C T F A

THE COSMETIC, TOILETRY, AND FRAGRANCE ASSOCIATION

May 26, 2000

E. EDWARD KAVANAUGH
PRESIDENT

Dr. C. W. Jameson
National Toxicology Program
Report on Carcinogens
MD EC-14
P.O. Box 12233
Research Triangle Park, NC 27709

RE: Substances Under Review for Possible Listing in the Report on Carcinogens, Tenth Edition (65 Federal Register 17889): Non-Asbestiform Talc

Dear Dr. Jameson,

The Cosmetic, Toiletry, and Fragrance Association[1] (CTFA) appreciates the opportunity to provide comments on the above referenced topic. Non-asbestiform talc is used within the personal care products industry, and thus, the review for possible listing in the Report on Carcinogens is of significant interest to CTFA members. The documents included in this submission address the basis of the nomination, and show conclusively that the listing of non-asbestiform talc in the 10th Report on Carcinogens is not scientifically justified.

Enclosed is a comprehensive review of scientific evidence relating to this topic prepared by Dr. Alfred P. Wehner, entitled "Cosmetic Talc is NOT a Carcinogen." This document directly addresses the basis of the nomination for possible listing in the Report on Carcinogens.

In addition, several relevant supporting documents are enclosed. They are:

- Transcript of a Workshop entitled Talc: Consumer Uses and Health Perspectives, jointly sponsored by the United States Food and Drug Association and the International Society of Regulatory Toxicology and Pharmacology. The workshop was held at the National Institutes of Health in Bethesda, Maryland on January 31-February 1, 1994.

[1] CTFA is the U.S. national trade association representing the personal care products industry. CTFA is comprised of over 300 active members that produce the vast majority of the cosmetics distributed in the U.S. and that also produce many over-the-counter drugs designed for dermal application. The association also has over 300 associate members that provide raw ingredients and suppliers and services to the industry. Many of CTFA's members are international companies that do business in foreign countries as well.

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- Publications related to the FDA/ISRTP Workshop (Regulatory Toxicology and Pharmacology, Vol. 21, p. 211-260, 1995).
- Comments on Toxicology, Special Issue: Talc, Volume 6(5), 1998.
- Wehner, A.P. Biological Effects of Cosmetic Talc. Food and Chemical Toxicology, Vol. 32(12), p. 1173-1184, 1994.

CTFA appreciates the opportunity to submit information on the proposed listing.

Sincerely,

[redacted]

G.N. McEwen, Jr., Ph.D., J.D.
Vice President - Science

Enclosures

Cosmetic Talc is NOT a Carcinogen

prepared for

The Cosmetic, Talc and Fragrance Association
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CONTENTS

Executive Summary

The National Toxicology Program (NTP) intends to review talc for possible listing in its Report on Carcinogens, Tenth Edition. As a Basis of Nomination the NTP cites the NTP-sponsored Lovelace study (TR 421, 1993), epidemiology studies suggesting an association between hygienic use of cosmetic talc and ovarian cancer, and a suggestion that occupational talc exposure has been associated with lung cancer in pottery workers.

This report presents well-documented scientific evidence to show that this particular Basis of Nomination has, in fact, no basis at all.

The Lovelace study had flaws in design and execution that led a panel of experts to declare it irrelevant for human risk assessment. Particularly the work by Morrow and by Oberdörster demonstrated conclusively that lung overload does induce malignancies. Even the low-dose groups in the Lovelace study experienced lung overload. Yet only the female rats of the high-dose group (18 mg/m^3) had a higher incidence of alveolar/bronchiolar adenomas and carcinomas than the controls; the male rats and the mice did not. By contrast, Wehner et al exposed hamsters to multiples of estimated baby exposures and found no histologic changes. Other investigators observed no neoplasms in rats and mice. This leads to the conclusion that (1) if lung overload is avoided, talc is not more carcinogenic than a nuisance dust, and (2) under conditions of lung overload, any dust --even titanium dioxide, frequently used as negative dust control-- can cause cancer.

Retrospective case-control studies provide rather fragile data because of numerous confounding variables and biases. Therefore a number of epidemiologists and statisticians believe that a relative risk (RR) or odds ratio (OR) of less than 2, or even less than 3, is of no biological significance although the data may be statistically significant. In 14 case-control studies in which an association between hygienic talc and ovarian cancer was observed, the RRs generally were about 1.5 with some of the data being barely statistically significant. Furthermore, the data generally failed to demonstrate a dose-response relationship and are often inconsistent, ambiguous and contradictory and therefore inconclusive. A dose-response relationship is essential in demonstrating causality, especially in weak associations. Results from five studies showed no association.

Epidemiology simply is too crude a tool for risk assessment at these low levels. This position is shared by the aforementioned panel of experts who after careful examination of all evidence declared that cosmetic talc does not present a risk to the consumer. No new evidence has been published since that time that would require a re-assessment of the experts' opinion.

This report lists numerous factors other than talc that have been associated with ovarian cancer, a disease whose etiology is still poorly understood. Many of these factors show a much more robust link to ovarian cancer than cosmetic talc.

Whether and how inanimate talc particles can migrate "upstream" in an anatomically and physiologically intact genital tract from the perineum to the ovaries without manipulation still needs to be resolved. Several affirmative findings have been shown to be flawed and could be explained as sample contamination. A sophisticated study using state-of-the-art techniques together with several other studies did not show any translocation. If talc particles were unable to translocate to the ovaries they, of course, could not cause ovarian cancer even if they were carcinogenic, which they are not.

Another question also needs to be resolved. Talc is a recognized fibrogenic agent. If talc particles were able to translocate from the perineum to the ovaries in sufficient numbers and remain there for a sufficiently long time to induce tumors, where is the ovarian fibrosis that one would expect to develop long before cancer? No such fibrosis has been reported in the literature.

For reasons outlined in this report it is inappropriate to relate a population of pottery workers to a population of cosmetic talc users. The former are occupationally exposed to an aerosol of numerous contaminants whereas the latter generally are only briefly exposed to cosmetic talc of high purity.

The report concludes with highlighting significant differences of physicochemical properties between cosmetic talc and asbestos.

In summary, no credible scientific study has shown that cosmetic talc causes cancer either in humans or in animals. Cosmetic talc is not genotoxic in vitro. A panel of experts declared cosmetic talc non-hazardous to humans. No new evidence has been published since the panel's findings that would require a re-examination of the panel's position. Therefore, the scientific evidence does not justify listing talc in NTP's Report on Carcinogens, Tenth Edition.

COSMETIC TALC IS NOT A CARCINOGEN

In the Federal Register (Draft approved March 29, 2000), the National Toxicology Program (NTP) announced its intent to review talc for possible listing in the Report on Carcinogens, Tenth Edition. Three reasons are given as a Basis of Nomination.

- The NTP-sponsored Lovelace study (NTP, 1992)
- Epidemiological studies suggesting an association between hygienic use of cosmetic talc and ovarian cancer
- A suggestion that occupational talc exposure has been associated with lung cancer in pottery workers

Although each of these issues has been repeatedly addressed in the past (see, for example, Wehner, 1994;1998), a comprehensive review and examination of scientific evidence relating to each of these topics will follow.

The NTP-sponsored Lovelace Study

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 18mg/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 is difficult to explain 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.

The study has flaws that do interfere with the interpretation of its results as previously pointed out (Wehner, 1994; Oberdörster, 1995). 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. Furthermore, the animals were exposed to micronized talc instead of regular cosmetic talc as used by consumers. This resulted in much smaller talc particles in the aerosol cloud with markedly different pulmonary deposition and clearance characteristics from regular-size cosmetic talc particles.

The investigators were unable to maintain target aerosol concentrations for the 18 mg/m^3 rat exposure group during 19 of the 113-122 weeks of exposure. For seven 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. 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 therefore is probably attributable to the high particle load in the lung (lung overload condition). 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.

Theophrastus Bombast von Hohenheim (1493-1541), the Swiss alchemist/physician scientist better known as Paracelsus, stated more than 450 years ago "dosis solum venenum facit" (only the dose makes a poison). This wisdom has been impressively demonstrated by Lee et al (1988,1985). These authors found a significant incidence of squamous cell carcinoma in the lungs of female CD rats exposed by inhalation for up to 104 weeks to 250 mg/m^3 titanium dioxide (TiO_2), a substance frequently used as a negative dust control. Roe fed rats chronically 20% lactose and subsequently found an increased cancer incidence in these animals (1989). This does not mean that TiO_2 and lactose are carcinogens and should be labeled as such. Statistically significant findings are not always biologically meaningful.

Oberdörster, one of the leading experts on pulmonary overload-related phenomena, states in his critical analysis of the Lovelace talc inhalation study that the lung cancers in female rats of the high-exposure group (18 mg/m^3) are a secondary effect as a consequence of chronic high pulmonary particle load and its associated chronic toxicity (1995).

