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CTFA
Cosmetic, Toiletry, and Fragrance Association

E. Edward Kavanaugh
President

July 14, 2004

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Dr. C.W. Jameson
National Toxicology Program
Report on Carcinogens
79 Alexander Drive
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P.O. Box 12233
Research Triangle Park, NC 27709

RE: Call for Public Comments on 21 Substances, Mixtures and Exposure Circumstances Proposed for Listing in the Report on Carcinogens, Twelfth Edition (69 Federal Register 28940): Cosmetic Talc

Dear Dr. Jameson,

The Cosmetic, Toiletry, and Fragrance Association (CTFA)[1] appreciates the opportunity to provide comments on the above referenced topic. Cosmetic talc is used within the personal care products industry, and thus, the review for possible listing in the 12th Report on Carcinogens (RoC) is of significant interest to CTFA members, as was talc's nomination for possible listing in the 10th RoC.

The basis for the nomination for listing in the 12th RoC is identified as "human epidemiological studies reporting an increased risk of ovarian cancer among women using talc for personal use." At the time of talc's previous nomination, CTFA submitted extensive comments addressing the issue of talc exposure and ovarian cancer. Our previous submissions show conclusively that the listing of cosmetic talc is not scientifically justified. This conclusion was supported by a 7-3 vote by the NTP Board of Scientific Counselors **not** to list talc not containing asbestiform fibers. There are not new data since the initial nomination and review that would change that conclusion.

Following the deferral of a listing decision for talc in the 10th RoC, a review article addressing NTP's deliberations regarding cosmetic talc and the RoC was published (Wehner, AP. Regulatory Toxicology and Pharmacology (2002) Vol. 36(1):40-50). This article supports a

[1] CTFA is the U.S. national trade association representing the personal care products industry. CTFA is comprised of nearly 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 approximately 300 associate members that provide raw ingredients and supplies and services to the industry. Many of CTFA's members are international companies that do business in foreign countries as well.

conclusion that cosmetic talc does not pose a cancer hazard; a copy is enclosed with this submission. An additional analysis prepared by the same author (Dr. Alfred Wehner) focused exclusively on the ovarian cancer issue is also enclosed.

Ovarian cancer epidemiology studies do not support a causative role for talc.

Three reviews addressing the issue of talc and ovarian cancer epidemiology studies were submitted by CTFA to NTP at the time of talc's review for listing in the 10th RoC, and are again enclosed here. The first of these reviews was co-authored by Dr. Kenneth Rothman (Professor, Department of Epidemiology and Medicine, Boston University), Dr. Harris Pastides (Dean, School of Public Health, University of South Carolina), and Dr. Jonathan Samet (Chairman, Department of Epidemiology, Johns Hopkins University); the other reviews were authored by Dr. Samuel Shapiro, Emeritus Director, Boston University of Public Health; and Joshua Muscat, M.P.H., American Health Foundation.

Briefly, arguments against listing talc in the RoC, as summarized in CTFA comments submitted to NTP April 24, 2001, are as follows:

The epidemiologic evidence does not support a causal association between talc use and ovarian cancer.[2] The dose-response pattern among talc users is inconsistent, and overall shows an inverse trend for both duration of use and frequency of use.[3] A plausible biological mechanism is lacking to explain a causal relationship. The majority of these studies were not specifically designed to test the hypothesis that talc use contributes to ovarian cancer.

The finding of a small increase in relative risk could be due to several potential confounding factors. Because these studies were largely retrospective studies and the applications of concern had occurred many years earlier, the composition of the material being used was not known and could have contained constituents and/or contaminants other than talc. A serious limitation of the data is that the true exposure of ovarian tissue to talc is by necessity unknown, and can only be poorly estimated using proxy measures (i.e., self-reporting of talc use in the perineal area). Additionally, use of talc-dusted diaphragms, which would clearly result in female reproductive tract exposure to talc, did not result in an increased relative risk of ovarian cancer (meta-analysis resulted in a summary odds ratio of 0.79).[4]

A meta-analysis published subsequent to consideration of talc for listing in the 10th Report on Carcinogens provides further support for a decision not to list.

A meta-analysis of epidemiology studies of perineal application of talc and ovarian cancer was published in 2003 (Huncharek, M., Geschwind, J.F., and Kupelnick, B. Anticancer Research Vol.

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[2] See enclosed reviews of the epidemiology studies by Dr. Kenneth Rothman et al; Dr. Samuel Shapiro; and Joshua Muscat.

[3] See enclosed review "Interpretation of Epidemiologic Studies on Talc and Ovarian Cancer" by Drs. Rothman, Pastides and Samet, Dose-response trends, pages 5-7.

[4] See enclosed review by Joshua Muscat, point #1, Testing the talc hypothesis using different epidemiologic measures.

23: 1955-1960). The analysis included sixteen observational studies and concluded that the "available observational data do not support the existence of a causal relationship between perineal talc exposure and an increased risk of epithelial ovarian cancer. Selection bias and uncontrolled confounding may account for the positive associations seen in prior epidemiological studies."

A copy of the publication is enclosed with this submission.

In summary, the available data on talc and ovarian cancer do not support the listing of cosmetic talc in the Report on Carcinogens. When cosmetic talc ("talc not containing asbestiform fibers") was reviewed by the NTP Board of Scientific Counselors for potential listing in the 10th Report on Carcinogens, the vote of 7-3 **not** to list reflected the lack of evidence supporting a listing.

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

Sincerely,

[Redacted]

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Enclosures

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Comments on Links between Hygienic Use of Cosmetic Talc and Ovarian Cancer

Introduction

On May 19, 2004, the National Toxicology Program (NTP) published a *Federal Register Notice* (**69**, 97:28940-28944) requesting public comments on 21 chemicals proposed for listing in the 12th edition of the Report on Carcinogens (RoC). Among the proposed chemicals was cosmetic talc. The rationale for reviewing cosmetic talc for possible listing in the RoC refers to human epidemiological studies reporting an increased risk of ovarian cancer among women using cosmetic talc for personal hygiene.

As project director and toxicologist at Battelle Pacific Northwest National Laboratory (1967-1989) I have conducted with my research team a number of studies with cosmetic talc, which have been published in peer-reviewed scientific journals and, having maintained my interest in this field, I am familiar with the relevant professional literature. I therefore consider myself qualified to comment knowledgably on the issues at hand.

I recently published a review of biological effects of cosmetic talc in the peer-reviewed journal *Regulatory Toxicology and Pharmacology*, based on 81 literature references (Wehner, 2002). This review included a detailed analysis of exactly the issues that prompted NTP to consider listing cosmetic talc in the 12th RoC, namely the reported weak association of hygienic talc use and ovarian cancer in several epidemiological studies, but not in others. For ready reference I am excerpting in my comments below relevant parts from my review.

Epidemiological Studies on Hygienic Talc Use and Ovarian Cancer

Epidemiology is a non-experimental science that yields fragile data which are subject to interpretation. Even with adequate statistical power, low risk levels are always suspect of possibly being due to confounding by measured or unmeasured risk factors or various biases, foremost among them recall bias in case-control studies. Epidemiology is too blunt a tool to reliably estimate relative risks (RR) less than 2. In his paper in *Science*, Taubes (1995) cites a number of prominent epidemiologists who postulate RRs or odds ratios (OR) of 3, or even 4, before results should be considered *biologically* significant and meaningful even though they might reach *statistical* significance with RRs or ORs of 2 or lower. Such studies can gain more weight if they are supported by consistency of results among the studies and by demonstrating consistent dose-response relationships (Wynder, 1987).

To the case in point, 21 case-control studies have been conducted to investigate a possible association of hygienic talc use and ovarian cancer. The results of 15 of these studies showed a weak, statistically (barely) significant link while 6 did not. The overall ORs or RRs in those studies reporting a positive association generally were below 2, mostly between 1.3 and 1.6. For details, analyses and critiques of the case-control studies I refer to Gross and Berg ((1995), Goodman (1995) and Muscat and Barish (1998).

All epidemiological studies published before 1994 were scrutinized by a panel of experts at a public workshop titled "Talc: Consumer Uses and Public Health Perspectives". The workshop, cosponsored by the International Society of Regulatory Toxicology and Pharmacy (ISRTP) and the U.S. Food and Drug Administration (FDA), was held January 31-February 1, 1994, in Bethesda, MD, and attended by close to 100 individuals from academia, government agencies, industry, private enterprise and the general public. Following are excerpted opinions expressed by the experts, as published in the executive summary (Carr, 1995).

Gori (Health Policy Center, Bethesda, MD) pointed out that human cancers are multifactorial diseases arising from a combination of simultaneous exposures to many potential etiologic determinants. To extricate the significance of any one of these factors from the integrated effects of all others is a challenging task. If one adds the technical problems in the execution of these studies, the "epidemiologic fog" is just as difficult to penetrate as the one generated by animal bioassays.

Rothman (1986), a leading theoretician on epidemiology who has extensively reviewed the difficulties of interpreting causal inferences, is quoted as follows: "Despite philosophic injunctions concerning inductive inference, criteria have commonly been used to make such inferences. The justification offered has been that the exigencies of public health problems demand action and that despite imperfect knowledge causal inferences must be made." This approach is scientifically untenable because it can lead to a solution being proffered before the cause of a problem has been identified.

In their review of epidemiological studies, Hartge (National Cancer Institute) and Harlow (Harvard University) point out the many interpretive difficulties of epidemiology as an observational science.

Wynder (American Health Foundation) stressed the specific problems of weak associations in epidemiology: Biases of respondents and investigators, known and unknown confounding factors, and "the irresistible urge to interpret results as if only a reduced set of variables of interest was operant, without acknowledging or controlling for a more multifactorial reality."

The panel pointed out biases (e.g., recall bias, publication bias) and potential confounders (e.g., parity, contraceptive use, ovulatory frequency, age at menarche and menopause, family history, diet) as well as exposure misclassification as inherent weaknesses of the retrospective case-control studies and found the epidemiological data "conflicting" and "equivocal." The panel concluded: "The possibility of an association of talc exposure and

ovarian cancer is an important hypothesis of potential public health importance. However, this association remains a research hypothesis whose verification or falsification needs additional study." That additional *epidemiological* studies would not serve this purpose is expressed in the last sentence of the executive summary: "However, epidemiologic studies have provided weak and conflicting risk signals for this association, and it is unlikely that further studies may prove adequate to raise concern at a level to warrant regulatory or public health measures" (Carr, 1995).

Since the workshop, additional epidemiological studies have been published (Purdie *et al*, 1995; Heller *et al*, 1996; Cook *et al*, 1997; Chang and Risch, 1997; Goddard *et al*, 1998; Cramer *et al*, 1999; Wong *et al*, 1999). None of these papers presented new evidence that would have required a reassessment of the conclusions of the workshop panel of experts. The results lacked dose-response relationships, were inconsistent and had the inherent weaknesses of retrospective case-control studies (various biases and confounding factors) that caused the experts to consider the pre-workshop studies inconclusive.

More specifically, Purdie *et al* reported an OR of 1.27 (CI 1.04 -1.54) which statistically is barely significant and falls within the controversial gray area below 2. Heller *et al* investigated ovarian asbestos fiber and talc particle burdens in 13 exposed and 17 control subjects with no history of known exposures. They found large numbers of asbestos fibers in approximately 70% of the asbestos-exposed group, *but also in 35% of the controls*. They also observed talc particles in 85% of the talc-exposed group, *but most remarkably also in 100% of the controls*! Cook *et al* reported an RR of 1.6 (CI 1.1-2.3). However, there was no trend in ORs with increasing numbers of perineal talc applications despite a fivefold difference between the lowest and the highest exposure groups, as criticized by Muscat and Wynder (1997). Chang and Risch found an overall OR of 1.42 (CI 1.08-1.86). Their data show an *inverse* dose-response relationship.

Cramer *et al* investigated the link of hygienic talc exposure and ovarian cancer in a case-control study involving 536 subjects and 523 controls. The authors observed an OR of 1.60 (CI 1.18-2.15) and calculated an overall OR of 1.36 for all epidemiological studies showing an association of genital talc use and ovarian cancer. The studies by Hartge *et al* (1983), Rosenblatt *et al* (1992), Tsonou *et al* (1993), Godard *et al* (1998), Wong *et al* (1999), and especially the prospective study by Gertig *et al* (2000), discussed separately below, showed no statistically significant link.

The paper by Gertig *et al* (2000) deserves special attention because it describes the only major *prospective* study specifically designed to investigate whether or not there is an association between hygienic use of cosmetic talc and ovarian cancer. As is generally acknowledged, prospective studies yield less fragile data than retrospective studies and therefore carry more weight. Yet the authors did not find a biologically meaningful link between hygienic use of cosmetic talc and ovarian cancer.

Participants in Gertig's 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 were diagnosed. This is the type of cancer most frequently observed in the (retrospective) case-

control studies. Gertig *et al* state: "We did not observe an overall association with ever use of talc and 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* (emphasis added) related to ovarian cancer, but the association was statistically not 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 (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), endometrial cancers, or mucinous cancers.

