures, and that a shedding hazard might exist by mechanical dislodging of the particles during surgery.

Rather than reviewing all publications of the last 15 years on talc granulomas, it is the limited objective of this section to show that talc granulomas following surgery can and do occur at various locations and that they can be induced experimentally in animal models. For relatively recent comprehensive reviews of various aspects of glove-related issues, reference is made to the papers by Ellis (1990) and Beck (1992), Fay and Sullivan (1992), White (1992) and Witmeyer (1992). Parenthetically, replacement of talc with cornstarch powder as a glove lubricant has resulted in starch granulomas (Wilson and Garach, 1981), starch peritonitis (Ellis, 1990; Loup *et al.*, 1979; Urdiales Cabal *et al.*, 1989) and intraperitoneal adhesions in rats (Kamffer *et al.*, 1992). With the trend since the 1980s towards powder-free gloves gaining momentum, complications from wound contamination with surgical glove powders may become rarer but not eliminated. To avoid allergic reactions (including anaphylactic shock) in sensitive individuals exposed to water-extractable latex proteins on medical gloves (Beezhold, 1992), vinyl, nitrile, neoprene and copolymer gloves are now available; generally, these gloves are powdered (Witmeyer, 1992).

Ingested talc

Under conditions of normal use, talc can be ingested in one of two ways. First, when used as intended as dusting powder, very small amounts of

talc dust may be inhaled. That portion of the talc particles which is deposited on the ciliated part of the respiratory tract will be transported cranially by the mucociliary escalator mechanism and then swallowed. There are no reports in the literature describing biological effects of these minute quantities of ingested talc. Secondly, talc accounts for the bulk of filler materials in tablets. Appreciable amounts of talc can be ingested with chronic heavy consumption of pills.

Anani *et al.* (1987) describe the case of a 46-year-old male who presented with abdominal pain. Further examination and a right hemicolectomy showed marked fibrosis of the intestinal wall in which birefringent particles with energy-dispersive spectra typical of those for talc were found. The anamnesis revealed that, at the age of 27 years, the patient was treated over a period of 28 months for pulmonary tuberculosis with tablets containing talc (183 g talc per 2670 g total tablet ingestion). The authors speculate that the tablets ingested during this antituberculosis therapy were the source of the talc found in the intestinal fibrosis. If this assumption is correct, the potential consequences of daily multiple pill use, as can be the case with vitamin and mineral supplements, should be more closely examined. Moderate pill consumption does not appear to present a risk. In their review of pharmaceutical excipients, Golightly *et al.* (1988) state, "Ingestion of talc is very unlikely to be toxic."

The Joint Expert Committee of Food Additives of the Food and Agriculture Organisation of the United Nations and the World Health Organization stated in its report on food additives that talc was not mutagenic *in vitro* or *in vivo* and allocated an acceptable daily intake "not specified" classification to food-grade (i.e. free of asbestiform particles) talc (FAO/WHO, 1987).

Discussion

The literature reviewed reflects several areas of concern regarding biological effects of cosmetic talc use.

Hygienic talc use and ovarian cancer

The presence of large numbers of talc particles in normal and diseased ovarian tissue seems indisputable although it is difficult to imagine how inanimate particles without locomotion of their own can breach the formidable cervical barrier and migrate 'upstream' against the ciliary beat of the fallopian epithelium to the ovaries. Several investigators have reported an association between hygienic use of talc and ovarian cancer; none claims to have established a causal relationship. The epidemiological evidence linking hygienic talc use with an increased risk of ovarian cancer generally is weak and sometimes inconsistent: confounding variables were often ignored; the reported increased risk ratios, in most

cases less than 2, are barely statistically significant, and epidemiological studies are not sensitive enough to estimate risk ratios less than 2. Talc use might be a causally unrelated marker for confounders associated with increased ovarian cancer risk such as, for example, vulvovaginal disease or obesity. There appears to be a consensus of opinion that more and better designed studies are needed before valid scientific judgement can be passed on whether or not there exists a causal relationship between hygienic talc use and increased ovarian cancer risk.