The concept of lung particle overload and its pathophysiological and toxicological implications, now widely accepted, was first proposed by Morrow (1988) more than a decade ago. Analysis of past chronic inhalation studies has shown that in many cases the animals had been exposed to excessively high aerosol concentrations. Excessive because large numbers of particles being deposited chronically in the deep lung overwhelm the capacity of the alveolar macrophages (AM) to clear the alveoli of the deposited particles. This condition leads to an increasing particle overload of the lung as a function of exposure time and dose. As is well known, chronic presence of (highly insoluble) particles even of low toxicity --such as TiO_2, toner, carbon black, talc and others-- induces an inflammatory tissue reaction. Chronic inflammatory processes, in turn, are recognized as potential contributing factors in the etiology of some malignant tumors. Phagocytic cells release reactive oxygen species which are genotoxic. As Morrow et al. (1996) state, "inflammatory cells (i.e. neutrophils, macrophages) when activated by various stimuli can produce genotoxic effects in both mammalian and bacterial cell systems. Thus, nongenotoxic agents when given at exposures sufficient to elicit the recruitment and activation of

inflammatory cells may cause genotoxic effects and potentially the neoplastic transformation of cells." The authors further observe, " the demonstrations that inflammatory doses of particles produce mutation in the rat lung epithelial cells and that the particle-elicited rat lung inflammatory cells are themselves mutagenic indicate there are factors which can contribute to rat lung tumor responses under inflammatory conditions."

The biological plausibility of a direct causal link between lung particle overloading and lung cancer has thus been established, further supported by the observation that excess cancer incidence was never observed in animal inhalation studies with cosmetic talc when lung clearance remained unimpeded.

But how does one differentiate between a nonspecific particle effect due to lung overload and true particle carcinogenicity or, in other words, which aerosol exposure concentrations will begin to affect AM activity with resultant particle overload?

Based on an analysis of published data Morrow (1988) proposed a volumetric rather than a mass overload hypothesis. According to Morrow, impairment of AM clearance may be initiated when the average phagocytized particle burden in the AM reaches 6% of the AM volume, and AM clearance activity ceases completely at or about 60%. Other investigators arrived at similar numbers (Dorries and Valberg, 1992; Lehnert, 1990; Oberdörster et al, 1992). Given the average number of AM in the rat lung and the average volume of a normal rat AM (1,000 μm^3), these data can be translated to a volumetric lung burden of approximately 1 μl of particles, having a density of 1, per gram of lung, at which level lung overload is reached.

The available knowledge base facilitates the design of an experimental protocol that avoids lung particle overload and the confounding variables it introduces. The general recognition of the lung overload problem is reflected by the fact that the University of Rochester and the International Society for Aerosols in Medicine sponsored a symposium Particle-Lung Interactions: Overload-related Phenomena (May 17-18, 1990, Rochester, NY) exclusively on that subject. Various confounding variables, including malignant tumor development, reportedly are being introduced into inhalation studies by overloading animal lungs. Examination of the Lovelace data clearly shows that lung overload occurred even in the low-dose (6 mg/m^3) exposure groups.

The increased incidence of pheochromocytomas in the adrenal medulla in rats of both sexes in the 18 mg/m3 exposure group remains a perplexing phenomenon that needs to be independently confirmed. There is no known mechanism by which highly insoluble, inanimate talc particles deposited in the lung can affect the adrenal medulla, with the possible exception of a nonspecific stress-related secondary effect owing to pulmonary overload, as suggested by Oberdörster.

In view of several critical flaws in the design and conduct of the Lovelace study, the panel of experts at a public workshop titled Talc: Consumer Uses and Health Perspectives, 1/31 - 2/1/94, Bethesda, MD, sponsored by the International Society of Regulatory Toxicology and Pharmacology in collaboration with the U.S. Food and Drug Administration, declared the results

of the study irrelevant to human risk assessment. It should be noted that the Lovelace investigators never implied any such claim.

In this context attention is called to an editorial in SCIENCE (12/14/90), perhaps the first "semiofficial" public criticism of the practice of overdosing animals. It states, "A questionable cornerstone of EPA policy is its dependence on studies involving administration of huge levels of chemicals to rodents and highly conservative models of extrapolations to low doses in humans with the further assumption that at trivial doses a carcinogenic effect exists." Human exposure to cosmetic talc is orders of magnitude lower than doses generally administered in animal studies.

In contrast to the observations in the Lovelace Study are the findings by Wehner et al (1977a), Wagner et al (1977), and Pickrell et al (1989). Wehner et al chose the Syrian golden hamster (Mesocricetus auratus) as their animal model because they have demonstrated the development of pulmonary lesions in this species following prolonged inhalation of asbestos, cobalt oxide or nickel oxide dusts and cigarette smoke. Exposure to chrysotile asbestos aerosol (7 hr/day, 5 days/wk, for 11 months; mean aerosol concentration 23 µg/l) resulted in a 100% incidence of asbestosis in the exposed animals (Wehner, Busch, Olson and Craig, 1975a). Exposure to aerosols of cobalt oxide (Wehner et al, 1977b) or nickel oxide (Wehner, Busch, Olson and Craig, 1975b) caused pneumoconiosis, and cigarette-smoke exposure significantly increased tumor incidence and epithelial lesions of the larynx (Wehner, Busch and Olson 1974). The positive response of the Syrian golden hamster to a variety of carcinogens has been reported by a number of investigators (Dontenwill, 1970; Dontenwill and Mohr, 1961; Herrold and Dunham, 1963; Mohr, 1970; Mohr, Wieser and Pielsticker, 1966; Montesano and Saffiotti, 1968; 1970; Smith, 1974). Montesano, Saffiotti, and Shubik (1970) used this species extensively as an animal model for the study of the pathogenesis of lung cancer and found it "markedly susceptible to various respiratory carcinogens and conveniently refractory to chronic pulmonary infections."

Wehner et al (1977a) exposed the 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., 1977c) indicate that from 0.05 to 6 µg 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. Deposition of talc particles in the lungs of the exposed animals was demonstrated by X-ray fluorescence and by X-ray diffraction. 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. For details reference is made to the original paper.

Pickrell et al. (1989) investigated the relationship between the aerosol concentration of talc and the resulting lung burdens and histological lesions. Rats were exposed to 0, 2.3, 4.3, and 17 mg talc/m^3 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/m^3, 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/m^3, 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.

Thus, no signs of malignant pulmonary neoplasms were seen in three animal models-- hamsters, rats, and mice– even at talc aerosol concentrations far exceeding those encountered by human consumers (Aylott et al, 1979; Russell et al, 1979). Studies by Lee et al and others show that under conditions of lung overload most any dust --even titanium dioxide-- can indeed cause cancer.

The Epidemiology Studies

An appropriate introduction to this controversial subject is a reference to an article by Gary Taubes (1995) in SCIENCE, titled "Epidemiology Faces Its Limits." It is subtitled "The search for subtle links between diet, lifestyle, or environmental factors and disease is an unending source of fear -- but often yields little certainty (Appendix 1). " The article explains that, because of the softness of epidemiological data, a number of epidemiologists consider relative risk or odds ratios below 3 or even below 4 of questionable or no biological significance. Epidemiology simply is too crude a tool to determine with any degree of confidence risks to humans in this range. An editorial by Hernberg (1998) in the Scandinavian Journal of Work, Environment and Health, titled "Inconclusive cancer epidemiology" contains further discussion of this topic.

Muscat and Barish address the epidemiological link between cosmetic talc and ovarian cancer in Appendix 2. Suffice it to say here that the epidemiological data associating cosmetic talc use with ovarian cancer are rather fragile because of numerous confounding variables and biases. Some authors report a statistically significant but weak association with relative risks or odds ratios generally about 1.5; other investigators did not observe this link. Some of the findings are inconsistent, ambiguous, or contradictory and therefore inconclusive. Most of the data fail to demonstrate a dose-response relationship, one of the primary prerequisites to demonstrate causality. Dose data often are imprecise or missing.

It is most important to note that all retrospective case-control studies as well as other relevant information published before 1994 were discussed at the FDA/ISRTP public workshop in 1994 and that the panel of independent experts concluded then that the use of cosmetic talc does not

present a risk to the consumer. Given the experts' judgment, only epidemiological papers published after the workshop will be dealt with in this document.

Several additional case-control studies on links between hygienic talc use and ovarian cancer have been published since the workshop (Purdie et al, 1995; Heller et al, 1996; Cook et al, 1997; Chang and Risch, 1997; Godard et al, 1998; Cramer et al, 1999; Wong et al, 1999). None of these papers presents any new information in that they yielded RRs or ORs in the same questionable region, about 1.5, that was judged to be inconclusive by the panel of experts at the workshop. Adding weak links to a weak chain does not make a stronger chain. In fact, Godard et al and Wong et al found no statistically significant association at all.