The capriciousness of epidemiological data even from prospective studies is illustrated by the observed *inverse* relationship between ovarian cancer and talc use on sanitary napkins. By the same token, this capriciousness might have pushed the relatively small serous invasive cancer groups (84/76) into the statistically barely 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 group, could account for the slightly higher cancer incidence, rather than talc use. Gertig *et al* point out the lack of a dose-response relationship in their study as well as in previous case-control studies and conclude that "the biologic evidence for the association of talc and ovarian cancer is incomplete."

In summary, the epidemiological data juxtapose questionable, statistically barely significant links in 15 studies versus negative results in 6 studies. The data are inconsistent, ambiguous, lack dose-response relationships and are therefore inconclusive. They do not support a causal relationship. Muscat and Barish (1998) concluded, "epidemiologic studies have generated but not tested the hypothesis that talcum powder is a risk factor for ovarian cancer."

Do Talc Particles translocate from the Perineum to the Ovaries?

This question is relevant to the epidemiological findings. If poorly soluble talc particles, deposited in the genital area, are suspected of causing ovarian cancer, they must be able to reach the ovaries in sufficient numbers and remain there for a sufficiently long period of time to cause this disease. The evidence for this to occur is as inconsistent, ambiguous and inconclusive as for the epidemiological studies.

It would violate the laws of physics if inanimate particles without locomotion of their own and unable to respond to chemotactic stimuli were capable on their own of migrating up the vagina, breach the formidable barrier presented by the cervix, traverse the uterus and swim "upstream" against the ciliary beat through the oviducts to reach the ovaries.

Yet, there are the observations by Henderson *et al* (1971; 1978) and others who reported numerous particles in or on ovarian tissues. Furthermore, there are the frequently cited publications by Egli and Newton (1961), Venter and Iturralde (1979) and DeBoer (1972) in support of particle translocation. In addition, it is well known that particles can achieve this feat if assisted by inadvertent or deliberate manipulation, the latter, for example, in patients in a supine or in the Trendelenburg position, or by a lacerated or a dilated cervix. Gases and liquids, such as radio-opaque contrast material and dyes, can be passed through the cervix by appropriate manipulation, and retrograde menstrual flow is a known phenomenon. But can particles such as talc translocate unaided from the perineum or the vagina to the ovaries under normal physiological and anatomical conditions?

Egli and Newton reported purported translocation of carbon black particles in two of three hysterectomy patients. The major flaw of their (non-quantitative) study was that their experimental protocol did not include examination of blank solution or filter samples as negative controls. This renders their results inconclusive as proof of translocation, as demonstrated by Wehner *et al* (1985). The latter authors attempted to replicate Egli and Newton's findings in cynomolgus monkeys, the animal model anatomically and physiologically most closely resembling the human female. Following Egli and Newton's experimental protocol as closely as possible, Wehner *et al* did, indeed, find carbon particles on the ovaries and in the solution with which the oviducts were rinsed. Had they ended their experiment at this point as Egli and Newton did, they would have confirmed particle translocation. However, upon examination of their filter and solution *blanks,* Wehner *et al* observed as many carbon black particles on and in the blanks as in the test samples. This strongly suggests a false positive by sample contamination with ubiquitous carbon black particles rather than particle translocation. The possibility of sample contamination and the paper by Lee *et al* (1995) on this subject is discussed below.

Venter and Iturralde (1979) also published seemingly convincing evidence of particle translocation. They deposited ^{99m}Tc-labeled human albumin microspheres (HAM) in the vaginas of 14 hysterectomy patients. After surgery, the uteri, oviducts and ovaries were analyzed for the radioactive tracer. In 9 of 14 cases radioactivity was detected in oviducts and ovaries. The weakness in the experimental design of that study is the use of only *one* radionuclide. Radioactive tracers are known to leach from the particles to which they are attached (Subramanian *et al*, 1995; Wehner *et al*, 1977; Wilkerson *et al,* 1977; Wehner and Wilkerson, 1981; Wehner *et al*, 1984). Bolles *et al* (1971) specifically describe this phenomenon for ^{99m}Tc-labeled HAMs. Particularly the findings by Wehner *et al* (1986) strongly suggest that Venter and Iturralde, too, observed a false positive, in this case by incorrectly assuming that the leached radioactive marker represented translocated HAMs. This problem can be avoided by using and analyzing for more than one radionuclide. Each radionuclide species has its own characteristic leaching rate. Leaching can be differentiated from particle translocation by comparing activities of several radionuclides in the neutron-activated bulk sample before exposure with these activities in the tissue samples after exposure.

Wehner *et al* (1986) deposited 125 mg neutron-activated talc, suspended in 0.3 ml physiological saline solution, in the posterior vaginal fornix of each of six sedated cynomolgus monkeys in each of 30 applications within a 45-day period, i.e., through at least one menstrual cycle. Two days after the final talc application the animals were sacrificed. Abdominal lavage fluid, ovaries, oviducts, uterus and vagina with cervix were collected for ∂-ray analysis. The radioisotopes ^{46}Sc, ^{60}Co, ^{59}Fe and ^{51}Cr in the activated talc were used as tracers. Six sham-exposed animals served as controls. Only the vaginas and cervices - i.e., the site of deposition - of the exposed animals contained varying quantities of talc. No talc was found in the uteri, oviducts, ovaries and the abdominal lavage fluid of the dosed monkeys. The system used for ∂-ray analysis could detect as little as ~ 0.5 μg talc, or approximately 1/250 000th of the talc quantity deposited with each application. Analysis of neutron activated talc is not only a very sensitive analytical technique, it also eliminates the problem of sample contamination by ubiquitous environmental talc.

Phillips *et al* (1978), using the rabbit as an animal model, observed no translocation of ^{3}H-labeled talc from the vagina to the ovaries.

The findings of DeBoer (1972) highlight the role of the cervix as a barrier. Before abdominal surgery he deposited a carbon black suspension into the uterus, the cervix or the vagina of more than 100 patients. He found rapid migration to the oviducts of particles deposited in the uterine cavity, and to a lesser degree of particles placed in the cervical canal. However, in only two of 37 patients did he observe translocation of particles deposited in the vagina. One of those two was a multipara (6 children) with a lacerated cervix. All of DeBoer's patients had been placed in the Trendelenburg position in which the legs are elevated at an angle of 45 degrees and the head being lower than the hips. In this position the abdominal organs are pushed toward the diaphragm by gravity. DeBoer observed that "in this position, especially under anesthesia, there is a negative intraabdominal pressure which may be sufficient to draw up material from the vagina into the uterus, particularly through a relaxed cervix."

This brief overview must suffice to demonstrate that the translocation studies are inconsistent and therefore inconclusive. For details I refer to the cited literature.

This still leaves the findings of Henderson *et al* (1971; 1978) unexplained. The authors reported large numbers of talc particles in and on human ovarian tissue. No plausible hypothesis has been proposed of how inanimate, poorly soluble particles can translocate unaided from the perineum to the ovaries under normal anatomical and physiological conditions. This suggests contamination with ubiquitous pollutants (talc and carbon particles, asbestos fibers) during sample collection and processing as a distinct possibility. This statement is supported by the findings of Wehner *et al* (1985) *versus* Egli and Newton (1961); by Heller *et al* (1996) who inexplicably found talc particles on the ovaries in 100% of their unexposed control group compared to 85% in the exposed group, and who observed asbestos fibers in 70% of their asbestos-exposed group, but also in 35% of their controls; and especially by the findings of Lee *et al* (1995).

Lee *et al* detected asbestos fiber contamination in paraffin of the tissue block during analysis of tissue samples for asbestos fibers. They state that this "raises significant concerns about the validity of analyses 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 relevance to the talc situation is striking. If it can be established that talc particles observed on ovarian tissue were deposited there by contamination rather than by translocation, the talc/ovarian cancer issue would be resolved. Even if the poorly soluble talc particles were carcinogenic - and no convincing evidence has ever been presented that they are - they would have to be capable of migrating from their site of deposition to the ovaries to be able to cause ovarian cancer.

Talc is a recognized fibrogenic agent. Assuming for the sake of discussion that talc particles are carcinogenic and somehow manage to translocate from the perineum/vagina to the ovaries in sufficient numbers and remain there for a sufficiently long period of time to cause cancer, where is the ovarian fibrosis that could be expected to occur long before cancer develops? Yet in none of the cases in which ovarian cancer has been linked to hygienic use of talc has ovarian fibrosis been reported. This question, first raised at the 1994 ISRTP/FDA workshop, is still awaiting an answer.

Meta-Analysis by Huncharek *et al*

Huncharek *et al* (2003) subjected the epidemiological data suggesting an association between hygienic use of cosmetic talc and ovarian cancer to meta-analysis. Meta-analysis is a statistical method, employed to results indicating weak associations, in an attempt to overcome the inherent problems of weak associations by pooling results of the studies. To be included in meta-analysis, studies have to meet stringent criteria.

Huncharek *et al* essentially confirm what I have documented in my comments. Their findings can best be summarized in their own words (p.1955): "Despite the availability of a number of observational studies suggesting an association between perineal talc application and ovarian cancer development, serious questions remain regarding the validity of this finding. These include: (1) the relatively small sample size of most studies limiting statistical power to detect an effect; (2) lack of consistent positive association across studies; (3) absence of demonstrable dose-response relationship; (4) lack of supporting evidence of carcinogenicity from animal or *in vitro* analyses; and (5) the possible presence of uncontrolled confounding producing a spurious positive association between talc use and ovarian cancer risk."

On two occasions in their paper, the authors refer to the "structural similarity between talc and asbestos, a well-recognized human carcinogen," further fuelling concern that there might be a causal relationship between hygienic talc use and ovarian cancer. This statement requires comment. "Structural similarity" is, of course, a subjective term and

can mean different things to different people. Be that as it may, it should be noted in this context that structural or even elemental similarity does not necessarily mean similar biological effects. Different physical properties (e.g., shape and surface characteristics) of elementally similar chemicals can have 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 asbestos species, consists of a two-layer silica-brucite sheet rolled into a number of tiny fibrils. Talc has 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. The aspect ratio of their fibers is believed to be mainly responsible for the carcinogenicity of asbestos fibers. Cosmetic talc does not contain fibers. Cosmetic talc is as similar to asbestos as graphite is to diamond.

Summary and Conclusion

As I have documented by appropriate literature references in my comments, the results of the epidemiological studies are inconsistent, ambiguous and inconclusive. Injection of talc into the ovaries of rats, a species recognized for its positive response to carcinogens, induced no cancers (Hamilton *et al,* 1984). Results of studies investigating translocation of talc from the perineum or the vagina to the ovaries also are inconsistent, ambiguous and inconclusive. Thus, no convincing evidence exists in the opinion of numerous experts and investigators cited in my comments to demonstrate a causal association between hygienic use of cosmetic talc and ovarian cancer.

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Respectfully submitted July, 2004

Dr. Alfred P. Wehner

Interpretation of Epidemiologic Studies on Talc and Ovarian Cancer

prepared by

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November 28, 2000

Executive Summary

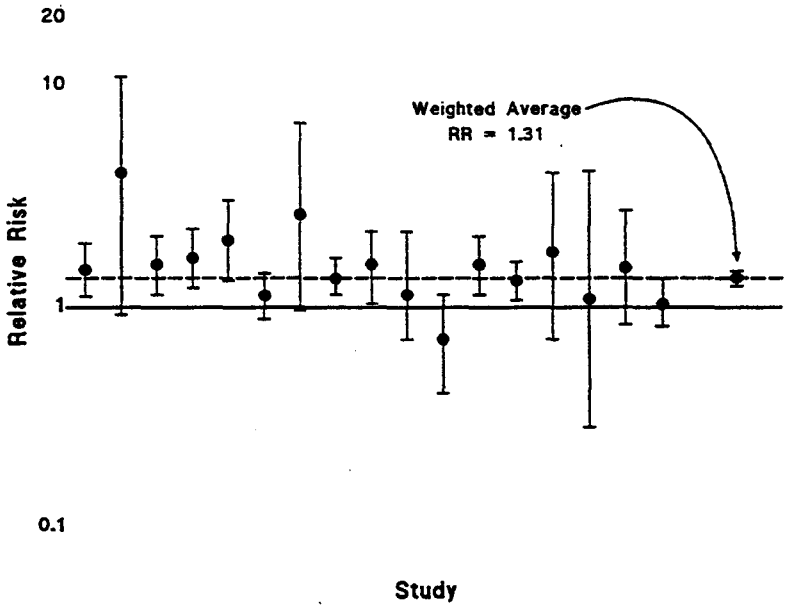
A weighted average of the results from epidemiologic studies to date measuring the relation between talc and ovarian cancer risk gives an overall relative risk of 1.31, with a 95% confidence interval of 1.21–1.41. Bias and causation are competing explanations for the weak positive association observed. This weak association could be an underestimate of a stronger association if there are errors in measuring talc exposure that apply uniformly to all study subjects (nondifferential misclassification). On the other hand, nondifferential misclassification does not bias an association that is null to begin with, so postulating nondifferential misclassification cannot shed light on whether the association results from a causal relation or not. Most of the published studies are interview-based case-control studies, subject to recall bias, which can readily give rise to associations of this magnitude. The evidence from these studies regarding recall bias is mixed. Uncontrolled confounding can also easily explain associations this weak; although no single confounding factor would seem to account for the overall effect, the combined effect of several such unidentified confounders could do so. In considering these competing explanations of bias and causation, the evidence in favor of a causal explanation is only the overall weak association of a relative risk of 1.31. The lack of a plausible biologic mechanism, on the other hand, weighs against a causal interpretation. Also weighing against a causal explanation is the dose-response pattern among talc users, which is an inverse trend for both duration of use and frequency of use. A causal relation would predict a positive trend, not an inverse trend. Based on these considerations, we suggest that the evidence to date does not indicate that talc can be "reasonably anticipated to be a human carcinogen."