An interesting question remains. Talc is a recognized fibrogen. If there are sufficient numbers of talc particles in ovarian tissues long enough to cause cancer, where is the ovarian fibrosis which one would expect to develop long before cancer occurs? The only references to ovarian granulomas are those by Mostafa *et al.* (1985) and Kupryjanczyk (1989).

Talc inhalation

In contrast to individuals occupationally exposed to industrial talc, talc pneumoconiosis from personal use of cosmetic talc appears to be extremely rare, occurring only following chronic abuse. When talc, a fibrogenic substance, is chronically deposited at doses sufficiently high to overwhelm the bronchopulmonary clearance mechanism, a fibrotic/ granulomatous tissue response can and will occur, as observed in humans and animals. Animal studies suggest that natural defence mechanisms, such as macrophages and mucociliary clearance, can cope with exposure to talc concentrations considerably exceeding estimated infant exposures, without lesion development (Wehner *et al.*, 1977c). If doses in animal experiments are increased substantially so as to result in pulmonary overload, the results can no longer be considered relevant for human risk assessment. The Lovelace study (NTP, 1992) is a case in point.

Paracelsus recognized some 450 years ago, "*dosis solum venenum facit*" (only the dose makes a poison). Lee *et al.* (1985) confirmed this dramatically by inducing a significant incidence of squamous cell carcinoma in lungs of female CD rats, exposed for up to 104 weeks to 250 mg titanium dioxide/m³, a substance long considered by many to be biologically inert and frequently used as negative dust control. Should titanium dioxide therefore be considered a carcinogen in rats—and in humans? There is no evidence in the literature to suggest that cosmetic talc, inhaled under conditions of normal use, can cause cancer in the human respiratory system.

Accidental inhalation of baby powder by infants presents a largely avoidable problem if physicians, nurses, parents and other individuals handling the infants are made aware of the potential danger and observe appropriate precautions, such as keeping the powder can out of reach of children. Considering the very large number of dustings administered daily to babies, these incidences fortunately are very rare.

Other studies

In vitro studies have shown that talc is fibrogenic and not genotoxic. The number of papers reporting talc granulomas caused by powdered surgical gloves indicates a certain concern. Calls for talc-free surgical gloves have been voiced. Cornstarch powder does not appear to be a suitable substitute as it, too, causes lesions. The use of talc on surgical gloves presents a special problem that does not affect the typical consumer of cosmetic talc. Ingestion of food-grade talc is unlikely to be toxic.

Conclusion

There is no conclusive evidence in the literature reviewed to indicate that cosmetic talc, when used as intended, presents a health hazard.