Purdie et al reported an OR of 1.27 (CI 1.04 - 1.54); Heller et al investigated ovarian asbestos fiber and talc particle burdens in a limited number of subjects (13 exposed and 17 with no history of known exposure). They reported large numbers of asbestos fibers in approximately 70% of the asbestos-exposed group, but also in 35% of the controls. They also found talc particles in 85% of the talc-exposed group, but most astonishingly also in 100% of the controls, casting doubt on the procedures and findings. This paper also cites, as so many others do, references that do not support what they are supposed to support (Egli and Newton, 1961; Venter and Iturralde, 1979). The paper also fails to cite references that do not support the view of the authors, suggesting either unfamiliarity with relevant technical literature or bias of the authors.

The study by Cook et al, reporting an RR of 1.6 (CI 1.1-2.3), has been criticized by Muscat and Wynder (1997) mainly, but not exclusively, because Cook et al found no trend in the odds ratios with increasing number of perineal application despite a fivefold difference between the lowest and the highest exposure categories. The lack of a trend argues against a biological effect. As Wynder (1987) points out, in epidemiological studies of weak association, dose-response trends are especially important to demonstrate causality. Furthermore, just as Heller et al, Cook et al cite literature references that do not support what they are supposed to support and they fail to list references that do not support their view. Cook et al were given the opportunity by the editor to reply to the critique by Muscat and Wynder but declined to do so.

Chang and Risch observed an overall OR of 1.42 (CI 1.08-1.86). Their data show a consistent inverse dose-response relationship as shown in the following excerpt of their Table 2.

After-bath talc use (months)	Adjusted OR	95% CI
<10	1.836	1.24-2.73
10-25	1.128	0.74-1.72
>25	0.95	0.61-1.49
Years of after-bath talc use	Adjusted OR	95% CI
<30	1.697	1.08-2.64
20-40	1.455	0.96-2.15
>40	0.865	0.54-1.38

As Wynder stated (1987), dose-response trends are especially important in studies of weak associations to demonstrate causality. Here, too, the references cited in the paper suggest unfamiliarity of the authors with the literature and the complexity of the talc issues, or bias.

Cramer et al conducted a case-control study (563 subjects, 523 controls) to investigate genital talc exposure and risk of ovarian cancer. They observed an OR of 1.60 (CI 1.18-2.15) and refer to their results as a significant, more or less causal, association between hygienic talc use and ovarian cancer. This position is in contrast to the judgment of the panel of experts at the 1994 public workshop; to the repeated arguments in this report (see, for example, Appendices 1 and 2) that an OR of 1.60 presents a (weak) statistical significance whose questionable biological significance has lead to what has been called the "talc controversy."

In addition to four recent studies (Purdie et al, 1995; Sushan et al, 1996; Cook et al, 1997; Chang and Risch, 1997), Cramer et al cite in support of their position the eight pre-workshop case-control studies whose questionable biological significance has been examined and rejected by the workshop's panel of experts. They also acknowledge the existence of the then three studies (Hartge et al, 1983; Rosenblatt et al, 1992; Tzonou et al, 1993) that do not show a statistically significant association between hygienic talc use and ovarian cancer. In the meantime two additional studies (Godard et al, 1998; Wong et al, 1999) also showed no significant association. This confronts 13 positive with five negative case-control studies. It is difficult to understand how Cramer et al can refer to these contradictory and ambiguous results as showing "consistency". Even more difficult to understand is the authors' statement that a summary odds ratio of 1.36 for all studies showing an association suggests that between 10 and 11% of ovarian cancers in the examined populations were caused by hygienic use of talc. As Muscat and Barish summarize so eloquently, "epidemiologic studies have generated but not tested the hypothesis that talcum powder use is a risk factor for ovarian cancer" (Appendix 2).

The authors make a number of statements in their Discussion section that require comments.

- Cramer et al concede "the relatively weak odds ratios observed" and that "the most obvious weakness in the argument for biologic credibility of the talc and ovarian cancer association is the lack of a clear dose response. Most talc and ovarian cancer studies that have addressed dose response, including this one, have failed to demonstrate consistent dose-response relationships..." (emphasis added). It is, of course, exactly these two points - a weak statistical association of questionable biological significance, and the lack of consistent dose-response relationships - upon which most of the skepticism toward the authors' position is based. Most toxicologists would not be willing to accept causality if no definite, consistent dose-response relationship can be established, especially in case of weak associations.

- Cramer et al state that their "current study found no evidence of elevated risk associated with genital use of a cornstarch-based powder...", apparently to contrast the claimed carcinogenic effect of talcum powder with non-carcinogenic cornstarch powder. Yet in the same sentence they concede that "...in all of these (cornstarch) studies the exposure was infrequent and the OR and the confidence interval was wide." The latter part of the

statement renders this juxtaposition baseless because if the exposures to talc had been as infrequent as those to cornstarch, they most likely would not have shown an elevated risk either.

- Cramer et al state, "...some key elements supporting the biologic plausibility of the association (between hygienic talc use and ovarian cancer) have been established. It has been demonstrated that inert particles contaminating the vagina can reach the ovaries (Venter and Iturralde, 1979)." The authors either are unfamiliar with the relevant scientific literature, or they are biased by quoting only literature references which support their opinion while ignoring those publications that do not fit their concept. Wehner et al (1986) and Wehner (1998, pp349-350) repeatedly explained in detail why Venter and Iturralde's work cannot be considered proof of inert particle translocation from the vagina to the ovaries.

- Henderson et al and others have, indeed, found talc in both normal and malignant ovarian tissue. However, until sample contamination by ubiquitous talc particles can be ruled out with certainty, these findings cannot serve as proof of talc translocation from the perineum/vagina to the ovaries. In this context it is relevant to refer to Lee et al (1995). The authors found asbestos contamination in the paraffin of the tissue block during analysis of tissue samples supposedly containing asbestos fibers. They state that their findings "raises significant concerns about the validity of analysis for asbestos in tissue embedded in paraffin. In particular, diagnoses in which the presence of asbestos in tissue samples is taken as being indicative of past asbestos exposure, especially for those cases in which no known exposure has occurred, and studies purporting to show migration of asbestos to other organs in the body following inhalation or ingestion of asbestos require critical re-evaluation. The need for re-evaluation is particularly acute if appropriate control blanks were not evaluated as part of the studies."

The analogy to the talc situation is striking. Particular reference is made to the findings by Wehner et al (1985) who tried to replicate the frequently referenced observations of Egli and Newton (1961). Egli and Newton did not include examination of appropriate control blanks in their experimental protocol. Most likely they misinterpreted sample contamination as carbon black particle translocation from the vagina to the ovaries.

- Cramer et al concede that "...Heller et al (1996) reported a poor correlation between the amount of talc in the ovaries and personal history of talc use." Heller et al found talc particles in ovarian tissue of 85% of talc-exposed women, but also in an inexplicable 100% of the control group with no known talc exposure. The most logical explanation for these bizarre findings appears to be sample contamination by ubiquitous talc particles (Wehner, 1998, p. 352; Lee et al, 1995).

- Cramer et al state, "Talc, as a chemical relative of asbestos, appears able to induce histologic changes that are similar to those of asbestos, at least in the lungs (Kleinfeld et al, 1967)." Had Cramer et al examined the publications by Kleinfeld et al, they would have found that the talc worker populations in New York State, whom Kleinfeld et al

examined, were exposed to dust which "...contained not only mineral talc but also other silicates such as serpentine, tremolite, anthophyllite, and other ingredients predominantly carbonates. More over, free silica was present in the dust in variable amounts..." To equate this heavy occupational exposure prior to protective OSHA regulations to a dust mixture containing known toxic components with consumer exposure to cosmetic talc is scientifically untenable. Furthermore, chemically similar agents do not necessarily have similar effects. The pharmacological action of certain elementally and structurally identical agents (isomers) depends on whether they are dextrorotary or levorotary. Last but not least, there are significant physicochemical differences between talc and asbestos (Appendix 3).

- Cramer et al refer to the lack of an animal model to conduct relevant experiments. Wehner et al (1985, 1986) have demonstrated the suitability of the cynomolgus monkey (Macaca fascicularis) for such tests. The anatomical and physiological similarities between this monkey and the human female are remarkable and their menstrual cycles are identical.

The paper by Godard et al describes a case-control study in French Canadians to compare risk factors between familial and sporadic ovarian cancer. The major factors identified by the authors were a family history of breast or ovarian cancer; late age at use of oral contraceptives which had a protective effect; and a late age at last childbirth which had a protective effect in familial cases only.

The authors also examined other potential risk factors, including hygienic talc use. Ever-versus-never perineal talc use in 101 sporadic case patients compared to 152 control subjects yielded a relative risk (RR) of 2.45 with a 95% CI of 0.85-7.07 and a P value of 0.098. Corresponding data for 51 familial case patients and 152 control subjects are RR 3.25; CI 0.85-12.4; P = 0.084. Combined values for all case patients versus 152 control subjects are RR 2.49; CI 0.94-6.58; P = 0.066. These statistics did not reach statistical significance, as shown by the large CIs and the high P values. These authors state, "...the literature reviewed does not provide any convincing evidence that pure talc, when used as intended, presents a health risk to women."