Introduction

In this document we offer an interpretation of the epidemiologic literature with respect to the causal hypothesis that talc exposure causes an increase in the occurrence of ovarian cancer. Overall, we identified 23 epidemiologic studies conducted since 1980 that have examined consumer talc exposure with respect to subsequent risk for ovarian cancer.[1-23] The search methodology is described in the appendix. Sixteen of these were case-control studies reporting new data with effect estimates for talc exposure,[2-5,7,10,11,13-15,17-19,21-23] and one was a cohort study reporting an effect estimate.[9] One study examined occupational exposure to talc in women, but there were few exposed women in this study[16]; the other studies did not report quantitative effect estimates. The importance of this comparatively small set of epidemiologic studies is underscored by the paucity of relevant animal research on this question.

Most of these published reports come from epidemiologic studies in which talc was not the primary focus. Perhaps for this reason, talc exposure information was often crude. In only a few of these studies was there any attempt to categorize talc exposure by frequency of use or duration of use. For the 17 studies that reported some epidemiologic measure of effect, it was usually a relative risk estimate for ovarian cancer given that there was some exposure to talc, compared with no exposure or minimal exposure. These results are depicted graphically in figure 1. The findings on balance indicate a slight positive association between talc exposure and ovarian cancer, with an overall weighted relative risk of 1.31, and a 95% confidence interval of 1.21–1.41.

Figure 1
Study-specific Relative Risk Estimates for Ovarian Cancer Among Talc Users, and Overall Weighted Average of Study Results



Issues Affecting Causal Inference

Inferring a causal relation from a pattern of epidemiologic results follows no recipe, but certain principles can be applied. To begin with, what alternative explanations might be offered to explain a pattern of positive findings? If an uncontrolled confounding factor or a study-related bias could explain the results, a causal inference is less reasonable. Second, is there a plausible biologic mechanism? For example, environmental tobacco smoke shows a weak association with lung cancer in numerous epidemiologic studies of never smokers, but the plausibility of the relation, based on the known constituents of the smoke and their effect in higher concentrations, among active smokers, makes a causal inference more reasonable. Third, is there a consistent dose-response trend in the data? With rare exception, every causal relation in epidemiologic research shows a progressive relation between various measures of increasing exposure. In this discussion paper, we address the following issues that we believe are potentially relevant to causal inference regarding talc and ovarian cancer:

1. Exposure misclassification
2. Recall bias
3. Confounding
4. Dose-response trends
5. Biologic mechanism

Below we discuss briefly the import of each of these topics with respect to the interpretation of the epidemiologic literature of talc and ovarian cancer. We omit discussion of the role of chance in explaining any of the findings, because the combined weight of the 17 studies in figure 1 indicates that chance alone is an unlikely explanation for the overall weighted average of relative risks from the studies of 1.31. Other possible issues, such as selection biases and reverse causation might be relevant, but appear less important to us in interpreting these results, so we have omitted them in the interests of brevity. (Reverse causation, for example, could occur if preclinical ovarian cancer prompted women to use talc; while this situation is possible in some instances, we do not think it is a realistic explanation for the observed effects.)

Exposure Misclassification

Nearly all the studies were case-control studies. It is commonly believed that the validity of case-control studies is worse than that of cohort studies, but this view is mistaken. The validity of a study depends on the specifics of the study design, the nature of the data, and the nature of the hypothesis that the study addresses. For example, a cohort study that examines the long-term risk of cancer among coffee drinkers after a one-time dietary assessment of coffee consumption would suffer from weak exposure assessment. Although the exposure information might be accurate for the time at which it was collected, the exposure status of cohort members will change with time and the initial measure might be only poorly correlated with a more meaningful measure of coffee consumption. The effect of having a poor measure of exposure will be considerable nondifferential misclassification, a type of error that introduces a bias into study results that tends to drive effect estimates towards the null condition of no effect. In contrast, it may be possible to get more detailed exposure information from study subjects in a case-control study, which might thus avoid some of the bias that would result from a cohort study.

Much like coffee consumption, talc exposure is likely to vary over time as women age and their reasons for deciding to use talc change. Consequently a single baseline assessment of talc exposure at the start of follow-up in a cohort may lead to effect estimates that are biased toward the null. If talc habits are steady over time, a single baseline assessment becomes more informative. Furthermore, if talc use influences cancer risk with a long induction period, talc assessment at the start of a cohort study is more meaningful than an assessment of coffee drinking on heart disease risk, which is thought to have only a short-term effect.

Case-control studies also suffer from exposure misclassification, but the potential exists to extract more detailed history of exposure from the subject interview. In most of these studies, the exposure metric is based on interview information. It is subject to inaccuracies from recall error, as well as inaccuracies reflecting the nature of the questions asked and their relation to any biologically relevant measure of talc exposure. Ideally one would wish to have a measure of talc dose within the upper reproductive tract. The actual measures obtained by interview, however, are likely to be only modestly correlated with a hypothetically ideal measure. The result of this inevitable non-differential misclassification would be to bias any real effect towards the null. Nevertheless, one cannot draw the conclusion that the overall slight positive relation between talc exposure and ovarian cancer must be an underestimate of a larger effect because of nondifferential misclassification. Non-differential misclassification does not introduce any bias toward the null if the association is null to begin with, so to draw the conclusion that the overall effect estimate from the 17 studies is an underestimate, one must already know or assume that there is an even stronger positive relation in the data. Thus, the prospect of non-differential misclassification in measuring talc exposure does not provide any help by itself in assessing whether talc is related to ovarian cancer.

Recall Bias

Cohort studies do not suffer from recall bias, but recall bias is an issue for case-control studies that obtain exposure information from subject interviews. Such was the case for all the case-control studies whose effects are summarized in figure 1. Recall bias can readily introduce enough bias to produce the modestly-sized overall effect (RR = 1.3) that emerges from these studies. As an example, one of us reported an association between Bendectin and congenital heart disease in 1979, with a RR of 1.6.[24] One possibility for that positive relation was recall bias, a strong consideration in light of the study design that produced the finding (the study was not designed to evaluate Bendectin, which was only an incidental finding). To resolve the issue, a second study was undertaken, this time aimed at evaluating an effect of Bendectin by eliminating recall bias using a different design.[25] The second study found a RR of 1.0, prompting the conclusion that the RR of 1.6 reported in the earlier study was due to recall bias. The amount of recall bias for Bendectin in the 1979 study amounted to an apparent effect that was much stronger than the overall effect estimate for talc and ovarian cancer in the combined studies in figure 1.

We believe that there is mixed evidence for recall bias in these studies. We base this interpretation on the few studies that examined the effect of talc separately among women who had a tubal ligation and those who did not. If recall bias were the explanation for the full effect seen in the published literature, we would predict that the effect of talc exposure would appear to be about the same for women who have a tubal ligation and those who did not, because tubal ligation is unlikely to affect recall bias. In contrast, it would likely affect any biologic action of

talc. Only three studies give information relevant to this question. In those studies, the evidence is mixed. In one study the effect of talc is greater among women who have not had a tubal ligation,[22] and in a second, talc use appeared to have no adverse effect among women who had either a hysterectomy or a tubal ligation.[23] In the third study,[2] however, there was little difference in the effect of talc for women with and without tubal ligation or hysterectomy and the effect for both groups was near null. Thus, the overall evidence on the possibility of recall bias is equivocal, with no clear answer as to whether recall bias can be eliminated as an explanation.

Confounding

Although there are some strong risk factors for ovarian cancer, for any of them to be confounding to an extent that could account for the positive relations that have been reported, they would have to be strongly correlated with talc use. Family history, ethnicity, obesity and some reproductive risk factors are positively associated with the risk of ovarian cancer, but the magnitude of these associations does not appear high enough to introduce enough confounding, even jointly, to explain completely the positive association. Of course, it remains possible that yet unidentified risk factors for ovarian cancer could be important confounders, and several such factors in the aggregate could give risk to an overall association as weak as the one between talc and ovarian cancer.

Dose-response trends

A nearly constant feature of causal relations in epidemiology and in the pathogenesis of cancer in particular is a monotonically increasing relation between measures of exposure and disease risk. Even when disease risk increases through a threshold phenomenon, progressive dose-response trends are observed because the exposure measure varies and smooths the step relation of a threshold into a gradual climb in risk. In contrast, many biases would not produce a monotonic dose-response relation. For example, Horwitz and Feinstein advanced a theory of "detection-bias" as a non-causal alternative to the theory that exogenous estrogens cause endometrial cancer.[26] According to this theory, administration of estrogens would provoke genital bleeding among some women, leading to a work up and to the diagnosis of pre-existing endometrial cancers, accounting for the observed association. This theory, however, predicted that the increase in endometrial cancer risk would be greatest for short-term users of exogenous estrogens and would decline toward no effect for longer-term users. In actual fact this inverse dose-response trend was not observed, undermining the detection bias theory.

Exposure to talc can be characterized by the age at which use started, the number of years of use, and the frequency of use (e.g., number of times per day or per week). Among the talc studies, several reported on either frequency of talc use or duration of talc use, or both. We combined the findings from these studies into a meta-regression,[27] an analysis that combines dose-specific information from various studies into a single weighted regression analysis. Each data point in a meta-regression represents one effect estimate at a given dose level; the data points are weighted by the precision of each estimate, back-calculated from the confidence interval for that estimate.

In figure 2 we show the data points and meta-regression line for frequency of talc use, and in figure 3 for duration of talc use. These regression analyses confirm the picture that one obtains from reading the individual studies (table 1): the dose-response relation across dose levels above zero for talc exposure is not increasing, but instead declines. Although

misclassification could flatten a dose-response curve, it would not produce an inverse dose-response curve. Thus, the observed pattern, whether based on individual studies or from the combined meta-regression analysis, is not consistent with a causal interpretation for talc exposure. Instead it suggests that some as yet unidentified bias accounts for the overall modest relation between talc exposure and ovarian cancer.

Figure 2
Trend in Relative Risk by Frequency of Talc Use Among Users

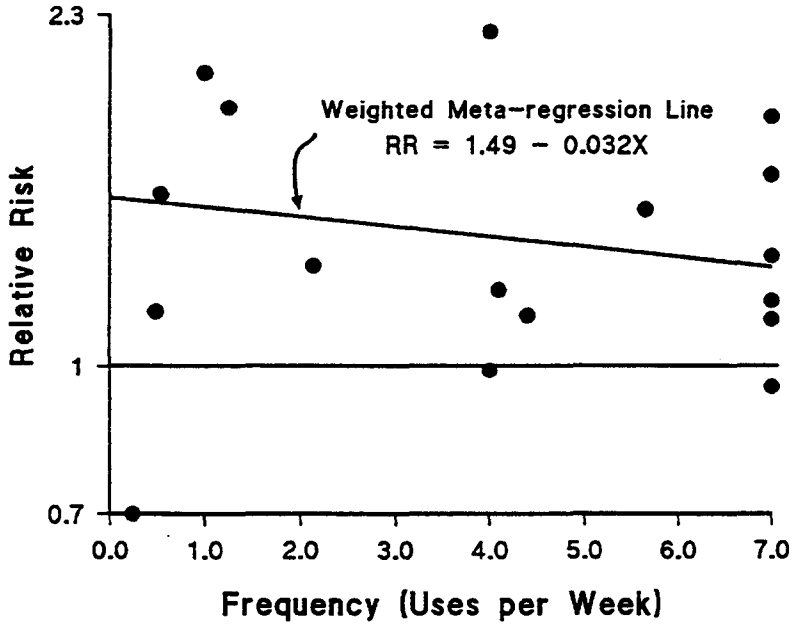


Figure 3
Trend in Relative Risk by Duration of Talc Use Among Users

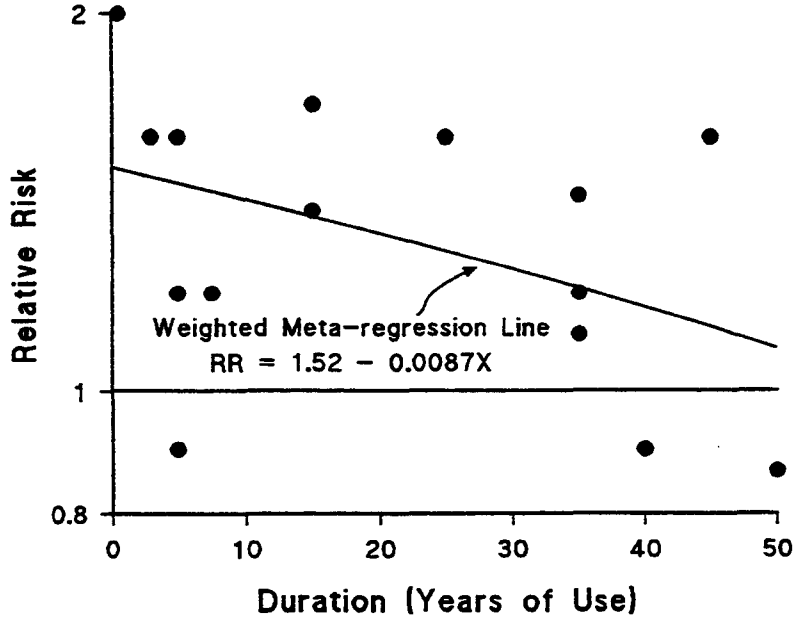


Table 1
Relative Risk Estimates of Ovarian Cancer by Frequency and Duration of Talc Use*