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REFERENCES

- Al-Sheikhli A. R. J. (1978) Bilateral post-intubation talc granulomata of the vocal cords. *Journal of Laryngology and Otology* 92, 735.
- Aylott R. I., Byrne G. A., Middleton J. D. and Roberts M. E. (1979) Normal use levels of respiratory cosmetic talc: preliminary study. *International Journal of Cosmetic Science* 1, 177.
- Anani P. A., Ribaux C. and Gardiol D. (1987) Unusual intestinal talcosis. *American Journal of Surgical Pathology* 11, 890.
- Baylis M. S., Henderson W. J., Pierrepont C. G. and Griffiths K. (1986) The aetiology of ovarian cancer. In *Gynaecological Oncology*. Edited by C. P. Morrow and G. E. Smart. pp. 157-000. Springer-Verlag, Berlin.
- BEC (1992) *Critiques of NTP Technical Report on the Toxicology and Carcinogenesis Studies of Talc in F344/N Rats and B6C3F₁ Mice and Perineal Exposure to Talc and Ovarian Cancer*. BEC Technical Report to CTFA. Richland, Washington, September.
- Beck B. D., Feldman J. A., Brain J. D. et al. (1987) The pulmonary toxicity of talc and granite dust as estimated from an in vivo hamster bioassay. *Toxicology and Applied Pharmacology* 87, 222.
- Beck W. C. (1992) Issues related to surgical gloves. *Biomedical Instrumentation and Technology* 26, 225.
- Beezhold D. H. (1992) Latex allergy. *Biomedical Instrumentation and Technology* 26, 238.
- Booth M., Beral V. and Smith P. (1989) Risk factors for ovarian cancer: a case-control study. *British Journal of Cancer* 60, 592.
- Brouillette F. and Weber M. L. (1978) Massive aspiration of talcum powder by an infant. *Canadian Medical Association Journal* 119, 354.
- Butenandt L., Däumling S. and Hager C. (1981) Akzidentelle Babypuder-Aspiration. *Monatsschrift für Kinderheilkunde* 129, 605.
- Chalmers T. C., Hewett P., Reitman D. and Sacks H. S. (1989) Selection and evaluation of empirical research in technology assessment. *International Journal of Technology Assessment and Health Care* 5, 521.
- Chappell A. G., Johnson A., Charles J. et al. (1979) A survey of the long-term effects of talc and kaolin pleurodesis. *British Journal of Diseases of the Chest* 73, 285.
- Chen Y., Wu P. C., Lang J. H., Ge W. J., Hartge P. and Brinton L. A. (1992) Risk factors for epithelial ovarian cancer in Beijing, China. *International Journal of Epidemiology* 21, 23.
- Cotton W. H. and Davidson P. J. (1985) Aspiration of baby powder. *New England Journal of Medicine* 313, 1662.
- Cralley L. J., Key M. M., Groth D. H., Lainhart W. S. and Ligo R. M. (1968) Fibrous and mineral content of cosmetic talcum products. *American Industrial Hygiene Association Journal* 29, 350.
- Cramer D. W., Harlow B. L., Willett W. C., Welch W. R., Bell D. A., Scully R. E., Ng W. G. and Knapp R. C. (1989) Galactose consumption and metabolism in relation to the risk of ovarian cancer. *Lancet* 2, 66.
- Cramer D. W., Welch W. R., Scully R. E. and Wojciechowski C. A. (1982) Ovarian cancer and talc. A case-control study. *Cancer* 50, 372.
- Cruthirds T. P., Cole F. H. and Paul R. N. (1977) Pulmonary talcosis as a result of massive aspiration of baby powder. *Southern Medical Journal* 70, 626.
- Davies R., Skidmore J. W., Griffiths D. M. and Moncrieff C. B. (1983) Cytotoxicity of talc for macrophages *in vitro*. *Food and Chemical Toxicology* 21, 201.
- De La Rocha S. R. and Brown M. A. (1989) Normal pulmonary function after baby powder inhalation causing adult respiratory distress syndrome. *Pediatric Emergency Care* 5, 43.
- Dietl J., Buchholz F. and Stoll P. (1986) Das ovarielle Deckepithel und seine histogenetische Beziehung zum Ovarialkarzinom. *Geburtshilfe und Frauenheilkunde* 46, 561.
- Ellis H. (1990) The hazards of surgical glove dusting powder. *Surgery, Gynecology and Obstetrics* 171, 521.
- Endo-Capron S., Renier A., Janson X., Kheuang L. and Jaurand M. C. (1993) *In vitro* response of rat pleural mesothelial cells to talc samples in genotoxicity assays (sister chromatid exchanges and DNA repair). *Toxicology in Vitro* 7, 7-14.
- FAO/WHO (1987) *Evaluation of Certain Food Additives and Contaminants. Thirtieth Report of the Joint FAO/WHO Expert Committee on Food Additives*. WHO Technical Report Series 751. WHO, Geneva.
- Fay M. F. and Sullivan R. W. (1992) Changing requirements for glove selection and hand protection. *Biomedical Instrumentation and Technology* 26, 227.
- Feigin D. S. (1989) Misconceptions regarding the pathogenicity of silicas and silicates. *Journal of Thoracic Imaging* 4, 68.
- Golightly L. K., Smolinske S. S., Bennett M. L., Sutherland E. W., III and Rumack B. H. (1988) Pharmaceutical excipients. Adverse effects associated with 'inactive' ingredients in drug products (Part II). *Medical Toxicology and Adverse Drug Experience* 3, 209.
- Greene M. H., Clark J. W. and Blayney D. W. (1984) The epidemiology of ovarian cancer. *Seminars in Oncology* 11, 209.
- Gutermuth M., Schirg E., Steinbacher D. and Weiss H. (1980) Akzidentelle Aspiration von Babypuder. *Intensivmedizin* 2, 83.
- Hamilton T. C., Fox H., Buckley C. H., Henderson W. J. and Griffiths K. (1984) Effects of talc on the rat ovary. *British Journal of Experimental Pathology* 65, 101.
- Harlow B. L., Cramer D. W., Bell D. A. and Welch W. R. (1992) Perineal exposure to talc and ovarian cancer risk. *Obstetrics and Gynecology* 80, 19.
- Harlow B. L. and Weiss N. S. (1989) A case-control study of borderline ovarian tumors: the influence of perineal