Wong et al (1999) examined the association of hygienic talc use and epithelial ovarian cancer in 221 subjects and 311 controls. They observed an overall OR of 0.92 (CI 0.24-3.62). A significant association between duration of talc use and development of the disease was not demonstrable for 1-9 years (OR 0.9; CI 0.6-1.5), for 10-19 years (OR1.4; CI 0.9-2.2), or for more than 20 years (OR 0.9; CI 0.6-1.2). The authors conclude that "a significant association between the use of talcum powder and the risk of developing epithelial ovarian cancer is not demonstrable, even with prolonged exposure."

The only new and remarkable study is the one by Gertig et al (2000), remarkable because it is the first and only major *prospective study* investigating the purported association between hygienic talc use and ovarian cancer. Prospective cohort studies yield somewhat less fragile data than retrospective case-control studies because the outcome of case-control studies may be confounded by recall and selection bias.

Participants in the Nurses' Health Study formed a cohort of 78,630 women for analysis. Within the study's 20-year duration, 307 cases of epithelial ovarian cancer --the type of cancer most observed in previous case-control studies-- were diagnosed.

Gertig et al state, "We did not observe an overall association with ever use of talc and epithelial ovarian cancer (RR = 1.09; 95% CI, 0.86-1.37). There was also no elevation in risk among daily users of perineal talc, and no trend was seen with increasing frequency of use. Talc use on sanitary napkins was inversely related to ovarian cancer, but the association was statistically non significant. Exclusion of use of talc on sanitary napkins from the ever use of talc variable did not substantially alter the results. We also evaluated the risk for women who used both perineal talc and talc on sanitary napkins but did not see an effect compared with never users of talc (RR = 0.90; 95% CI, 0.59-1.37)."

Only when the authors stratified by histological subtype did they observe a statistically barely significant increase in risk for ever talc use for *serous invasive* cancers (RR =1.40; 95% CI, 1.02-1.91) but not for all serous cancers (including borderline cancers), endometrioid cancers, or mucinous cancers. For women who reported ever daily use of talc, the RR of invasive serous cancer was 1.19 (95% CI, 0.98-2.26). The RRs for ever talc users of less than once per week and one to six times per week were 1.29 (95% CI, 0.81-2.04) and 1.49 (95% CI, 0.77-2.11), respectively (P for trend = 0.05).

The capriciousness of epidemiological data even from prospective studies is illustrated by the authors' observation that talc use on sanitary napkins was inversely related to ovarian cancer. By the same token, this capriciousness might have pushed the relatively small serous invasive cancer groups (84/76) into the barely statistically significant region (multivariate RR 1.40, 95% CI, 1.02-1.91). Furthermore, a slightly higher random incidence of the mutant genes BRCA1 and/or BRCA2 (for which was not tested) in the talc-using serous invasive cancer group compared to their non-talc-using counterpart could account for the slightly increased cancer incidence, rather than talc use.

Gertig et al point out the lack of a dose-response relationship in their as well as in those previous case-control studies. A consistent dose-response relationship is , of course, the condition sine qua non for establishing a causal association between any agent and its biological effect(s), especially in weak associations.

The authors conclude that " the biologic evidence for the association of talc and ovarian cancer is incomplete." To which it must be added, "inconsistent, ambiguous, contradictory and therefore inconclusive."

Factors Other than Talc Linked to Ovarian Cancer

It is important to realize in this context that very little is known about the etiology of ovarian cancer. A number of physiological events, societal practices and exposure to certain chemicals

have been statistically linked to the incidence of this disease, but causality has not been established for any of them.

Daly and Obrams (1998) provide a more recent overview of the epidemiology and risk assessment for ovarian cancer. Their statement in their summary that cosmetic talc applied to the perineum "has been consistently (emphasis added) associated with ovarian cancer risk" must be rejected because this association has been anything but consistent (see section The Epidemiology Studies and Appendices 1 and 2 in this report). A review of the paper by Daly and Obrams shows that there are numerous risk factors other than talc linked to ovarian cancer. A number of these risk factors have considerable higher risk ratios than those attributed to cosmetic talc use in some, but not all, of the case-control studies with talc.

Based on their review of the literature and supported by 90 references, the authors present three hypotheses regarding the etiology of ovarian cancer: "(1) continuous uninterrupted cell division and regeneration of ovarian epithelium with each ovulation providing opportunity for mutation and malignant transformation; and (2) pituitary gonadotropin stimulation leads to malignant transformation; and (3) the ovary is exposed to carcinogens that can travel to the ovary via the vagina and fallopian tubes." As to (1) and (2), Dietl et al (1986) and Venter (1981) have expressed similar thoughts, as shown below. As to (3), the question of particle translocation from the perineum to the ovaries is far from settled as discussed in the following section of this report.

Daly and Obrams list several risk groups, among them exogenous hormones; endogenous hormones; body mass index (BMI); dietary factors; waist-to-hip ratio; physical activity; certain medications; and genetic risk factors. More specifically, ovarian cancer was increased 2.5-fold in women with polycystic ovarian syndrome, a condition associated with increased levels of luteinizing hormone and adrenal androgens. Subgroups in that population had ORs as high as 10.5 and 15.6. A cohort study of women with chronic endometriosis, who might experience various hormonal and or immunological abnormalities had an RR of 4.2 for ovarian cancer.

Referring to Purdie et al (1995), Mink et al (1996) and Barber et al (1995), Daly and Obrams call attention to body mass index (BMI); waist-to-hip ratio and physical exercise; and significantly greater body weight in the first year of life, respectively, as risk factors for ovarian cancer. More specifically, Purdie et al observed that Australian women with a BMI greater than the 85th percentile had approximately double the ovarian cancer risk of women in the middle 30% of the BMI range. The trend of increasing cancer risk with BMI remained significant in multivariate analysis. In this context the paper by Rosenblatt et al (1998) is of particular interest. The authors found that women in the highest BMI quartile were more likely to powder their perinea (OR = 1.6; 95% CI 1.1-2.6) and there appeared to be a close response relationship between the number of perineal powder applications and BMI ($P < 0.002$). Thus, when obesity is associated with an increased incidence of ovarian cancer, and when obese women powder their perinea significantly more frequently than women with normal BMI, then talc use inevitably becomes associated with the higher incidence of ovarian cancer. However, in this case talc use is not the driver of this relationship. Other factors, such as alcohol and tobacco use and douching, were also found to be related to perineal use of powder, thus presenting additional confounders.

Contrary to the constant emphasis of the benefits of physical exercise, Mink et al observed a direct relationship between physical activity and ovarian cancer. Women engaging in regular leisure physical activity had a 1.5-fold higher risk and those engaging in vigorous physical activity experienced a 2.5-fold greater risk. Women in the upper three quartiles of waist-to-hip ratio were at two-fold higher risk but the data showed no dose-response relationship.

In their section on Genetic Epidemiology, Daly and Obrams discuss the role of the two genes BRCA1 and BRCA2, discovered in 1994 and 1995, whose mutant forms are significantly linked to ovarian cancer. Among the many papers dealing with this subject is one by Whittemore et al (1997).

Daly and Obrams conclude their review with an overview of current research. They state: "The interaction of familial factors, BRCA1, BRCA2, and other genes conferring potential susceptibility with known reproductive and environmental risks is an area of intense study. The specific effects of age at first birth, incomplete pregnancies (i.e., spontaneous abortions, still-births, and ectopic pregnancies) on the risk of ovarian cancer are still being studied. The effect of tubal ligation on blood flow and transfer of substances from the uterine environment to the ovary, and the potential effect on secretion of gonadal steroids, are also subjects of continued investigation.

Other areas currently under study include infertility and use of specific agents to induce fertility; more detailed data collection on history of perineal talc use; dietary factors, adiposity and physical activity; HRT, especially combined estrogen-progesterone therapy; other medications; levels of circulating ovarian steroids, FSH, LH; GALT gene activity; p53 and k-ras mutations; LOH in tumor tissues; alleles of blood group substances; variations in glycolipid syntheses; tumors of borderline malignancy and subgroups of ovarian cancer by pathologic type.

The ultimate goal of these efforts is to apply our understanding of the events leading to ovarian carcinogenesis to novel therapeutic and preventive approaches. The recent identification of genes which play a critical role in the malignant transformation of ovarian epithelium not only identifies a group of women with a significantly increased risk of disease, but also provides new molecular tools to characterize the carcinogenic process and to identify potential sites for its interruption."

Harlow and Cramer (1995) investigated in two combined case-control studies the link between self-reported use of antidepressants or benzodiazepine tranquilizers and risk of epithelial ovarian cancer. They reported an overall adjusted odds ratio of 1.8, but an OR of 3.5 for women whose first use of these medications predated age 50.