Citation	Frequency (Applications/wk)	Relative Risk	95% Confidence Interval
Booth et al.1989	7.00	1.30	0.80-1.90
	1.00	2.00	1.30-3.40
	0.25	0.70	0.30-1.80
Chang and Risch 1997	1.25	2.00	1.24-2.73
	4.40	1.13	0.74-1.72
	7.00	0.95	0.61-1.49
Cramer et al. 1999	4.00	2.21	1.37-3.56
	7.00	1.17	0.78-1.76
	7.00	1.57	0.80-3.10
Gertig et al. 2000	0.50	1.14	0.81-1.59
	4.00	0.99	0.67-1.46
	7.00	1.12	0.82-1.55
Harlow et al. 1992	0.55	1.50	0.80-2.70
	4.10	1.20	0.60-2.20
	7.00	1.80	1.10-3.00
Whittemore et al. 1988	2.14	1.27	0.82-1.96
	5.65	1.45	0.94-2.22

Citation	Duration (years)	Relative Risk	95% Confidence Interval
Chang and Risch 1997	15	1.70	1.09-2.64
	35	1.44	0.96-2.15
	50	0.86	0.54-1.38
Harlow et al. 1992	5	1.20	0.50-2.60
	25	1.60	1.00-2.70
	45	1.60	1.00-2.70
Ness et al. 2000	1	2.00	1.00-4.00
	3	1.60	1.10-2.30
	7.5	1.20	0.80-1.90
	35	1.20	1.00-1.50
Whittemore et al. 1988	5	1.60	1.00-2.57
	35	1.11	0.74-1.65
Wong et al. 1999	5	0.90	0.60-1.50
	15	1.40	0.90-2.20
	40	0.90	0.60-1.20

* For Open-ended Categories, the Values Assigned Assume that the Upper Category Boundary Corresponds to a Maximum Frequency Equal to Daily Use and a Maximum Duration of Use of 60 Years

Biologic Mechanism

The most plausible biological mechanism relating to the development of ovarian cancer concerns ovulation and the hormonal factors affecting it. Specifically, factors that suppress ovulation, such as gravidity, breast feeding, oral contraceptive use, tubal ligation and hysterectomy appear to reduce strongly the risk of ovarian cancer. Body mass index may also affect ovarian cancer risk. Medical conditions that may affect ovulation and also appear to increase the risk of ovarian cancer include endometriosis, ovarian cysts, and hyperthyroidism.

It does not appear plausible, however, that talc exposure has a direct effect on ovulation. If talc exposure is correlated with factors that affect ovulation, that correlation would produce confounding, as discussed above. If talc were a cause of ovarian cancer, it is presumably through a different mechanism than the many risk factors already known to affect ovarian cancer risk. There is no other evidence regarding such a mechanism, nor any clear evidence that talc applied perineally or on diaphragms makes its way physically to the ovaries. Ness et al suggest that inflammation may mediate ovarian cancer risk and that talc may play a role by causing inflammation.[17] This theory merits further investigation, although the tenability of the theory rests on the issue of whether talc particles physically reach the ovaries. Without a clear biologic mechanism for talc to cause ovarian cancer, an inference that talc does cause ovarian cancer would be an example of a "black-box" inference, meaning that the inference lacks a biologic foundation. "Black-box" inferences, such as the inference some draw that electromagnetic fields increase the risk for various cancers, are not necessarily invalid, but they are inherently more tenuous than inferences that are rooted in biologic explanations.

Conclusion

The only evidence to support a causal interpretation is the overall modest positive association seen in most of the epidemiologic studies that we have cited. The association is weak enough to be plausibly explained by unidentified bias. Recall bias is one possibility, but unidentified confounding could also readily give rise to the weak level of association that confronts us from these studies. Bias and causation are competing explanations for the weak positive association observed, an association that could be an underestimate of a stronger real association if nondifferential misclassification has diluted it. In considering these competing explanations, the lack of a plausible biologic mechanism based on the evidence to date weighs against a causal interpretation. More important, there is also positive evidence against a causal association: the inverse dose-response trend for both duration of use and frequency of use, a pattern that could not be explained by a causal relation. Based on these considerations, we suggest that the evidence to date does not indicate that talc can be "reasonably anticipated to be a human carcinogen."

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Appendix

Literature Search Methodology

The literature search was designed to find published epidemiologic studies specifically relating to the perineal use of non-asbestiform talc. The 2000 NTP Draft Report was used as the initial resource to locate applicable studies. To identify other relevant publications, an on-line search was performed in Dialog and using the internet. In addition, medical and scientific resources such as Medline, Toxline, and SciSearch were queried using various keyword terms including "talc," "non-asbestiform," "ovarian cancer," and "perineal." The search was limited to papers published after 1980, because asbestiform products were removed from the market in 1976. Once relevant articles were obtained, bibliographies were "tree-searched" to identify other applicable studies that may have been omitted during the on-line search. "Tree-searching" involves reading an article's bibliography, and then identifying citations that may contain appropriate information based on the title or author. "Tree-searching" identified early studies or those not recorded in on-line databases.

Non-asbestiform Talc and the Risk of Epithelial Ovarian Cancer.

A statement submitted to the Cosmetics, Toiletries and Fragrance Association (CTFA) for presentation to the NTP Board of Scientific Counselors.

December 1, 2000

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EXECUTIVE SUMMARY

In response to NTP's consideration of non-asbestiform talc as reasonably anticipated to be a carcinogen to the human ovary, a critical review of the epidemiologic evidence was conducted in the context of its potential for carcinogenicity. Associations identified in 16 case-control studies and one cohort study are overall of very low magnitude. In addition, there is strong evidence to suggest bias and confounding in the published studies. These alternative explanations have not been ruled out. Further, the application of standard criteria for causation to the data set as a whole indicates that none of these criteria are satisfied. Particularly troublesome are the inconsistencies seen across studies in subgroup analyses including different modes of exposure and different cancer outcome subtypes. Further, dose-response effects in terms of frequency or duration of exposure in those studies where the information was available have generally not been evident; in fact, much of the data contradict any dose response effects. Lastly, pending the opinion of expert toxicologists there is no plausible biological evidence to support the hypothesis that non-asbestiform talc increases the risk of ovarian cancer.

It is concluded that the epidemiologic data on non-asbestiform talc and ovarian cancer do not satisfy standard criteria for causality, and that classification of non-asbestiform talc as "reasonably anticipated to be a human carcinogen" is not supported by the epidemiological evidence.

INTRODUCTION

The National Toxicology Program (NTP) has submitted a draft report for consideration by its Board of Scientific Counselors entitled "Report on Carcinogens. Background Document for Talc: Asbestiform and Non-Asbestiform." In the Summary Statement (pages iii and iv), the following claim is made:

> The use of talc for perineal dusting on sanitary napkins and diaphragms has been associated with ovarian cancer. Fourteen of 16 case control studies of human ovarian cancer provided evidence for an association with the use of talc (presumably cosmetic grade, but information on fibrous content is lacking). A recent large prospective cohort study did not demonstrate an overall increase in risk for ovarian cancer with talc use (Gertig et al. 2000). However, in this study talc use was significantly associated with one subtype of ovarian cancer, invasive serous ovarian cancer. Risk of this tumor type was also elevated in several case-control studies (Harlow et al. 1992, Chang and Risch 1997, Cook et al. 1997, Wong et al. 1999, and Cramer et al. 1999). There is conflicting evidence concerning transport of talc through the genital tract to the ovary (Hamilton et al. 1984). Several studies provided evidence that factors preventing translocation of talc to the ovary, such as tubal ligation or hysterectomy, reduce the risk associated with talc use (Harlow et al. 1992, Whittemore et al. 1988, Cramer et al. 1999). Risk of ovarian cancer associated with talc use is unlikely to be a consequence of confounding or other biases.

Taken together, the findings are adduced as constituting sufficient evidence to classify non-asbestiform talc as a substance reasonably anticipated to be a carcinogen to the human ovary.

I have been asked by the CTFA to evaluate the epidemiologic evidence concerning the use of non-asbestiform talc in relation to the risk of epithelial ovarian cancer. To that end I have reviewed the studies referred to in the Draft Report, together with other relevant material. Based on my evaluation, I conclude that there are no valid epidemiologic data to implicate non-asbestiform powders in the etiology of epithelial ovarian cancer. In addition, the published epidemiologic evidence concerning elevated risks for all talc exposures, in whatever form or composition, is of questionable validity. Even the study that initially generated the hypothesis that exposure to talc may increase the risk of ovarian cancer (Cramer et al. 1982) is of questionable validity.

Contrary to what is stated in the NTP Report, bias and confounding are not only possibilities, but the published studies contain data to suggest that they are likely. The studies also suggest that several biases are generally present, and that they tend to be in the same direction in all the studies that have not yielded null findings. Moreover, the magnitude of the reported statistically significant overall relative risk (RR) estimates has been low—in all instances 1.9 or less, and mostly 1.5 or less. For such low estimates, epidemiologic methods are seldom, if ever, capable of making the distinction between bias, confounding, and causality (Shapiro 2000).

As it is beyond the scope of this evaluation to undertake a study by study review of the evidence, I have prepared a global critique. Before commencing that critique, however, it is necessary to point out two major, and critical, errors in the Draft Report.

First, contrary to what is stated in the Report, there are virtually no data that associate the use of diaphragms (including diaphragms known to have been stored in talc powder) with an increased risk of ovarian cancer. The findings have been so uniformly negative that Cramer et al. (1999), in their most recent case control study elected not to collect data on diaphragm use on the grounds that earlier studies had established that such exposure has been shown not to increase the risk of ovarian cancer (see also below: selection bias).

Second, contrary to the claim that the epidemiologic studies have evaluated exposure to talc that is "presumably cosmetic grade," (*i.e.*, non-asbestiform) there are at most only indirect and imprecise data on the risk associated with non-asbestiform talc. That claim is only inferred, based on exposure that took place after 1976. However, supplies of talc-containing powders may commonly have been stored before they were sold, after which they may then have been used for appreciable periods of time before fresh supplies were purchased. Thus the inference that after 1976, exposure was to non-asbestiform talc, may not be justified. All that can be assumed is that at some unknown time after 1976, the ratio of the use of asbestiform to non-asbestiform talc presumably declined.

CRITIQUE

Below, the assembled epidemiologic evidence to implicate talc in the etiology of ovarian cancer is evaluated according to standard criteria used to assess causality in epidemiologic research (Hill 1965, Susser 1991). The criteria are not mutually exclusive, but to justify any causal inference a reasonable combination of them must be present.

Temporality

An absolute requirement for causal inference is that the exposure must antedate the onset of the illness. For ovarian cancer, it is impossible to determine the time of onset with any precision. In that circumstance, lag-time analysis must be used in order to ensure that all exposures that are assessed have a strong likelihood of having taken place before the disease commenced. Exposures in the distant past have been assessed in the different studies, but they have mostly been ignored in the evaluation of dose response effects, in terms either of duration or frequency of use. Lower abdominal symptoms, such as vaginal bleeding, could lead to the use of powders. That is, ovarian cancer could sometimes have "caused" talc exposure, rather than the reverse. For the estimation of overall risk, only one case-control study (Cook et al. 1997), and two follow-up studies (Hankinson et al. 1993, Gertig et al. 2000) have clearly specified the exposures in an effort to establish an unambiguous temporal sequence of events.

Strength (Magnitude) of the Association

In observational studies, bias and confounding can never be entirely excluded as possible explanations for an observed association. However, if in any given study, the risk among the exposed is increased many-fold relative to the non-exposed (high relative risk estimate), and if the methods used in the research are reasonably adequate, it is likely that even if plausible sources of bias could be eliminated, the RR would remain elevated. For example, the relative risk of lung cancer among heavy smokers has been shown to be increased some 30-fold in countless studies. Some of the studies (including the original pioneering work by Doll and Hill (1950) that was among the first to document the association) are known not to have been free of bias (Doll and Hill 1964, Doll and Peto 1976). However, there are no plausible biases that could conceivably have accounted for a 30-fold increase in the risk. Had it been possible to avoid the various biases, doing so would have had (at most) only a minor effect on the magnitude of the RR—a strong if slightly attenuated association would still have been present.