- exposure to talc. *American Journal of Epidemiology* 130, 390.
- Hartge P., Hoover R., Leshner L. P. and McGowan L. (1983) Talc and ovarian cancer. *Journal of the American Medical Association* 250, 1844.
- Hayden G. F. and Sproul G. T. (1984) Baby powder use in infant skin care. Parental knowledge and determinants of powder usage. *Clinical Pediatrics* 23, 163.
- Healey G. B. and McDonald D. F. (1977) Talc granuloma presenting as a testicular mass. *Journal of Urology* 118, 122.
- Henderson W. J. and Griffiths K. (1979) Talc on surgeons' gloves (letter). *British Journal of Surgery* 66, 599.
- Henderson W. J., Hamilton T. C., Baylis M. S., Pierrepont C. G. and Griffiths K. (1986) The demonstration of the migration of talc from the vagina and posterior uterus to the ovary in the rat. *Environmental Research* 40, 247.
- Henderson W. J., Hamilton T. C. and Griffiths K. (1979) Talc in normal and malignant ovarian tissue. *Lancet* i, 499.
- Henderson W. J., Joslin C. A. F., Turnbull A. C. and Griffiths K. (1971) Talc and carcinoma of the ovary and cervix. *Journal of Obstetrics and Gynaecology of the British Commonwealth* 78, 266.
- Henderson W. J., Melville-Jones C., Wilson D. W. and Griffiths K. (1978) Oxygen incineration and electron microscope X-ray microanalysis of mineral particles in biological tissues. *Journal of Histochemistry and Cytochemistry* 26, 1087.
- Hildick-Smith G. Y. (1976) The biology of talc. *British Journal of Industrial Health* 33, 217.
- Hildick-Smith G. Y. (1977) Talc—recent epidemiological studies. In *Inhaled Particles IV*. Edited by W. H. Walton. pp. 655–665. Pergamon, Oxford.
- Hollinger M. A. (1990) Pulmonary toxicity of inhaled and intravenous talc. *Toxicology Letters* 52, 121.
- Joly D. J., Lilienfeld A. M., Diamond E. L. and Brass I. D. J. (1974) An epidemiologic study of the relationship of reproductive experience to cancer of the ovary. *American Journal of Epidemiology* 99, 190.
- Kaiser W., Otten G., Kohnlein H. E. and Kitzinger H. (1982) Unspezifische Gewebsreaktionen durch Handschuh-Puder. *Fortschritte der Medizin* 100, 1213.
- Kamffer W. J., Jooste E. V., Nel J. T. and de Wet J. I. (1992) Surgical glove powder and intraperitoneal adhesion formation. *South African Medical Journal* 81, 158.
- Khan M. A., Brown J. L., Logan K. V. and Hayes R. I. (1983) Suture contamination by surface powders on surgical gloves. *Archives of Surgery* 118, 738.
- Kupryjanczyk J. (1989) Adenomatoid tumour of the ovary and uterus in the same patient. *Zentralblatt für allgemeine Pathologie und pathologische Anatomie* 135, 437.
- Lee K. P., Trochimowicz H. J. and Reinhardt C. F. (1985) Pulmonary response of rats exposed to titanium dioxide by inhalation for two years. *Toxicology and Applied Pharmacology* 79, 179.
- Longo D. L. and Young R. C. (1979) Cosmetic talc and ovarian cancer. *Lancet* ii, 349.
- Lord G. H. (1978) The biological effects of talc in the experimental animal: a literature review. *Food and Cosmetics Toxicology* 16, 51–57.
- Loup P., Besson A., Critsotakis J. and Mosimann R. (1979) Peritonite à amidon. *Helvetica chirurgica acta* 45, 733.
- McCormick M. A., Lacouture P. G., Gaudreault P. and Lovejoy F. H. (1982) Hazards associated with diaper changing. *Journal of the American Medical Association* 248, 2159.
- McGowan L., Parent L., Lednar W. and Norris H. J. (1979) The woman at risk of developing ovarian cancer. *Gynecologic Oncology* 7, 325.
- Mofenson H. C., Greensher J., DiTomasso A. and Okun S. (1981) Baby powder—a hazard! *Pediatrics* 68, 265.