Other overviews of etiology and epidemiology of ovarian cancer are those by Herbst (1994), Westhoff (1996), Sorenson Hulka (1997), and Shen et al (1998). All of them are similar in that they review the same well-known and well-described factors linked positively or negatively to ovarian cancer. The former include infertility; infertility drugs; menstrual history; family history; genetic factors; dietary factors and others as reviewed in this section. The latter include parity; breast feeding; oral contraceptives; tubal ligations and hysterectomy.

Herbst concludes that overall more than 90% of ovarian cancers occur sporadically and no single cause of ovarian cancer has been uncovered. On talc, Herbst comments "Talc has also been proposed as an environmental factor, but the magnitude of the association is small and it does not appear to be a factor in most ovarian carcinomas."

Westhoff summarizes, "A positive family history substantially increases risk; mutations in the BRCA1 gene may be responsible for about 5% of cases. No other exposures have been consistently associated with disease risk."

Sorenson Hulka provides an epidemiological analysis of breast and gynecological cancers. Ovarian cancer is dealt with on less than two pages with emphasis on hormonal interactions. Talc is not mentioned at all.

Shen et al are listed here as an example of a review based on poor background research and biased data presentation. This statement is based on the observation that Shen et al singled out talc among the numerous factors associated with increased ovarian cancer risk by stating "Some case-referent studies suggest a modest-to-moderate excess in association with genital talc application." In their discussion section the authors opined, " There are very few studies on chemical agents in the occupational or general environment, and the evidence is grossly insufficient. *The only exception is genital talc application, with 9 interview-based case-referent studies that provide rather consistent suggestions for a modest-to-moderate excess*" (emphasis added). Their "evidence" is presented as a part of their Table 2. Eight of the nine studies cited by the authors predate the judgment of the independent panel of experts. One of these eight studies is the one by Chen et al who report a risk ratio of 3.9 (CI 0.9 - 10.6), based on 7 subjects and 8 controls! The authors ignore those case-control studies that did not show a link between hygienic talc use and ovarian cancer. They also ignored, or were unaware of, the lack of dose-effect relationships and other shortcomings of these studies, as they have been pointed out repeatedly in this report and elsewhere (e.g., Wehner 1994, 1998). Last but not least they ignored, or were unaware of, the judgment of the panel of independent experts. In summary, their "evidence" in the form of the nine case-control studies is anything but consistent. It is, in fact, inconsistent, ambiguous, contradictory and therefore inconclusive as documented in this report.

In their overview of risk factors in the etiology of epithelial ovarian cancer Tortolero-Luna et al (1994) from the Department of Gynecologic Oncology at the University of Texas M.D. Anderson Cancer Center cite among risk factors age, race, nulliparity, infertility, a history of endometrial or breast cancer, and a family history of ovarian cancer. The authors state further, "Other factors have been suggested in the etiology of ovarian cancer, but their role is still inconclusive. Among these factors are the use of talc, fertility drugs, and postmenopausal estrogen therapy; age at menarche and at menopause; dietary factors (fat intake, protein intake, total caloric intake); an intolerance to lactose; the consumption of coffee and alcohol; and a history of mumps and other infectious diseases." They further list in this category of inconclusive or insufficiently investigated risk factors obesity; gall bladder disease; thyroid disease; exposure to diethylstilbestrol; use of antidepressants, anticonvulsants, or psychotropic drugs; ionizing radiation; and occupational exposure to benzene, paint, asbestos, or metals.

In their similar 1995 publication, Tortolero-Luna and Follen Mitchell state, " The etiology of ovarian cancer remains unknown... Age, race, nulliparity, history of endometrial or breast cancer, and family history of ovarian cancer have been consistently associated with increased invasive epithelial ovarian cancer risk; parity, oral contraceptive use, history of breast feeding, tubal ligation, and hysterectomy have been associated with a reduction in risk. The role of several factors, including age at menarche, age at menopause, infertility, use of fertility drugs, estrogen replacement therapy, talc use, dietary factors, lactose intolerance, and history of mumps and other infectious diseases, remain inconclusive."

Tortolero-Luna and Follen Mitchell conclude, "The etiology of ovarian cancer is multifactorial. Several factors have been consistently observed to modify the risk of ovarian cancer; however, the roles of many other factors remain inconclusive. Although the proposed hypotheses to explain the pathogenesis of ovarian cancer (incessant ovulation and hypergonadotropic hypogonadism) appear to account for the majority of known risk factors, the explanation for some factors remains unclear. Furthermore, some reproductive and hormone factors appear to be in conflict with these hypotheses. More epidemiologic, clinical, and basic research is needed to clarify inconsistencies in the etiology of ovarian cancer. The identification of genetic markers will allow elucidation of the mechanisms of carcinogenesis. Further epidemiologic studies need to include histologic-specific analysis and address the effects of variation in reproductive patterns, current OC formulations, use of fertility drugs, and the interactions between genetic factors and environmental and reproductive characteristics."

In considering mechanisms that might be involved in ovarian carcinogenesis, Venter (1981) points to the extremely high concentrations of gonadotropins 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 estrogens 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.

Cramer et al (1989; 1994) suggested that lactose consumption might be a dietary risk factor and lower transferase activity a genetic risk factor (OR = 2.2; 95% CI, 1.1-4.5). Mettlin and Piver also found a statistically significant increase in ovarian cancer risk in whole-milk drinkers (OR =

3.1; 95% CI, 1.8-5.5). However, Risch et al (1994) and Herrington et al (1995) observed no such links.

Tzonou et al (1993) observed a statistically significant (P for trend = 0.007) and dose-dependent association between hair dyeing and risk of ovarian cancer. Compared to never-users, women dyeing their hair up to 4 times a year had an RR of 1.74 (CI 0.91 - 3.32). Those dyeing their hair 5 or more times had an RR of 2.16 (CI 1.19 - 3.89). The authors found no evidence for an association between perineal talc use and ovarian cancer, and they found a reduced risk (RR 0.51; CI 0.26 - 1.02) in users of analgesics, mostly salicylates.

Whittemore et al (1989) found the ovarian cancer risk in women who had regularly consumed coffee for more than 40 years 3.4 times higher than in women who had never regularly consumed coffee. This relationship is much more robust ($p = 0.01$) than the relationship that they found with perineal talc use (RR = 1.4; $p = 0.06$). Neither association showed a dose-response relationship.

Ness and Cottreau (1999) and Ness et al (2000) link, among other factors, ovarian epithelial inflammation to ovarian cancer. They point out that ovulation entails ovarian epithelial inflammation. Inflammation, in turn, entails cell damage, oxidative stress, and elevations of cytokines and prostaglandins, all of which may be mutagenic. The authors speculate that factors such as endometriosis, cysts, hyperthyroidism and talc might be associated with an inflammatory response of the ovarian epithelium and thereby potentially a carcinogenic response. As far as talc is concerned, this hypothesis faces an old and so far unresolved problem. Talc is a well-recognized fibrogenic agent. If talc particles were, indeed, able to translocate from the perineum to the ovaries in sufficient numbers and manage to remain there sufficiently long to cause cancer, where is the fibrosis that should have been caused long before cancer, if talc were indeed carcinogenic?

Factors associated with a significantly decreased risk of ovarian cancer include parity; use of oral contraceptives; breast feeding; tubal ligation and hysterectomy, as reviewed by Tortolero-Luna and Follen Mitchell (1995) and by Daly and Obrams (1998). Not all investigators observed a decreased risk of ovarian cancer in women with tubal ligation. Blockage of the passage for toxins from the vagina to the ovaries has been offered as a seemingly logical explanation for the reduced ovarian cancer risk following tubal ligation. However, the ability of inanimate particles without locomotion of their own to migrate unassisted from the perineum "upstream" through a physiologically and anatomically intact genital tract to the ovaries has been questioned (Wehner et al, 1985; 1986). Another perhaps more attractive hypothesis points out that it is usually multipara who have their tubes ligated, and multiparity significantly reduces ovarian cancer risk. Thus it might be multiparity rather than the surgical procedure which is the driver of the observed phenomenon.

Cramer and Xu (1995) speculate that tubal ligation blocks or reduces the access of uterine growth factors which would otherwise reach the ovaries through uteroovarian circulation.

The purpose of this section is to show (1) that ovarian cancer is a multifactorial disease whose etiology is still poorly understood, and (2) that numerous factors have been associated with this disease, many of them showing a much more robust link than that observed in a few inconsistent case-control studies.

Does Talc Translocate from the Perineum to the Ovaries?

If talc particles were able to cause ovarian cancer they must be able to reach the ovaries from wherever they are deposited. But can inanimate talc particles without locomotion of their own and unable to respond to chemotactic stimuli move under normal anatomical and physiological conditions from the perineum through the vagina, breach the formidable barrier of the cervix, traverse the uterus and then "swim" upstream against the ciliary beat in the oviducts to reach the ovaries, seemingly defying the laws of physics?