For weak associations (*i.e.*, RRs of 2.0 or less), the situation is entirely different: minor sources of bias and confounding may readily account for them. If all sources of bias could be avoided, there may be no association at all. For this reason, making a confident distinction between bias and causality is almost invariably beyond the resolving power of observational research (Shapiro 2000). For RRs that are considerably below 2.0 (say, 1.5 or less), it is virtually impossible to do so (Shapiro 2000).

In the case-control studies of talc exposure and ovarian cancer, the finding that first gave rise to the hypothesized association with ovarian cancer was a statistically significant overall RR estimate of 1.92 (Cramer et al. 1982). In one subsequent study, it was 1.60 (Cramer et al. 1999). In the remaining studies, all statistically significant overall RR estimates were 1.6 or less (Chang and Risch 1997, Cook et al. 1997, Cramer and Xu 1995, Green et al. 1997, Ness et al. 2000, Purdie et al. 1995). This general trend of declining RR is strongly suggestive of the well-known phenomenon of regression to the mean and it favors chance as an explanation for the initial hypothesis-generating association (Cramer et al. 1982).

A meta-analysis combining the various studies has been published in which the summary overall RR estimate was 1.3 (Gross and Berg 1995). The validity of the application of meta-analysis to observational data is highly questionable (Shapiro 1997). In addition, as is the case here, when there is marked heterogeneity among the studies in terms of their methods (see below: consistency) and the definition of the outcomes and the exposures studied, as well as in the confounding factors that were taken into account, it is generally accepted that findings derived from meta-analysis are not only questionable, but uninterpretable (Shapiro 1997, Greenland 1994). In the present case, that lack of interpretability is compounded by the low magnitude of the summary RR estimates.

Some have argued that the fact that the reported risk estimates, although small, have been positive in 14 out of 16 case control studies, as well as in a meta-analysis (which, incidentally, is not independent of the 16 studies), points to causality. That argument assumes that bias and confounding did not tend to be in the same direction across the studies. Yet in observational research the same biases are commonly present, and in the same direction, in more than one study. In addition, as explained below, there is evidence in the published studies to suggest that this was the case (see below: selection bias; information bias).

In addition to overall RRs derived from analyses of the total data in the various studies, analyses of subgroups have also been performed. Some of the findings in the subgroups have been invoked as evidence to support causality. For example, as mentioned above, in their initial hypothesis-generating study, Cramer et al. (1982) reported an overall RR of 1.92 (95% confidence interval, 1.27-2.89) for women exposed to perineal dusting, or to talc applied to sanitary napkins, or to both. That estimate was based on 92 exposed cases and 61 exposed controls. They also examined multiple subgroups, in one of which (exposure to perineal dusting *in combination* with exposure to sanitary napkins dusted with talc, and *in combination* with exposure to diaphragms stored in talc) the RR was 3.28 (1.68-6.42). In that subgroup analysis there were only 32 exposed cases and 13 exposed controls. Moreover, as indicated by the 95% confidence intervals, the RR of 3.28 was statistically compatible with the overall and best RR estimate of 1.92. The "blip" of 3.28 was identified in the course of multiple comparisons in which "significant" associations would have been expected to occur by chance.

The procedure of exploring multiple subsets of data in the search for "statistically significant" associations is known as "data dredging," and it is not valid unless there are well formulated hypotheses, specified *a priori*.

Other examples of subgroup analyses abound in the published studies. Thus, in some instances there have been overall associations with all types of ovarian cancer (*e.g.*, Green et al. 1997). In others overall associations have not been identified (*e.g.*, Hartge et al. 1983), or they have been weak and nonsignificant (*e.g.*, Harlow and Weiss 1989). Instead, causality has been suggested based on subgroup analyses carried out in the search for elevated RRs. Some "significant" associations, virtually all of them with RRs below 1.5, have been identified only with specific subtypes of epithelial ovarian cancer. Again, the use of multiple comparisons in order to "dredge" for positive associations is not valid; inevitably, some will turn up by chance. In addition, as a separate issue discussed below (see below: consistency), the associations with the specific subtypes have been inconsistent across the studies.

In summary, the overall associations identified in the published studies have almost without exception been of low magnitude. Even the associations identified in subgroups have generally been of low magnitude. None of the studies satisfy the causal criterion of high magnitude associations.

Statistical Stability

The criterion of statistical stability requires that data derived from relatively unbiased and unconfounded studies should be sufficiently robust so that chance, as an alternative explanation of any given association, is only a remote possibility. That requirement, however, is not independent of the requirement that the association should also be of sufficient magnitude to ensure that bias and confounding are also remote possibilities. Weak associations simply impose the need for greater numbers in order to achieve "statistical significance." Thus, biased data, if plentiful enough, can become "robust", and "statistically significant." In the face of the low magnitude of the associations that have generally been observed, the "statistical significance" of the reported associations cannot be invoked to support causality.

Dose-Response Effects

If talc increases the risk of ovarian cancer there should be evidence to suggest a dose-response effect either in terms of frequency or duration of exposure, or both. Yet in the preponderance of the studies, when possible dose-response effects have been looked for, they have not been evident. Moreover, much of the data have contradicted any dose-response effects. For example, Booth et al. (1989) reported RRs of 0.7, 2.0, and 1.3 for monthly, weekly, and daily exposure, respectively. Under causal assumptions, it is not plausible that daily use would carry a lower risk than weekly use. Or to give another example, Cramer et al. (1999) reported RRs of 1.84, 1.43, and 1.43, respectively, for

lifetime total talc applications of <3,000, 3,000-10,000, and >10,000; again it is not plausible that the smallest number of applications would carry the highest risk.

Virtually the only instances in which suggestions of dose-response effects have been found were again in subgroup analyses; for example, among women classified by frequency of exposure after the exclusion of exposures during pregnancy, oral contraceptive use, and following sterilization (Cramer et al. 1999). Such *post hoc* analysis of the data is not valid, and it is again based on multiple comparisons.

Consistency

An inference of causality is supported if the findings among several studies, carried out by different investigators who use different strategies, nevertheless converge on the same relatively invariant associations. For talc exposure, the studies have been markedly inconsistent. Some have reported statistically significant overall associations between talc use and invasive cancer (Chang and Risch 1997, Cramer at al. 1999, Gertig et al. 2000), while another study found an association between talc use and tumors of low malignant potential (Harlow et al. 1992). Other studies have not reported significant overall associations, but only associations within subgroups classified according to cancer subtypes: sometimes the associations have been with serous tumors (Cook et al. 1997, Cramer et al. 1999, Gertig et al. 2000), sometimes with endometrioid tumors (Harlow et al. 1992). Even Cramer et al, the originators of the talc hypothesis, have published contradictory findings. Their original study, conducted in 1982, found that histologic characteristics of tumors developing in women with perineal exposure to talc did not differ significantly from those in women without perineal exposure to talc. In contrast, their subsequent study of 1999 found a statistically significant association between talc use and serous invasive cancer.

The studies have also been inconsistent in terms of other subgroup associations. Thus the great majority of the findings have suggested that the use of diaphragms stored in talc does not increase risk. With regard to other routes of exposure, sometimes the strongest associations have been with perineal dusting (Cook et al. 1997, Eltabbakh et al. 1998, Green et al. 1997, Harlow et al. 1992), sometimes with powder application to sanitary napkins (Ness et al. 2000, Rosenblatt et al. 1992), and sometimes with applications that have not been further described (Cramer et al. 1999, Cramer and Xu 1995).

There has also been no consistent pattern across the relevant studies that would make clinical or biological sense. For example, it has been proposed that sexual intercourse might facilitate the migration of talc up the female genital tract (Cramer et al. 1999). In that case, the highest risk, surely, might be for diaphragm use; yet none has been found. Remarkably, in the face of this striking inconsistency, Cramer et al. (1999) elected not to study diaphragm use in their last study. When testing a hypothesis, it is not valid to exclude factors that constitute genuine exposures even if their association with ovarian cancer has been negative in other studies (see also below: information bias). The next highest risk might be for regular perineal dusting, an association that has been repeatedly sought, but only inconsistently found. By the same reasoning a somewhat weaker

association might be expected for application of talc to sanitary napkins, as they would usually only be used for four or five days per month. However, the RRs for those exposures have commonly been higher than for regular applications of talc to the perineum. Finally, it might be expected that the RRs would be lowest for generalized occasional body exposure to talc, or for application to unspecified sites; yet in some studies the risk associated with such applications has been higher than for more intense applications (see above: dose-response effects).

In summary, the studies have not only failed to satisfy the criterion of consistency, but if anything, they have commonly revealed trends that were opposite to what might reasonably have been expected, under causal assumptions, as dose-response effects.

Systematic Bias

As mentioned above, bias can never be entirely ruled out in observational research, and in the face of RR estimates below 2.0 its possible existence, even when studies are well performed, limits interpretability. That interpretability is even further limited when, as in the present instance, there is strong evidence to suggest the presence of bias. The role of selection bias and information bias is discussed below.

Selection Bias

Selection bias exists when, on the null, the cases and noncases selected for study are not independent of the exposure of interest. In the majority of the case-control studies, the response rates have been low, generally below 70% among the cases, and seldom much higher among the controls (and probably lower still in those studies that recruited controls through random digit dialing).

It is generally accepted that possible selection bias becomes a major concern when enrollment rates in the targeted population are low. For example, among the cases, talc use could have been markedly different among women with invasive cancer, compared to those with tumors of low malignant potential. Specifically, it is reasonable to assume that women who are hygiene conscious would preferentially use powders, and undergo more frequent gynecological examinations, so that borderline tumors might be preferentially diagnosed among powder users. For the same reason, even among women with invasive cancer, the diagnosis might be made earlier among users than among nonusers. Thus cases who are users could fall inside the time frame of the study, while nonusers may only come to diagnosis after the study is completed.

The same problems are relevant to low recruitment rates among targeted controls. For example, hygiene-conscious women would tend to use talc more frequently than non-hygiene-conscious women. If there is a difference in the recruitment rates according to hygiene consciousness, this could bias the results.

Perhaps the most egregious example of selection bias was the original study of Cramer et al. (1982) that generated the hypothesis. In that study, only 45% of the eligible controls, and 72% of the eligible cases participated. For the cases it might be argued that an appreciable proportion had died, and that their pattern of powder use was unlikely to be different from that of the survivors. That argument is speculative, and open to question. Moreover, with only a 45% recruitment rate among the controls, no hypothesis was justified in the first place, and the findings must be categorically rejected.

The only way to confidently avoid selection bias due to under-enrollment would be to recruit 100%, or close to 100%, of all targeted cases or controls in a study base, specified *a priori*. With ovarian cancer a high recruitment rate is difficult to accomplish, but difficulty is not a criterion of causality. In the face of the poor recruitment rates in the majority of the case control studies, it is simply not possible to claim that the associations are unlikely to be accounted for by selection bias. It should also be noted that exactly the same selection biases would operate in the identification of cases and noncases in a cohort study.

Finally, possible selection bias was not adequately assessed in the published studies. Firstly, as explained above, borderline tumors should have been excluded, since their inclusion was much too likely to be dependent on life style factors, including the use of talc-containing powders. Secondly, as also explained, even invasive tumors may selectively have been included in the various studies because of earlier diagnosis among powder users. This possibility could have been assessed, at least in part, by the evaluation of risk stratified according to the staging of the cancer. Under causal assumptions the association should then have been evident even among the most advanced cases that would inevitably have come to diagnosis without any further possibility of delay. An assessment according to stage has not been done.

Further strong evidence to support the likelihood of selection bias is that in two successive analyses of follow-up data from the Nurses Health Study, there was no overall association with the use of talc (Hankinson et al. 1993, Gertig et al. 2000). Follow-up was for more than 20 years, and at most, only a few cases could have been missed during the last year or two of follow-up.

In summary, given the multiple potential sources of selection bias present among virtually all the studies, selection bias could readily have accounted, partially or wholly, for the statistically significant overall relative risks of 1.9 or less that have been observed in the various studies. Given the low recruitment rate in the original hypothesis-generating study, even that hypothesis itself was based on unsatisfactory data. Contrary to what has been stated by some authors, selection bias is not only possible in all the studies that reported positive associations, but likely.

Information Bias

Information bias exists when, under the null, the recording of exposure status is not independent of status as a case or a noncase. Following the initial hypothesis-generating study in 1982, the possibility that talc-containing powders may increase the risk of ovarian cancer was given extensive and repeated publicity. Thus, the strong likelihood is that the cases would repeatedly have probed their memories (as well as have had their memories probed for them by medical attendants) in order to remember every possible occasion when they had used talc-containing powders. They may also have tended to overestimate the duration or frequency of use, especially use that took place years previously. Healthy control women, by contrast, would not have been motivated to remember with the same intensity.

There is strong evidence in the published data to suggest that there was major information bias. Some of that evidence has already been mentioned. Thus, the absence of an association with diaphragms stored in talc could be explained by a lack of awareness among the cases that the use of diaphragms could have represented exposure to talc. In addition, the paradoxical data, in multiple studies, in which RRs were higher for short duration than for long duration exposures, and higher for a small number of talc applications than for a large number, also strongly support the likelihood of information bias. Indeed, it is difficult to conceive of another explanation, and information bias is a far more plausible explanation of the patterns that have been observed than possible causality.