- Mostafa S. A. M., Barger C. B., Flower R. W., Rosen-shein N. B., Parmley T. H. and Woodruff J. D. (1985) Foreign body granulomas in normal ovaries. *Obstetrics and Gynecology* 66, 701.
- Motomatsu K., Adachi H. and Uno T. (1979) Two infant deaths after inhaling baby powder. *Chest* 75, 448.
- Mussi N. C., Borghetti V. L. M., Mussi M. M. et al. (1979) Aspiração aguda de talco. *Journal of Pediatrics* 47, 233.
- National Toxicology Program (1992) *NTP Technical Report on the Toxicology and Carcinogenesis Studies of Talc in F344/N Rats and B6C3F₁ Mice*. NIH Publication No. 92-3152. National Institutes of Health, Bethesda, MD.
- Pairaudeau P. W., Wilson R. G., Hall M. A. and Milne M. (1991) Inhalation of baby powder: an unappreciated hazard. *British Medical Journal* 302, 1200.
- Pelling D. and Evans J. G. (1986) Long-term peritoneal tissue response in rats to mould-release agents and lubricant powder used on surgeons' gloves. *Food and Chemical Toxicology* 24, 425–430.
- Pfenninger J. and D'Appuzzo V. (1977) Powder aspiration in children. Report of two cases. *Archives of Disease in Childhood* 52, 157.
- Pickrell J. A., Snipes M. B., Benson J. M. et al. (1989) Talc deposition and effects after 20 days of repeated inhalation exposure of rats and mice to talc. *Environmental Research* 49, 233.
- Pratt P. C., George M. H., Mastin J. P. and Roggli V. L. (1985) Crystalline foreign particulate material in hernia sacs. *Human Pathology* 16, 1141.
- Rosenblatt K. A., Szklo M. and Rosenshein N. B. (1992) Mineral fiber exposure and the development of ovarian cancer. *Gynecologic Oncology* 45, 20.
- Rumack B. H. (1982) Diapers and poisons (editorial). *Journal of the American Medical Association* 248, 2164.
- Russell R. S., Merz R. D., Sherman W. T. and Siverson J. N. (1979) The determination of respirable particles in talcum powder. *Food and Cosmetics Toxicology* 17, 117–122.
- Scatarige J. C. and Stitik F. P. (1988) Induction of thoracic malignancy in inorganic dust pneumoconiosis. *Journal of Thoracic Imaging* 3, 67.
- Sheikh K. M. A., Dugal K., Relfson M., Gignac S. and Rowden G. (1984) An experimental histopathologic study of surgical glove powders. *Archives of Surgery* 119, 215.
- Simsek F., Türkeri L., Ilker Y., Küllü S. and Akdas A. (1992) Severe obstruction of the urinary tract due to talcum powder granuloma after surgery. *International Urology and Nephrology* 24, 31.
- Sparrow S. A. and Hallam L. A. (1991) Talc granulomas (letter). *British Medical Journal* 303, 6793.
- Swanson-Biearman B., Coughlin D. J., Dean B. S. and Krenzelok E. P. (1991) Massive talc aspiration: it still occurs. *Veterinary and Human Toxicology* 33, 383.
- Tolbert T. W. and Brown J. L. (1980) Surface powders on surgical gloves. *Archives of Surgery* 115, 729.
- Tzonou A., Polychronopoulou A., Hsieh C., Rebelakos A., Karakatsani A. and Trichopoulos D. (1993) Hair dyes, analgesics, tranquilizers and perineal talc application as risk factors for ovarian cancer. *International Journal of Cancer* 55, 408.
- Tukiainen P., Nickels J., Taskinen E. et al. (1984) Pulmonary granulomatous reaction: talc pneumoconiosis or chronic sarcoidosis? *British Journal of Industrial Medicine* 41, 81.
- Urdiales Cabal G., Lamamie de Clairac E., Sampedro Nuno A. and Diaz-Faes Cervero M. (1989) Peritonitis granulomatosa por almidón. A propósito de un caso. *Revista Española de las Enfermedades del Aparato Digestivo* 75, 411.
- Venter P. F. (1981) Ovarian epithelial cancer and chemical carcinogenesis. *Gynecologic Oncology* 12, 281.
- Wagner J. C., Berry G., Cooke T. J., Hill R. J., Pooley F. D. and Skidmore J. W. (1977) Animal experiments