The experimental evidence is controversial. Several studies purporting to have demonstrated such a translocation were seriously flawed rendering their results questionable (Wehner et al, 1985; 1986). Findings of talc or asbestos fibers in ovarian tissue could be explained by sample contamination. Even so-called "clean" country air contains several thousand microscopically small airborne particles per cubic centimeter. Carbon particles and talc particles, among others, are known to be ubiquitous, and asbestos fibers have been found in air samples collected in the Antarctic. In this context reference is made to the paper by Lee et al (1995), discussed elsewhere in this report.

As long as there is the possibility of tissue sample contamination, inappropriate tissue sample collection and sample processing that could explain the presence of particles in ovarian tissue, these possibilities must be investigated and ruled out before one can accept translocation as a valid explanation. On the other hand, if talc particles under normal physiological circumstances cannot translocate to the ovaries, they cannot cause ovarian cancer even if they were carcinogenic which they are not. At this point the talc issue would be resolved.

Wehner et al (1986), using neutron-activated talc in cynomolgus monkeys and state-of-the-art equipment, did not detect any talc particle translocation from the vagina to the ovaries in their animal model that physiologically and anatomically resembles the human female more than any other model. Several other investigators also failed to observe translocation in their studies.

One critical question has remained unanswered over the years. Talc is a recognized fibrogenic agent. If talc particles were to manage translocating to the ovaries in sufficient numbers and remain there sufficiently long to cause cancer, would one not expect fibrosis to develop long before cancer? Yet ovarian fibrosis has never been described in the studies linking hygienic talc use with ovarian cancer.

Finally, results with pleurodesis provide further proof that cosmetic talc is not carcinogenic. Pleurodesis is the deliberate creation of a fibrous adhesion between the visceral and parietal layers of the pleura. It is performed surgically by inserting talc into the pleural canal to treat

recurrent spontaneous pneumothorax and other conditions. There is not a single report in the scientific literature suggesting that inhalation of cosmetic talc causes lung cancer or mesothelioma in consumers. Pleurodesis has not caused any such lesions in approximately 200 patients up to 40 years after the procedure (Chappell et al, 1979; Weisberg and Kaufman, 1986).

Occupational Exposure of Pottery Workers and Lung Cancer

As a Basis of Nomination of talc as a carcinogen, the NTP states "...recently published epidemiology studies that suggests that talc exposure among pottery workers has been associated with lung cancer..."

NTP's premise must be rejected because occupational exposure of pottery workers to high concentrations of complex dust mixtures is vastly different from those encountered by consumers using cosmetic talc in terms of dust composition, talc quality, aerosol concentration and exposure duration.

Occupational exposure of talc miners and millers and of pottery workers to industrial dusts encountered in their trades in decades past has resulted in pulmonary and pleural malignancies in some exposed populations (Kleinfeld et al, 1967; 1974; Dement et al, 1980; Stille and Tabershaw, 1982; Lamm et al, 1988; Brown et al, 1990; Thomas, 1990; Thomas and Stewart, 1987) but not others (Rubino et al, 1976; Wergeland et al, 1990; Leophonte et al (1991). The talc worker populations investigated by Kleinfeld et al (1967; 1974) in New York state were exposed to dust which "contained not only mineral talc but also other silicates such as serpentine, tremolite, anthophyllite, and other ingredients predominantly carbonates. Moreover, free silica was present in the dust in variable amounts..." It should be noted here that the R.T. Vanderbilt Company, Inc., operator of the upper New York State talc mining and processing activities, states that "Our New York State tremolitic talc product and ore body does not contain tremolite or anthophyllite asbestos but a rather considerable amount of nonasbestiform tremolite and a much smaller amount of nonasbestiform anthophyllite" (Kelse, 1994). The important difference between asbestiform tremolite or anthophyllite fibers and non-asbestiform tremolite or anthophyllite cleavage fragments is explained below.

In addition to crystalline silica and talc dust the workers studied by Thomas and Thomas and Stewart "may also be exposed to ...soda ash, borate minerals, fluorspar, phosphate minerals, pigments and numerous substances used in glasses, including antimony, chromium, copper, iron, titanium and many others." Selevan and Dement (1979) observed increased mortality ($p < 0.05$) from all types of malignant neoplasms of the respiratory tract in miners but not in millers. Talc workers investigated by Rubino et al, by Wergeland et al, and by Leophonte et al were exposed to "pure" talc and showed no significant increase in mortality from malignant lung tumors. These findings demonstrate the importance of talc *quality* and precise mineralogical analysis.

Gamble from the National Institute of Occupational Safety and Health conducted a nested case-control study of lung cancer among New York talc workers, analyzing the previously published data. Gamble concludes that the negative slope of the exposure-response curve in the talc-

exposed populations "is the opposite to the effect one would expect if talc exposure were to increase the risk of lung cancer, is consistent with exposure-response relationships observed in populations mining nonasbestiform amphiboles, and is inconsistent with results from asbestos-exposed populations.

The standard mortality ratio for lung cancer (as well as for several other causes of death) are elevated in this group of talc workers. However, after adjustment for the confounding effect of smoking and the postulated role of very high exposures of short-term workers, the risk ratio for lung cancer decreases with increasing tenure. The lack of an exposure-response gradient is not consistent with a causal relationship. The time occurrence of lung cancer among these talc workers is more congruent with a smoking than a talc etiology."

There are no reports in the literature describing pulmonary malignancies in humans following exposure to cosmetic talc of the purity standards set by the Cosmetic, Toiletry and Fragrance Association since 1976 and adhered to by all reputable manufacturers. Purity standards governing industrial talc use are outlined by Zazenski in Appendix 3.

However, the issue is more complex and confusing than it appears, in part owing to regulatory and mineralogical ambiguities in defining asbestos and by rigidly employing the 3:1 aspect ratio (ratio of fiber length to width) in counting "fibers" (Kelse and Thompson, 1989). Wylie et al also propose abandoning the aspect ratio criterion (Wylie et al, 1993). Typically, aspect ratios for single asbestos fibers are reported as having means ranging from 20:1 to 100:1 while asbestos fiber bundles may have lower aspect ratios. Furthermore, the minerals anthophyllite, tremolite and actinolite have both an asbestos member and a non-asbestos member. Both asbestos and non-asbestos members of one of these mineral families will have identical chemical composition and nearly identical crystal structure. If the mineral grows in a single crystal fiber with no cross-linking between adjacent crystals it will have very high aspect ratios and is considered by mineralogists to be asbestos. If the mineral grows in blocks where cross-linking occurs between individual crystals it may "cleave" along a crystal lattice and produce elongate particles but their aspect ratios will be much smaller than those of asbestos fibers. These fibers do not have the internal crystal strength of the asbestos fibers and will break into shorter structures called "cleavage fragments". Asbestos fibers are flexible whereas cleavage fragments are brittle. There are no optical properties other than aspect ratio and morphology that can be used to differentiate the asbestos from the non-asbestiform varieties of these minerals. The latter are non-carcinogenic in contrast to certain true asbestiform fibers such as tremolite.

Products containing certain types of talc which contain cleavage fragments have been mistakenly identified as asbestos or have been called asbestos. A case in point is the material identified by some analysts as 3-4% tremolite asbestos in paint applied to a school. This material is not tremolite asbestos but misidentified non-asbestiform tremolite cleavage fragments.

The Occupational Safety and Health Administration (OSHA) has formally recognized the significant differences between asbestiform tremolite, anthophyllite and actinolite as compared to non-asbestiform tremolite, anthophyllite and actinolite cleavage fragments (OSHA, 1992). Following are excerpts from OSHA's summary.

"OSHA has reviewed available relevant evidence concerning the health effects of nonasbestiform tremolite, anthophyllite and actinolite and has also examined the feasibility of various regulatory options. Based on the entire rulemaking record before it, OSHA has made a determination that substantial evidence is lacking to conclude that nonasbestiform tremolite, anthophyllite and actinolite present the same type or magnitude of health effect as asbestos. Further, substantial evidence does not support a finding that exposed employees would be at a significant risk because nonasbestiform tremolite, anthophyllite and actinolite was not regulated in the asbestos standards.

OSHA hereby lifts the Administrative Stay, removes and reserves 29 CFR 1910.1101, and amends the revised asbestos standards to remove nonasbestiform tremolite, anthophyllite and actinolite from their scope."

As to the more immediate question of the association between pharmacological-grade talc use and cancer, reference again is made to pleurodesis. As stated on pages 16-17, this procedure has not caused any lung cancer or mesothelioma in approximately 200 patients up to 40 years following the procedure.

Physicochemical Similarities between Asbestos and Talc

Sometimes physicochemical similarities between asbestos and talc are given as a reason to suspect talc to be a carcinogen. While the rationale of physicochemical similarity suggesting similar biological effects is valid in a number of cases, it does not hold true for talc and asbestos. This statement is based on the following observations.