Further strong evidence to support the likelihood of information bias is that no overall association was observed in two successive analyses of follow-up data in the Nurses Health Study (Hankinson et al. 1993, Gertig et al. 2000). The exposures were recorded before the cancers were diagnosed, and these data had the considerable advantage of being free of information bias. Only one positive association was observed in this study, a statistically significant RR of 1.4 for serous tumors. Again, however, that association was discovered in the course of multiple comparisons.

Confounding

Confounding exists when a factor is associated both with the exposure, and independently, with the outcome. The known risk factors for ovarian cancer include infertility or low parity (or both), a family history of breast or ovarian cancer (BRCA1), history of tubal ligation or hysterectomy, and probably, high socioeconomic status (Purdie et al. 1995). Several of the published studies have not adequately allowed for these factors. Factors such as socioeconomic status, for example, could both have been determinants of talc use, and independently, of the risk of ovarian cancer.

Coherence

The criterion of coherence requires that the findings should be broadly consistent with other epidemiologic data on talc exposure, including occupational exposure. Hartge and Stewart 1994 have evaluated the risk of ovarian cancer among persons occupationally exposed to talc; no associations were found. Heller et al. 1996 found no difference in the number of talc particles present in the ovaries of ovariectomized women who did and did not regularly use talc.

Biological Plausibility

A causal inference would receive some support if there were experimental data in animals to suggest that talc applied to the perineum travels up the female genital tract, and then increases the incidence of ovarian cancer. Again I am not qualified to judge, and I must defer to my colleagues in toxicology. However, my understanding is that the only evidence to hint at any carcinogenicity is one study referred to in the Draft Report that documented the occurrence of tumors in the rat lung and adrenal gland. There is no evidence that talc is carcinogenic to the ovary. There is also no experimental evidence that talc applied to the perineum even reaches the ovaries, and there are animal (monkey) data to refute this hypothesis (Wehner et al. 1986).

CONCLUSIONS

I have reviewed the epidemiologic studies of the risk of epithelial ovarian cancer in relation to exposure to talc. When assessed against the standard criteria of causality, none of the positive associations satisfy any of them. All of the associations have been of low magnitude; plausible and even likely sources of bias have not been ruled out. In addition, the more valid studies, the follow-up studies in particular, do not suggest that talc increases the overall risk of ovarian cancer. Subgroup associations have not been consistent, and the analyses that have given rise to those associations were not valid.

Contrary to what is stated in the Draft Report, the published evidence does not meet the standard required to classify talc as being reasonably anticipated to be a carcinogen.

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EXECUTIVE SUMMARY

Re: Solicitation of Public Comment to NTP Board of Scientific Counselors; Nomination of NonAsbestiform Talc as "reasonably anticipated to be a human carcinogen in the 10th Report on Carcinogens."

The NTP reviewed 16 case-control studies and one cohort study that reported relative risk estimates of ovarian cancer associated with cosmetic talc use. These studies are critically reviewed in the Appendix. The majority of these studies were not specifically designed to test the talc hypothesis, but included at least one question on ever having applied cosmetic talc to the perineum. The first report on this association came from a community-based case-control study (Cramer et al. 1982). All but three of the subsequent studies were based on a similar case-control design, except for two hospital-based case-control studies (Rosenblatt et al. 1992, Wong et al. 1999) and one cohort study (Gertig et al. 2000). A number of methodologic and interpretational concerns have been raised in these studies that would mitigate against either a causal interpretation (Muscat et al. 1998) or a "reasonably anticipated" conclusion.

These include:

1. The actual biological 'exposure' of ovarian tissue to talc has been measured by poorly defined proxy measures. The assumption that ovarian tissue is contaminated with talc from perineal dusting is based on putative physiological actions including penetration of the female reproductive tract from external talc dust, and translocation of talc particles to the ovaries. This is supported by studies showing no relationship between cosmetic talc burden in healthy ovarian tissue and lifelong perineal talc dusting. In contrast, the use of talc-dusted diaphragms provides a more valid exposure measurement for testing the hypothesis that talc burden in the ovaries of women with ovarian cancer is greater than the talc burden in the ovaries of woman with healthy ovaries. The use of talc-dusted diaphragms, by definition, results in female tract exposure to talc. Considering the anatomy of the female reproductive tract, it is difficult to describe mechanisms by which an inert particle such as talc is able to translocate to the ovaries under non-experimental conditions. A meta-analysis of the association between talc-dusted diaphragm usage and ovarian cancer risk resulted in a summary odds ratio of 0.79 (95% CI 0.46, 1.38).

2. Recall bias in questions on "ever versus never" using perineal talc exposure might have resulted in spurious associations. Post-operative side effects of radiation treatment of malignant ovaries might include perineal skin rash and irritation, leading to increased talc use. The four case-control studies based on case interviews that were conducted in the hospital immediately after diagnosis found little or no association with perineal talc use. In studies with positive associations, recall bias might also have occurred due to heightened awareness of the hypothesis in case subjects. It has not been demonstrated that recall bias can be ruled out as an alternate explanation for positive findings.

3. The validity and the reliability of questions on perineal talc dusting exposure have never been measured. The validation of exposure measures is a necessary component of proper epidemiologic research.

4. In most studies, there was no trend in the odds ratios associated with increasing duration, frequency or cumulative perineal talc exposure. In many of the studies with dose information, the risk was lower with the highest lifetime exposures relative to the lowest lifetime exposures. These epidemiologic findings are inconsistent with known carcinogenic mechanisms.

5. There are conflicting findings on ovarian cancer risk associated with perineal talc exposure in sterilized women compared to women with intact reproductive organs.

6. Publication bias, in the form of incomplete presentation of numerical study results, needs to be addressed as a limitation of the epidemiologic studies being evaluated here.

The following describes in greater detail the outline presented in the Executive Summary.

1. Testing the talc hypothesis using different epidemiologic measures

The presence of talc dust in ovarian cancer tissue was first reported in 1971 (Henderson et al. 1971). The observation of a high rate of ovarian cancer in World War II female gas mask assemblers exposed to asbestos (Berry et al. 2000), a fiber with a similar chemical but not morphologic composition to talc, helped raise the hypothesis that cosmetic talc may cause ovarian cancer. It currently seems questionable if asbestos can induce ovarian malignancy. Malignant mesothelioma in the peritoneal cavity, which is believed to be caused by asbestos (Price 1997), can present as ovarian cancer. Even using modern diagnostic methods, peritoneal mesothelioma is difficult to distinguish from ovarian masses (Clement et al. 1996, Sato et al. 2000). Asbestos fiber burden in healthy ovaries was found to correlate with reported asbestos exposure, although comparisons with malignant tissue are unavailable (Heller et al. 1999).

Heller et al. (1996) determined talc particle counts in ovarian specimens from 24 women undergoing oophorectomy and compared these counts to reported history of talc dusting. No relationship was found between cosmetic talc burden in healthy ovarian tissue and lifelong perineal talc dusting. Although the lack of an association in the Heller et al. findings could be due to contamination or reflect nonuniform distribution of talc particles in ovarian tissue, this recent study raises questions over whether reported associations between perineal talc exposure and ovarian tumors in case-control studies reflects a carcinogenic action of talc. The validity of these epidemiologic associations has also been questioned because it is unknown whether talc dust in the perineal area can actually penetrate the female reproductive tract, and then translocate to the ovaries against physiological forces working in the opposite direction.

Although the epidemiologic literature has focused primarily on external perineal exposure, the talc hypothesis would appear to be tested with greater precision and validity by questions on the use of talc-dusted diaphragms. The use of talc-dusted diaphragms, by definition, results in female reproductive tract exposure to talc. In fact, experimental translocation of talc particles to the ovary in women was achieved with deliberate or inadvertent manipulation of patients in the supine position (as cited in Wehner 1998). Although data on the use of talc-dusted diaphragms have been reported in some epidemiologic studies, this literature is sparsely referred to, and no formal evaluation of the results has been conducted. The reasons for this probably reflect simply that perineal talc-dusting is more common than the use of talc-dusted diaphragms and can be examined with greater statistical precision in epidemiologic studies. If the use of talc-dusted diaphragms occurred more commonly than perineal dusting, it is likely that the epidemiologic literature would have focused primarily on talc-dusted diaphragms as the relevant risk factor. In any case, it can be concluded that use of talc-dusted diaphragm results in exposure of the reproductive tract to talc. Intuitively, the association with talc-dusted diaphragms appears to provide a better test of the talc hypothesis.

Consequently, a meta-analysis of the association between talc-dusted diaphragm and ovarian cancer risk was conducted (Greenland 1987). The results are shown in Tables 1 and 2 of this document. Crude odds ratios and 95% confidence intervals were calculated based on the

exposure rates in cases and controls. In some studies, the OR was calculated but was based on an inappropriate control group; e.g. subjects who reported no exposure to any talc. For these studies, the OR was recalculated based on women who never used talc-dusted diaphragm as the reference group. The summary crude odds ratio associated with use of talc-dusted diaphragm was 0.79 (95% CI 0.46, 1.38).

Using this exposure measure, it can be concluded that there is no relationship between ovarian cancer and talc exposure. Limitations in this conclusion include lack of any data with cumulative exposure and possible confounding. In a meta-analysis of ten studies that examined talc dusting and ovarian cancer risk, Gross and Berg (1995) found little difference between the summary crude odds ratio and the summary adjusted odds ratio. Similarly, it appears unlikely that confounding could have obscured a positive association with talc-dusted diaphragms. There are some uncertainties in the interpretation of these findings. Diaphragms are used with contraceptive jelly, which could affect migration of talc particles. However, the jelly is normally applied to the rim and the surface of the diaphragm that faces the vaginal entrance. Jelly is not normally applied to the surface of the diaphragm that faces the cervix. Cramer et al. (1982) point out that talc-dusted diaphragms might be washed prior to their use. If this does occur, the extent to which this impacts on the study findings depend on how these questions were asked, or whether women volunteered to provide this information if not asked.

2. Recall bias

A pattern of small but elevated odds ratios for a particular exposure is not uncommon in epidemiologic research. Although it might seem intuitive that consistent findings across case-control studies could not be attributed to bias, some examples will serve to refute this notion. For example, in a meta-analysis of 12 case-control studies of dietary fat and breast cancer, the OR for the upper quartile of fat consumption relative to the lowest quartile was 1.46 ($p<0.0001$) (Howe et al. 90). In contrast, a pooled analysis of 7 cohort studies of dietary fat intake and breast cancer found an OR of 1.05 (95% CI 0.94-1.16) in the highest quintile relative to the lowest quintile of fat consumption (Hunter et al. 1996). One possible explanation for the discrepancy in the findings is recall bias in the case-control studies. Alternatively, changes in the levels of the exposure (e.g., dietary fat consumption) might have obscured an association in the cohort studies. In order to determine which explanation is more likely where case-control and cohort data conflict, it is useful to find examples in which there would not be any changes in the exposure categorization in the cohort studies. Examples would include studies in which the exposure is classified as ever versus never in middle age or older age adults.

One example is based on the literature of environmental tobacco smoke exposure and the risk of breast cancer. In a meta-analysis of 5 case-control studies of ever versus no exposure, the OR was 1.8 (95% CI 1.4-2.5). However in a pooled analysis of raw data from three cohort studies, the relative risk was 1.1 (95% CI 0.9-1.4). (Wartenberg et al. 2000). Similarly, while the majority of case-control studies that examined the association between having ever dusted the perineum with talc and ovarian cancer found increased risks, no association was observed in the Nurses Health Study (Gertig et al. 2000). The lack of an association in the Nurses Health Study was not due to exposure misclassification since middle aged nurses in their 40's or 50's who reported never using dusting powder would start using talc powder after the baseline period. By

definition, in a never versus ever classification, exposure misclassification could not occur in cohort members who reported ever using perineal talc. An increased risk was observed in one histologic subgroup of ovarian cases in the Nurses Health Study, a finding that requires further study.

The above examples of conflicting findings in case-control versus cohort studies were selected from the breast cancer literature since the methodologic issues in female breast cancer studies might be expected to be similar to that for ovarian cancer. However, the above examples do illustrate that recall or other forms of bias might result in spurious findings in case-control studies even when an increased risk has been observed in multiple case-control studies.

Recall bias in case-control studies can either be nondifferential or differential. Nondifferential recall bias occurs when the extent of bias is equal between cases and controls and results in an attenuated association. Nondifferential bias results in an underestimation of risk, whereas differential bias can result in a spurious association. It seems plausible that differential recall bias occurred in the case-control studies of talc perineal dusting and ovarian cancer. It is possible to speculate that for a cancer with few known causes and a poor prognosis, there might be a greater interest or a greater attention paid to questions on talc powder use in cases than controls. In these studies, the primary focus was on hormonal and reproductive risk factors. A question or series of questions on genital talc dusting might be considered quite unusual and striking to case subjects who are most likely unfamiliar with the hypothesis of talc dusting. Healthy controls would not have any incentive to ponder this question. Although it is possible to speculate on these scenarios, it is necessary to examine the epidemiologic literature to determine the presence and extent of recall bias. For example, differential recall bias could be inferred by comparing studies that used women with gynecologic or obstetric conditions with studies that used population controls or hospital controls with non-gynecologic conditions. An ideal control group would be women with ovarian cysts who might also be expected to respond to questions on talc dusting in a similar way as cases with ovarian cancer. If studies using women with ovarian cysts as controls also showed an increased risk for ovarian cancer associated with talc dusting, recall bias could be eliminated as a possible explanation. However, none of the case-control studies of ovarian cancer used a design based on controls with reproductive diseases.