- with talc. In *Inhaled Particles*. Vol. IV, Part 2. Edited by W. H. Walton and B. McGovern. pp. 647-654. Pergamon, Oxford.
- Wagner T. J. and Hindi-Alexander M. (1984) Hazards of baby powder? *Pediatric Nursing* **10**, 124.
- Wehner A. P., Hall A. S., Weller R. E., Lepel E. A. and Schirmer R. E. (1985) Do particles translocate from the vagina to the oviducts and beyond? *Food and Chemical Toxicology* **23**, 367-372.
- Wehner A. P., Tanner T. M. and Buschbom R. L. (1977a) Absorption of ingested talc by hamsters. *Food and Cosmetics Toxicology* **15**, 453-455.
- Wehner A. P., Weller R. E. and Lepel E. A. (1986) On talc translocation from the vagina to the oviducts and beyond. *Food and Chemical Toxicology* **24**, 329-338.
- Wehner A. P., Wilkerson C. L., Cannon W. C., Buschbom R. L. and Tanner T. M. (1977b) Pulmonary deposition, translocation and clearance of inhaled neutron-activated talc in hamsters. *Food and Cosmetics Toxicology* **15**, 213-224.
- Wehner A. P., Zwicker G. M., Cannon W. C., Watson C. R. and Carlton W. W. (1977c) Inhalation of talc baby powder by hamsters. *Food and Cosmetics Toxicology* **15**, 121-129.
- Weissberg D. and Kaufman M. (1986) The use of talc for pleurodesis in the treatment of resistant empyema. *Annals of Thoracic Surgery* **41**, 143.
- Wells I. P., Dubbins P. A. and Whimster W. F. (1979) Pulmonary disease caused by the inhalation of cosmetic talcum powder. *British Journal of Radiology* **52**, 586.
- West R. O. (1966) Epidemiologic study of malignancies of the ovaries. *Cancer* **19**, 1001.
- White N. D. (1992) Understanding latex. *Biomedical Instrumentation and Technology* **26**, 232.
- Whittemore A. S., Wu M. L., Paffenbarger R. S., Jr, Sarles D. L., Kampert J. B., Grosser S., Jung D. L., Ballon S. and Hendrickson M. (1988) Personal and environmental characteristics related to epithelial ovarian cancer. II. Exposure to talcum powder, tobacco, alcohol, and coffee. *American Journal of Epidemiology* **128**, 1228.
- Wilkerson C. L., Wehner A. P. and Rancitelli L. A. (1977) Leaching of radionuclides from neutron-activated talc in serum and in dilute hydrochloric acid. *Food and Cosmetics Toxicology* **15**, 589-593.
- Wilson D. F. and Garach V. (1981) Surgical glove starch granuloma. *Oral Surgery, Oral Medicine, Oral Pathology* **51**, 342.
- Witmeyer R. J. (1992) Trends in glove product and process development. *Biomedical Instrumentation and Technology* **26**, 235.
- Yusuf S., Peto S. R., Lewis J., Collins R. and Sleight P. (1985) Beta blockade during and after myocardial infarction: an overview of the randomized trials. *Journal of Progressive Cardiovascular Disease* **27**, 335.