Elemental similarity does not necessarily mean similar biological effects. Different physical properties (e.g., shape and surface characteristics) of elementally similar chemicals can be responsible for significantly different biological effects. The pharmacological action of certain elementally and structurally identical agents (isomers) depends on whether they are dextrorotary or levorotary. The crystal structure of chrysotile, the most common type of asbestos, consists of a two-layer silica-brucite sheet rolled into a number of tiny fibrils. Talc comprises three-layer silica-brucite-silica sheets stacked together in small platy packets. The outer surface of chrysotile is brucite (MgOH) which is relatively soluble and hydrophilic. The outer surface of talc is silica which is highly insoluble and hydrophobic.

In contrast to chrysotile and crocidolite, talc is not genotoxic, as demonstrated by Endo-Capron et al (1993). The authors studied genotoxicity of three talc samples in rat pleural mesothelial cells, using genotoxicity assays for unscheduled DNA synthesis (UDS) and sister chromatid exchanges (SCEs). Attapulgite 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.

Conclusions

NTP's Basis of Nomination rests on (1) an animal inhalation study that has been declared by experts "irrelevant for human risk assessment", (2) epidemiology studies which have generated but not tested the hypothesis that hygienic use of cosmetic talc presents a risk for ovarian cancer. Some of them show an association of hygienic talc use and ovarian cancer while others do not, with results that were considered by experts inconsistent, ambiguous and contradictory and therefore inconclusive, and (3) the suggestion that occupational talc exposure has been associated with lung cancer in pottery workers, a finding irrelevant to cosmetic talc use for reasons explained in this document.

As has been abstracted in this report, no reputable scientific study has demonstrated that cosmetic talc causes cancer either in humans or in animals. Cosmetic talc is not genotoxic. In 1994, an independent panel of experts declared cosmetic talc non-hazardous to humans. No new findings have been published since 1994 that would require re-examination of the experts' position. Therefore, the scientific evidence does not justify listing talc in NTP's Report on Carcinogens, Tenth Edition.

References

Aylott R.I., Byrne G.A., Middleton J.D. and Roberts M.E. (1979) Normal use levels of respiratory cosmetic talc: preliminary study. Int J Cosm Sci 1, 177-186.

Barker D.J., Winter P.D., Osmond C. et al. (1995) Weight gain in infancy and cancer of the ovary. Lancet 345, 1087-1088.

Brown D.P., Sanderson W., and Fine L.J. (1990) Health hazard evaluation report no. 90-390 and MHETA 86-012. R.T. Vanderbilt Company. Gouverneur, New York. September, 1990. National Institute of Occupational Safety & Health, Cincinnati, Ohio.

Chang S. and Risch H.A. (1997) Perineal talc exposure and risk of ovarian carcinoma. Cancer 79, 2396-2401.

Chappell A.G., Johnson A., Charles J. et al. (1979) A survey of the long-term effects of talc and kaolin pleurodesis. Br J Dis Chest 73, 285-288.

Cook L.S., Kamb M.L. and Weiss N.S. (1997) Perineal powder exposure and risk of ovarian cancer. Am J Epidemiol 145, 459-465.

Cramer D.W. (1989) Galactose consumption and metabolism in relation to the risk of ovarian cancer. Am J Epidemiol 130, 904.

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, 66-71.

Cramer D.W., Liberman R.E., Titus-Ernstoff L., et al. (1999) Genital talc exposure and risk of ovarian cancer. Int J Cancer 81,351-356.

Cramer D.W. and Xu H. (1995) Epidemiologic evidence for uterine growth factors in the pathogenesis of ovarian cancer. Ann Epidemiol 5, 310-314.

Daly M. and Obrams G.I. (1998) Epidemiology and risk assessment for ovarian cancer. Seminars in Oncology 25,255-264.

Dement J.M., Zumwalde R.D., Gamble J.F., Fellner W., DiMeo M.J., Brown D.P., and Wagoner J.K. (1980) Occupational exposure to talc containing asbestos - morbidity, mortality and environmental studies of miners and millers. National Institute for Occupational Safety and Health. Cincinnati, Ohio. DHEW (NIOSH) Publication No. 80-115.

Dietl J., Buchholz F. and Stoll P. (1986) Das ovarielle Deckepithel und seine histogenetische Beziehung zum Ovarialkarzinom. Geburtshilfe und Frauenheilkunde 46, 561-566.

Dontenwill W. (1970) Experimental investigations on the effect of cigarette smoke inhalation on small laboratory animals. In Inhalation Carcinogenesis (CONF-691001). Edited by M.G. Hanna, Jr., P. Nettesheim and J.R. Gilbert. p. 389. NTIS, Springfield, VA.

Dontenwill W. and Mohr U. (1961) Carcinome des Respirationstrakts nach Behandlung von Goldhamstern mit DiŠthylnitrosamin. Z Krebsforsch 64, 305-312.

Dorries A.M. and Valberg P.A. (1992) Heterogeneity of phagocytosis for inhaled versus instilled material. Am Rev Respir Dis 146, 831.

Egli G.E. and Newton M. (1961) The transport of carbon particles in the human female reproductive tract. Fert Steril 12, 151-155.

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). Toxic in Vitro 7, 7-14.

Gamble J.F. (1993) A nested case control study of lung cancer among New York talc workers. Int Arch Occ Environ Health 64, 449-456.

Gertig D.M., Hunter D.J., Cramer D.W., Colditz G.A., et al. (2000) Prospective study of talc use and ovarian cancer. J Natl Cancer Inst 92, 249-252.

Godard B., Foulkes M.B., Provencher D. et al (1998) Risk factors for familial and sporadic ovarian cancer. Amer J Obstet Gynecol 179, 403-410.

Harlow B.L. and Cramer D.W. (1995) Self-reported use of antidepressants or benzodiazepine tranquilizers and risk of epithelial ovarian cancer: evidence from two combined case-control studies. Cancer Causes Control 6, 130-134.

Heller D.S., Gordon R.E., Westhoff C. and Gerber S. (1996) Asbestos exposure and ovarian fiber burden. Am J Ind Med 29, 435-439.

Herbst A.L. (1994) The epidemiology of ovarian carcinoma and the current status of tumor markers to detect disease. Am J Obstet Gynecol 170, 1099-1107.

Hernberg S. (1998) Inconclusive cancer epidemiology. Scand J Work Environ Health 24, 161-164.

Herrinton L.J., Weiss N.S., Beresford S.A., et al. (1995) Lactose and galactose intake and metabolism in relation to the risk of epithelial ovarian cancer. Am J Epidemiol 141, 407-416.

Herrold K.M and Dunham L.J. (1963) Induction of tumors in the Syrian golden hamster with diethylnitrosamine (N-nitrosodiethylamine). Cancer Res 23, 773.

Kelse J.W. (1994) Memorandum to Ronald E. Myers, U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards, Research Triangle Park, NC, dated 3/21/1994.

Kelse J.W. and Thompson C.S. (1989) The regulatory and mineralogical definitions of asbestos and their impact on amphibole dust analysis. Am Ind Hyg Assoc J 50(11), 613-622.

Kleinfeld M., Messite J., Kooyman O. and Zaki M.H. (1967) Mortality among talc miners and millers in New York State. Archs Envir Hlth 14, 663-667.

Kleinfeld M., Messite J. and Zaki M.H. (1974) Mortality experiences among talc workers: A follow-up study. J Occup Med 16, 345-349.

Lamm S.H., Levine M.S., Starr J.A. and Tirey S.L. (1988) Analysis of excess lung cancer risk in short-term employees. Am J Epidemiol 127, 1202-1209.

Lee K.P., Trochimowicz H.J. and Reinhardt C.F. (1985) Pulmonary response of rats exposed to titanium dioxide by inhalation for two years. Toxicol Appl Pharmacol 79, 179-192.

Lee R.J., Florida R.G. and Stewart I.M. (1995) Asbestos contamination in paraffin tissue blocks. Arch Pathol Lab Med 119, 528-532.

Lehnert B.E. (1990) Alveolar macrophages in a particle "overload" condition. J Aerosol Med 3(Suppl 1), S9-S42.

Leophonte P., Didier A. and Charlet J.P. (1991) Revue des Maladies Pespiratoires 8(Suppl 1), A184.

Mink P.J., Folsom A.R., Sellers T.A., et al. (1996) Physical activity, waist-to-hip ratio, and other risk factors for ovarian cancer: A follow-up study of older women. Epidemiology 7, 38-45.

Mohr U. (1970) Effects of diethylnitrosamine in the respiratory system of Syrian golden hamsters. In: Morphology of Experimental Respiratory Carcinogenesis p. 255. P.Nettesheim, M.G. Hanna, Jr. and J.W. Deatherage, Jr. (eds). NTIS, Springfield, VA.