In most of the case-control studies on talc and ovarian cancer, cases were interviewed after discharge from the hospital or were identified from cancer registries. Post-operative treatment of ovarian cancer includes radiation to the pelvic area, which might result in skin rashes or irritation in the perineum/genital area. It is feasible that this leads to increased talc use following diagnosis. The increased risks observed in these studies might reflect post-diagnosis use of talc. This is supported by the fact that in the four studies in which cases were interviewed directly in the hospital at diagnosis, there was little or no association with overall talc use or perineal talc use (Hartge 1983, Harlow and Weiss 1989, Rosenblatt et al. 1992, Whittemore et al. 1988). The summary of individual studies attached to this response provides more information on case-control methodologies. In some studies that did find positive associations, subjects were asked about exposure prior to diagnosis. However, it is uncertain whether case subjects with a high degree of morbidity that used talc after diagnosis would make the distinction.

In summary, there have been no attempts to scientifically determine whether alternative explanations such as recall bias resulted in spurious increased risks in case-control studies of talc and ovarian cancer. Since recall bias is a plausible alternative explanation, as has been shown in other examples of case-control studies, the associations with talc dusting cannot be considered a causal relationship. The burden of proof in carcinogen identification depends on the demonstration of scientific fact and ruling out alternate explanations. There have been no attempts to identify and rule out possible alternate explanations despite research efforts that have been ongoing for almost two decades.

3. Validity and reliability

In many fields of epidemiologic research, especially studies with exposures that give rise to low odds ratios, extensive validation work is done prior to using the exposure measure in case-control or cohort studies. For example, in nutritional epidemiology, the validity of a food frequency questionnaire (FFQ) is usually determined by comparison of responses to food diaries. FFQs with low-validity scores are often considered too imprecise for its proper use in epidemiology and few studies are published without demonstrating at least moderate single-order or partial correlations with food diary data. Studies of environmental tobacco smoke and cancer or coronary disease outcomes have been supported by studies demonstrating a high degree of concordance between reported smoke exposure and biological markers of tobacco smoke metabolites. Occupational studies of cancer and environmental air pollutants, water pollutants and electromagnetic fields also commonly employ complex exposure measures using environmental hygiene measurements.

The validity of reported exposures to genital talc powder has never been determined. There have been no attempts to compare reported talc usage and frequency with a log maintained over a defined amount of time (e.g., two weeks, month). It is possible to conduct validity tests on current but not past talc usage patterns.

In the absence of validity testing, it is common to infer the validity of the exposure measurement by repeated questionnaires. If the same response is provided on two or more separate occasions, it suggests that the exposure measure is possibly valid, although inaccurate information can be obtained from both readings. There have been no attempts to determine the reliability of self-reported history of perineal talc powder use. In one study that evaluated the reliability of questions on menstrual history, percent agreement for age at menopause and at menarche and other variables ranged from 70-90% (Bean et al. 1980). Recollection of menstrual cycle length was considered unreliable, and it might be suspected that questions on perineal talc dusting are to some extent unreliable also. Indeed lifelong usage patterns are unknown, but respondents in epidemiologic studies are forced to provide information in terms of a regular lifetime pattern. Talc powder use might be sporadic, seasonal or change with circumstances (e.g., sexual activity, parity).

Concerns over measurement error are done prior to the design, collection and analysis of epidemiologic studies. Epidemiologic studies of perineal talc dusting and ovarian cancer have been conducted over the past 18 years, yet no attempts have been made to determine the extent to

which talc usage questions measure what they purport to measure. Measurement error can have a major impact on the results of epidemiologic studies (Kelsey et al. 1986).

4. Dose-response relationship

The fundamental aspect of carcinogenic mechanisms is that the likelihood of tumor initiation and promotion is directly related to cumulative genetic damage and cellular insults (Wynder et al. 1992). In the studies that provide information on dose response, the ORs associated with the intensity, duration or cumulative exposure do not generally show an increasing trend, as would be expected in a causal association. In fact, by and large the smallest associations are seen with the lowest levels of exposure. These findings are inconsistent with known mechanisms of carcinogenic action. The NTP document notes that the "evidence for causality is weakened by the absence of the exposure response trends in most studies." A dose-response trend is a necessary condition for inferring causality and the absence, much less an inverse trend, is incompatible with accepted paradigms of causality. The NTP notes that this lack of a trend might be due to "the difficulty of measuring exposures by retrospective recall." If this is the case, then the arguments presented in this response regarding adequate exposure definition, validity of measurement, and recall bias would argue against a causal interpretation.

5. Tubal ligation

The NTP document noted that the association with talc dusting was apparent only in women who never underwent tubal ligation in the study by Cramer et al. (1999). Similar findings were noted in the Harlow et al. (1992) and Whittemore et al. (1988) studies, but not in the Gertig et al. (2000) study.

The NTP document did not make mention that the association between after bath talc use and ovarian cancer in the Chang and Risch (1997) study was the same for women who underwent tubal ligation and women who did not have this procedure. In the study by Wong et al. (1999), there was no difference in the risk of ovarian cancer associated with talc use between women who had tubal ligation or hysterectomy (OR=0.9, 95% CI 0.4, 2.2) and those with no history (OR=1.2, 95% CI 0.8, 1.6). Although not stated in the NTP document, in the Whittemore et al. (1988) study women who were exposed to talc prior to tubal ligation or hysterectomy had an increased risk only for 1-9 years of exposure. The OR for 10+ years was 1.11 (0.74-1.65). In addition, inverse trends with duration of talc exposure were found after adjustment for tubal ligation (Ness et al. 2000).

6. Publication bias

Publication bias is the failure to report numerical negative findings. The investigation by Chang and Risch (1997) was specifically designed to assess talc exposure and ovarian cancer risk. However, the authors omitted from the publication findings on the association with talc-dusted diaphragm. Similarly, Cramer et al. (1999) readily acknowledge "we did not assess potential talc exposure from diaphragms or condoms, exposures not found to be associated with ovarian cancer in our previous studies." Thus, the authors specifically omitted data that would potentially refute their hypothesis. Chen et al. (1992) found a positive association with talc dusting. Other sources

of talc exposure were collected but odds ratios were not calculated because it was stated that there was no association.

Summary

A number of epidemiologic studies have found small but consistent associations with ever having dusted the perineum with talc powder or use of a talc-dusted sanitary napkin and the risk of ovarian cancer. Some studies show a greater risk in women with tubal ligation, whereas an equal number or more find no difference. These findings raise the hypothesis that talc use is associated with ovarian cancer, but do not test the hypothesis. Proper epidemiologic methods require determining the extent to which alternative explanations account for study findings. These include bias, confounding and the accuracy of exposure measurement—methodologic issues inherent in all epidemiologic designs. The one cohort study of talc dusting and ovarian cancer risk found no overall association, raising the possibility of recall bias as an alternative explanation in case-control studies. Misclassification in the cohort study is unlikely using an "ever versus never" exposure measure. An increased risk in one histologic subgroup in the cohort study adds to the uncertainty in these data. Many studies had no information on dose of exposure, and the lack of an overall dose-response relationship in those studies with this information argues against a causal interpretation. Indeed the inverse trend found in several studies is incompatible with the known mechanisms of carcinogenesis.

There was no summary association between ovarian cancer and using a talc-dusted diaphragm, an exposure measurement that perhaps has greater validity than perineal talc dusting in reflecting ovarian exposure to talc. The overall risk fell below unity although the association was not statistically significant. The precisions of these results were affected by publication bias in which some studies that were designed specifically to test the talc hypothesis failed to report or test the association with talc-dusted diaphragms.

The epidemiologic data on talc exposure are conflicting, but do not support the hypothesis that cosmetic talc is "reasonably anticipated" to be a human carcinogen for the ovary.

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Table 1. Crude odds ratios for talc-dusted diaphragm and ovarian cancer.

Study, year	Exposure (y/n)	Exposure note	Cases	Controls	Crude odds ratio	Cornfield 95% CI
1. Booth,1989	Ever		30	74		
	Never		178	329	0.75	0.33, 2.02
2. Cook, 1997	Ever		154	256	0.96	0.52, 1.76
	Never		22	35		
3. Cramer, 1982	Ever		22	19	1.18	0.59, 2.35
	Never		193	196		
4. Harlow, 1992	Ever	Diaphragm or partner	20	21	0.97	0.49, 1.92
	Never		215	218		
5. Harlow, 1989	Ever		11	27	0.51	0.22, 1.13
	Never		105	131		
6. Hartge, 1983	Ever		25	41	0.72	0.40, 1.3
	Never		110	130		
7. Ness, 2000	Ever		10	33	0.53	0.25, 1.13
	Never		757	1334		
8. Rosenblatt, 1992	Ever	Education-adjusted OR=3.0	14	5	1.82	0.55, 6.34
	Never		60	39		
9. Whittemore, 1988	Ever		9	19	1.38	0.57, 3.28
	Never		179	520		

Table 2. Meta-analysis of studies of talc-dusted diaphragm and ovarian cancer

Study, year	Crude odds ratio	95% CI	Variance	Weight (W)
1. Booth, 1989	0.75	0.85, 2.02	0.1754	5.70
2. Cook, 1997	0.96	0.52, 1.76	0.0978	10.22
3. Cramer, 1982	1.18	0.59, 2.35	0.1251	7.99
4. Harlow, 1992	0.97	0.49, 1.92	0.1214	8.24
5. Harlow, 1989	0.51	0.22, 1.13	0.1840	5.43
6. Hartge, 1983	0.72	0.40, 1.3	0.0899	11.12
7. Ness, 2000	0.53	0.25, 1.13	0.1470	6.80
8. Rosenblatt, 1992	1.82	0.55, 6.34	0.3728	2.68
9. Whittemore, 1988	1.38	0.57, 3.28	0.2035	4.91
Σ				63.09
OR	0.86	0.59, 1.40		

APPENDIX: ANALYTIC EPIDEMIOLOGY STUDIES
USE OF COSMETIC TALC AND RISK OF OVARIAN CANCER

CITATION, LOCATION	STUDY TYPE, POPULATION	EXPOSURE RATE OF GENITAL TALC IN CONTROLS AND DEFINITION	RISK ESTIMATES		COMMENTS
Booth et al. 1989 England	Hospital-based case-control study 235 cases with histologically confirmed epithelial ovarian cancer and 451 age-matched hospitalized controls.	59% The exposure is simply called 'talc use in the genital area.'	**Reported Frequency of Talc Use** Never Rarely Monthly Weekly Daily	**Relative Risk (95% CI)** 1.0 (reference) 0.9 (0.3-2.4) 0.7 (0.3-1.8) 2.0 (1.3-3.4)* 1.3 (0.8-1.9)	Cases do not appear to be newly diagnosed and study might contain prevalent cases. Case response rate was 84 percent. An evaluation of response bias not done. No information on duration of exposure. No association found with talc-dusted diaphragm.

* Denotes statistically significant *increase* in risk.
▼ Denotes statistically significant *decrease* in risk.

APPENDIX: ANALYTIC EPIDEMIOLOGY STUDIES
COSMETIC TALC AND RISK OF OVARIAN CANCER (Continued)

CITATION, LOCATION	STUDY TYPE, POPULATION	EXPOSURE RATE OF GENITAL TALC IN CONTROLS AND DEFINITION	RISK ESTIMATES		COMMENTS
Chang and Risch 1997 Canada	Case-control (population-based) 450 cases with borderline and invasive ovarian carcinoma. 564 community-based age-matched controls.	After bathing: 32%	**Talc Use** None Any **After Bath Talc Use** <10 10-25 >25 **Years of After-Bath Talc Use** <30 30-40 >40 **Histologic Type** Invasive Borderline Serous Mucinous Endometroid	**Odds Ratio (95% CI)** 1.000 (reference) 1.420 (1.08-1.86)* 1.836 (1.24-2.73)* 1.128 (0.74-1.72) 0.951 (0.61-1.49) 1.697 (1.09-2.64)* 1.435 (0.96-2.15) 0.865 (0.54-1.38) 1.513 (1.13-2.02)* 1.237 (0.76-2.02) 1.336 (0.96-1.85) 1.585 (0.97-2.58) 1.671 (1.00-2.79)	Interviews in cases occurred 3-4 months after diagnosis. Information pertaining to one year prior to diagnosis was excluded. The authors state in the abstract that "a borderline statistical association was detected between duration of talc exposure and risk (OR 1.09, 95% CI 0.98-1.21, per 10 years of exposure." This conclusion is a misrepresentation of the data. It is unstated but the 'statistical association' that was found appeared to be based on a linear model. (The model parameters were not stated.) The data clearly do not show a linear increase with duration after 30 years of use. The exposure-response relationship is U-shaped, with a decreased risk associated with >40 years of use. There was no difference in risk between subjects ever having had sterilization and other subjects. The authors conclusion that 'this investigation supports previous contentions that exposure to talc may increase risk of ovarian cancer' is unsubstantiated by the data on duration of use, frequency of use and risk estimates stratified by history of sterilization. Risk estimates were adjusted for several possible confounders.