Mohr U., Wieser O. and Pielsticker K. (1966) Die Minimaldosis für die Wirkung von Diäthylnitrosamin auf die Trachea beim Goldhamster. Naturwissenschaften 53, 229.

Montesano R. and Saffiotti U. (1968) Carcinogenic response of the respiratory tract of Syrian golden hamsters to different doses of diethylnitrosamine. Cancer Res 28, 2197-2210.

Montesano R. and Saffiotti U. (1970) Carcinogenic response of hamster respiratory tract to single subcutaneous administration of diethylnitrosamine at birth. J Natl Cancer Inst 44, 413-417.

Montesano R., Saffiotti U. and Shubik P. (1970) The role of topical and systemic factors in

experimental respiratory carcinogenesis. In Inhalation Carcinogenesis. Edited by M.G. Hanna, Jr., P. Nettesheim and J.R. Gilbert. p. 353. NTIS, Springfield, VA.

Morrow P.E. (1988) Possible mechanisms to explain dust overloading of the lungs. Fund Appl Toxicol 10, 369-384.

Morrow P.E., Haseman J.K., Hobbs C.H., Driscoll K.E., Vu V. and Oberdörster G. (1996) The maximum tolerated dose for inhalation bioassays: Toxicity vs overload. Fund Appl Toxicol 29, 155-167.

Muscat J.E. and Wynder E.L. (1997) Re: Perineal powder exposure and the risk of ovarian cancer. Am J Epidem 146, 786 (letter).

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 Institute of Health, Bethesda, MD.

Ness R.B. and Cottreau C. (1999) Possible role of ovarian epithelial inflammation in ovarian cancer. J Natl Cancer Inst 91, 1459-1467.

Ness R.B., Grisso J.A., Cottreau C. et al. (2000) Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer. Epidemiology 11, 111-117.

Oberdörster G. (1995) Lung particle overload: Implications for occupational exposures to particles. Reg Tox Pharmacol 27, 123-135.

Oberdörster G., Ferin J. and Morrow P.E. (1992) Volumetric loading of alveolar macrophages (AM): A possible basis for diminished AM-mediated particle clearance. Exp Lung Res 18, 87-104.

OSHA (1992) Federal Register, 57, No. 110, June 8, 1992.

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. Environ Res 49, 233.

Purdie D., Green A., Bain C. et al. (1995) Reproductive and other factors and risk of epithelial ovarian cancer: An Australian case-control study. Survey of Women's Health Study Group. Int J Cancer 62, 678-684.

Risch H.A., Jain M., Marrett L.D., et al. (1994) Dietary lactose intake, lactose intolerance, and the risk of epithelial ovarian cancer in southern Ontario (Canada). Cancer Causes Control 5, 540-548.

Roe F.J.C. (1989) p 575. In: Biological Interaction of Inhaled Mineral Fibers and Cigarette Smoke. Wehner and Felton (eds) Battelle Press, Columbus, OH .

Rubino C.F., Scansetti G., Piolatto G. and Romano C.A. (1976) Mortality study of talc miners and millers. J Occup Med 18, 186-193.

Russell R.S., Merz R.D., Sherman W.T. and Sivertson J.N. (1979) The determination of respirable particles in talcum powder. Fd Cosmet Toxic 17, 117-122.

Selevan S.G., Dement J.M., Wagoner J.K. and Froines J.R. (1979) J Environ Path Toxicol 2, 273.

Shen N., Weiderpass, E., Anttila et al. (1998) Epidemiology of occupational and environmental risk factors related to ovarian cancer. Scand J Work Environ Health 24, 175-182.

Smith W.H. (1974) Experimental studies on biological effects of tremolite talc on hamsters. In Proceedings of the Symposium of Talc, Washington, DC, May 8, 1975. Information circular 8639. p. 43. Compiled by A. Goodwin. US Bureau of Mines.

Sorenson Hulka S. (1997) Epidemiologic analysis of breast and gynecologic cancers, pp 17-29. In: Etiology of Breast and Gynecological Cancers (eds: C. Marcelo Aldaz et al.) PCBR 369, Wiley-Liss, Inc.

Stille W.T. and Tabershaw I.R. (1982) The mortality experience of upstate New York talc workers. J Occup Med 24, 480-484.

Taubes G. (1995) Epidemiology faces its limits. Science 269, 164-169.

Thomas T.L. (1990) Lung cancer mortality among pottery workers in the United States. IARC Sci Publ 97, 75-81. IARC, Lyon France.

Thomas T.L. and Stewart A. (1987) Mortality from lung cancer and respiratory disease among pottery workers exposed to silica and talc. Am J Epidem 125, 35-43.

Tortolero-Luna G. and Follen Mitchell M. (1995) The epidemiology of ovarian cancer. J Cell Biochem Suppl 23, 200-207.

Tortolero-Luna G., Follen Mitchell M. and Rhodes-Morris H.E. (1994) Epidemiology and screening of ovarian cancer. Obstet Gynecol Clin N Amer 21, 1-23.

Tzonou A., Polychronopoulou A., Hsieh C-c., et al. (1993) Hair dyes, analgesics, tranquilizers and perineal talc application as risk factors for ovarian cancer. Int J Cancer 55, 408-410.

Venter P.F. (1981) Ovarian epithelian cancer and chemical carcinogenesis. Gynecol Oncol 12, 281-285.

Venter P.E. and Iturralde M. (1979) Migration of particulate radioactive tracer from the vagina to the peritoneal cavity and ovaries. S Afr Med J 55, 917-919.

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.

Wehner, A.P. (1994) Biological Effects of Cosmetic Talc. Fd. Chem. Toxic. 32, 1173-1184.

Wehner, A.P. (1998) Is Cosmetic Talc "Safe"? Comments on Toxicology 6, 337-366.

Wehner A.P., Busch R.H. and Olson R.J. (1974) Effect of chronic cigarette smoke on tumor incidence in the Syrian golden hamster. pp 360-368. In: Experimental Lung Cancer, Carcinogenesis and Bioassays. E. Karbe and J.F. Park (eds) Springer Verlag, New York.

Wehner A.P., Busch R.H., Olson R.J. and Craig D.K. (1975a) Chronic inhalation of asbestos and cigarette smoke by hamsters. Environ Res. 10, 368-383.

Wehner A.P., Busch R.H., Olson R.J. and Craig D.K. (1975b) Chronic inhalation of nickel oxide and cigarette smoke by hamsters. Am Ind Hyg Assoc J 36, 801-810.

Wehner A.P., Busch R.H., Olson R.J. and Craig D.K. (1977b) Chronic inhalation of cobalt oxide and cigarette smoke by hamsters. Am Ind Hyg Assoc 38, 338-346.

Wehner A.P. and Craig D.K. (1972) Toxicology of inhaled NiO and CoO in Syrian golden hamsters. Am Ind Hyg Assoc 33, 146-155.

Wehner A.P., Hall A.S., Weller R.E. Lepel E.A. and Schrimer R.E. (1985) Do particles translocate from the vagina to the oviducts and beyond? Fd ChemToxic 23, 367-372.

Wehner A.P., Weller R.E. and Lepel E.A. (1986) On talc translocation from the vagina to the oviducts and beyond. Fd ChemToxic 24, 329-338.

Wehner A.P., Wilkerson C.L., Cannon W.C. et al. (1977c) Pulmonary deposition, translocation and clearance of inhaled neutron-activated talc in hamsters. Fd Cosmet Toxic 15, 213-224.

Wehner A.P., Zwicker G.M., Cannon W.C., Watson C.R. and Carlton W.W. (1977a) Inhalation of talc baby powder by hamsters. Fd Cosmet Toxic 15, 121-129.

Weissberg D. and Kaufman M. (1986) The use of talc for pleurodesis in the treatment of resistant empyema. Ann Thor Surg 41, 143.

Wergeland E., Andersen A. and Baerheim A. (1990) Morbidity and mortality in talc-exposed workers. Am J Ind Med 17, 505.

Westhoff C. (1996) Ovarian Cancer. Annu Rev Public Health 17, 85-96.

Whittemore A.S., Gong G. and Itnyre J. (1997) Prevalence and contribution of BRCA1 mutations in breast cancer and ovarian cancer: Results from three U.S. population-based case-control studies of ovarian cancer. Am J Hum Genet 60, 496-504.

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. Am J Epid 128, 1228-1240.

Wong C., Hempling R.E., Piver M.S. et al (1999) Perineal talc exposure and subsequent epithelial ovarian cancer: A case-control study. Obstet Gynecol 93, 372-376.

Wylie A.G., Bailey K.F., Kelse J.W. and Lee R.J. (1993) The importance of width in asbestos fiber carcinogenicity and its implications for public policy. Am Ind Hyg Assoc J 54(5), 239-252.

Wynder E.L. (1987) Guidelines to the epidemiology of weak associations. Prev Med 16, 211-212.