* Denotes statistically significant *increase* in risk.
▼ Denotes statistically significant *decrease* in risk.

APPENDIX: ANALYTIC EPIDEMIOLOGY STUDIES
COSMETIC TALC AND RISK OF OVARIAN CANCER (Continued)

CITATION, LOCATION	STUDY TYPE, POPULATION	EXPOSURE RATE OF GENITAL TALC IN CONTROLS AND DEFINITION	RISK ESTIMATES		COMMENTS
Chen et al. 1992 Bejing, China	Case-control (population-based) Cases were 112 women with newly diagnosed epithelial ovarian cancer from 1984-1986. Controls were 224 women matched to cases by age.	2% Subjects were asked if they used dusting powder on their abdomen or perineal region for 3 or more months. All exposure information sought was with reference to events occurring 3 or more years before the date of diagnosis (equivalent date in controls).	**Dusting Powder ≥3 Months** No Yes	**Relative Risk (95% CI)** 1.0 (reference) 3.9 (0.9-10.6)	Despite nonsignificant finding with very wide confidence interval, the authors report this finding in the abstract. No details are provided on what types of powder are used in China. Prevalent cases were interviewed after discharge. Response rate in cases was 51% although findings for hormone/reproductive factors similar to other studies, the same conclusion cannot be reached with regard to talc exposure. Information obtained for 3 or more years prior to diagnosis. The authors reported investigating several sources of talc exposure. They state that the only exposure associated with an increased risk was dusting powder. The authors provided no data and failed to present odds ratios associated with talc exposures that were unrelated to ovarian cancer risk. No information on risk by frequency and duration of exposure. Risk estimate was adjusted for education and parity.

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APPENDIX: ANALYTIC EPIDEMIOLOGY STUDIES
COSMETIC TALC AND RISK OF OVARIAN CANCER (Continued)

CITATION, LOCATION	STUDY TYPE, POPULATION	EXPOSURE RATE OF GENITAL TALC IN CONTROLS AND DEFINITION	RISK ESTIMATES		COMMENTS
Cook et al. 1997 Washington	Case-control (population-based) Cases were 313 white women aged 20-79 years in three counties of western Washington who were diagnosed with borderline (n=79) or invasive (n=234) ovarian cancer from 1986-1988. Controls were 422 white women living in the same area identified via random digit dialing. All were matched to cases by age.	39.3% Users were asked about the circumstances in which they used genital powder, as well as the duration, frequency and types of powder used. Cases were asked to refer only to the period before their diagnoses; controls were asked to consider a comparable period.	**Lifetime Genital Powder Application** None Any **Types of Exclusive Users** Never users Perineal dusting after bathing only Diaphragm storage only Powder on sanitary napkins only Genital deodorant spray only **Histologic type** Controls Serous tumors Mucinous tumors Endometroid tumors Other tumors	**Relative Risk (95% CI)** 1.0 (reference) 1.5 (1.1-2.0)* 1.0 (reference) 1.8 (1.2-2.9)* 0.8 (0.4-1.4) 1.5 (0.6-3.6) 1.5 (0.8-3.0) 1.0 (reference) 1.7 (1.1-2.5)* 0.7 (0.4-1.4) 1.2 (0.6-2.3) 1.8 (1.1-2.8)*	Prevalent cases interviewed after discharge. Cases were identified by a registry and interviewed months after diagnosis, although the exact number is unstated. Risk factor information was recorded only for exposures that occurred before diagnosis. The authors concluded that a history of perineal dusting or use of genital deodorant sprays had a modest influence on the development of epithelial ovarian tumors, whereas storing a diaphragm in powder or powdering sanitary napkins had no effect. Selection bias may have affected the results, especially since prevalent cases are used. Interviews were obtained for 64.3 percent of eligible cases, and 72.3 percent of eligible controls. Furthermore, the authors noted that the completeness of reporting may have differed between cases and controls. The Odds ratio in the highest exposure category (>10,000 applications) was the same (1.8) as in the lowest exposure category <<2,000) applications. This is a five-fold difference in reported exposure, a difference unlikely to be due poor recall. Risk estimates were adjusted for age. There were no other statistical confounders. When specific histologic categories of ovarian tumor were examined, any genital powder use was associated with an elevated risk for serous tumors and the nonspecific category of "other tumors."

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APPENDIX: ANALYTIC EPIDEMIOLOGY STUDIES
COSMETIC TALC AND RISK OF OVARIAN CANCER (Continued)

CITATION, LOCATION	STUDY TYPE, POPULATION	EXPOSURE RATE OF GENITAL TALC IN CONTROLS AND DEFINITION	RISK ESTIMATES		COMMENTS
Cramer et al. 1999 Massachusetts and New Hampshire	Case-control (population-based) Cases were 563 women diagnosed with invasive or borderline epithelial ovarian cancer from 5/1992-3/1997. Controls were 523 women from the general population matched by age and residence.	Any perineal: 18.2%. Perineal dusting:15.9% Subjects were asked about their exposure to talc one year before diagnosis for cases and one year before the interview for controls. Women were asked whether they had "regularly used talc, baby, or deodorizing powders dusted or sprayed. Data collected included method and site of application, husband's use, age at first use, types used, applications per month, and total years of genital use.	**Genital Use** No genital exposure Any genital exposure **Type of Personal Use** No personal use Dusting perineum Dusting sanitary napkin Dusting underwear Multiple uses genital area **Frequency of Use/Month** <30 30-39 40+ **Age at First Use** <20 20-25 >25 **Years of Use** <20 20-30 >30 **Total Applications** <3,000 3,000-10,000 >10,000 **Applications Censored** <3,000 3,000-10,000 >10,000	**Odds Ratio (95% CI)** 1.00 (reference) 1.60 (1.18-2.15)* 1.00 (reference) 1.45 (0.97-2.18) 1.45 (0.68-3.09) 1.21 (0.40-3.63) 2.15 (1.30-3.57)* 2.21 (1.37-3.56)* 1.17 (0.78-1.76) 1.57 (0.80-3.10) 1.46 (1.03-2.07)* 1.87 (1.03-3.39)* 1.54 (0.64-3.72) 1.86 (1.16-3.00)* 1.33 (0.76-2.30) 1.44 (0.91-2.26) 1.84 (1.12-3.03)* 1.43 (0.84-2.41) 1.43 (0.92-2.22) 1.54 (1.01-2.35)* 1.72 (1.08-2.76)* 1.80 (1.02-3.18)*	Prevalent cases were identified from registries and interviews occurred months after diagnosis. Information was collected on exposures that occurred at least one year prior to diagnosis. The authors concluded that the data demonstrate a significant association between the use of talc in genital hygiene and risk for ovarian cancer. Only 52 percent of identified cases were included. The authors state that recall bias is not likely to be a factor in this study since the exposure occurred over many years. Consistent dose-response trends were not observed across age at first use, years of use or total applications. While risk increased with increasing censored application (*i.e.*, when uses following hysterectomy or tubal ligation and uses during pregnancy or OC use were excluded), this model included women who used talc in non-genital areas. Risk estimates were adjusted for age, study center, tubal ligation, BMI, parity, OC use, primary relative with breast or ovarian cancer, and other categories of genital talc use (except where noted). Data not presented in "Risk Estimate" column: • A significant risk was observed among ever users who were parous before their first live birth. • A significant risk was observed only among women with the serous invasive histologic sub-type of ovarian cancer. • An elevated risk was not observed among married women with husbands who used talc.

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APPENDIX: ANALYTIC EPIDEMIOLOGY STUDIES
COSMETIC TALC AND RISK OF OVARIAN CANCER (Continued)

CITATION, LOCATION	STUDY TYPE, POPULATION	EXPOSURE RATE OF GENITAL TALC IN CONTROLS AND DEFINITION	RISK ESTIMATES		COMMENTS
Cramer et al. 1982 Boston, Massachusetts	Case-control (population-based) Cases were 215 white females with epithelial and borderline ovarian malignancies. Controls were 215 women from the general population matched by age, race and residence.	Any perineal: 28.4% Perineal dusting: 30.5%.	**Talc Use on Perineum** None Any **Type of Exposure** None Dusting powder *or* on napkins Dusting powder *and* on napkins	**Odds Ratio (95% CI)** 1.0 (reference) 1.92 (1.27-2.89)* 1.0 (reference) 1.55 (0.98-2.47) 3.28(1.68-6.42)*	Prevalent cases were interviewed at least several months after diagnosis. No mention is made if risk factor information pertained to prior to the diagnosis date. Only 45 percent of eligible controls and 72 percent of eligible cases participated in the study. There is an increased risk with perineal dusting, but no dose-response information is presented. No association was found with talc-dusted diaphragms.

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APPENDIX: ANALYTIC EPIDEMIOLOGY STUDIES
COSMETIC TALC AND RISK OF OVARIAN CANCER (Continued)

CITATION, LOCATION	STUDY TYPE, POPULATION	EXPOSURE RATE OF GENITAL TALC IN CONTROLS AND DEFINITION	RISK ESTIMATES		COMMENTS
Gertig et al. 2000 USA	**Prospective cohort** (population-based) Subjects were participants of the Nurses' Health Study, a prospective cohort of 121,700 registered nurses living in 11 of the larger states in the United States. All subjects were married, female nurses aged 30-35 years. After exclusions, 78,630 women formed the cohort for analysis (984,212 person-years). Ovarian cancers were diagnosed in 307 women, 121 of whom were talc users.	Subjects were asked about the frequency with which they applied "talcum, baby powder, or deodorizing powder" to their "perineal (private) areas." (Response categories included: no, < 1x/week, 1-6x/week and daily.) Subjects were also asked if they applied any of these agents on their sanitary napkins (yes, no). "Ever talc use" was classified as ever talc use on either the perineal area or sanitary napkins.	**Ever Perineal Talc Use** No Yes **Talc Use on Perineum** Never <1x/week 1-6x/week Daily **Serous Invasive Cancers, Ever Perineal Use** No Yes <1x/week 1-6x/week Daily	**Relative Risk (95% CI)** 1.00 (reference) 1.09 (0.84-1.37) 1.00 (reference) 1.14 (0.81-1.59) 0.99 (0.67-1.46) 1.12 (0.82-1.55) 1.00 (reference) 1.40 (1.02-1.91)* 1.29 (0.81-2.04) 1.49 (0.77-2.11) 1.49 (0.98-2.26)	The authors concluded that the results provide little support for any substantial association between perineal talc use and ovarian cancer risk overall; however, perineal talc use may modestly increase the risk of invasive serous ovarian cancer. As this study used a prospective cohort design, recall bias was avoided and selection bias was reduced. A dose-response trend was not observed with increasing frequency of use. Risk estimates were adjusted for age, parity, duration of oral contraceptive use, body mass index, tubal ligation history, smoking status, and postmenopausal hormone use. While the association between ever perineal use and invasive serous cancers was statistically significant, women over age 45 seemed to account for this association. These women may have been exposed to asbestiform talc. Furthermore, a stratified analysis by frequency of use (< 1x/wk, 1-6x/wk, daily) did not reveal significant associations for any sub-group, nor did it reveal a clear dose-response pattern. While the talc hypothesis depends on the ability of fibers to migrate up a patent genital tract to the ovaries, no differences in risk were observed between women who had reported tubal ligation and those who had not. NOTE: Similar to Hankinson et al. 1993, subjects were participants of the Nurses' Health Study.

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APPENDIX: ANALYTIC EPIDEMIOLOGY STUDIES
COSMETIC TALC AND RISK OF OVARIAN CANCER (Continued)

CITATION, LOCATION	STUDY TYPE, POPULATION	EXPOSURE RATE OF GENITAL TALC IN CONTROLS AND DEFINITION	RISK ESTIMATES		COMMENTS
Godard et al. 1998 Montreal, Canada	Case-control (population-based) Cases were 170 women aged 20-84 years with histologically confirmed primary ovarian carcinomas or borderline tumors diagnosed from 1995-1996. Controls were randomly selected 170 women frequency-matched to cases by age and ethnic group.	Any: 4.7%.	**Use of Talc on Perineum** Never Ever **Sporadic Cancer Patients** Never Ever **Familial Cancer Patients** Never Ever	**Relative Risk (95% CI)** 1.00 (reference) 2.49 (0.94-6.58) 1.0 (reference) 2.45 (0.85-7.07) 1.0 (reference) 3.25 (0.85-12.4)	Prevalent cases were ascertained in oncology clinics. These are not newly diagnosed cases. No mention is made as to whether risk factor information was collected prior to diagnosis. The very low exposure rate in controls raises questions on what exactly is being measured. Another Canadian study (Chang and Risch 97) found that 35.6% of controls reported talc use. Of the eligible cases and controls, the response rates were 87 percent and 89 percent, respectively. Data on frequency and duration of talc use were not collected.

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APPENDIX: ANALYTIC EPIDEMIOLOGY STUDIES
COSMETIC TALC AND RISK OF OVARIAN CANCER (Continued)

CITATION, LOCATION	STUDY TYPE, POPULATION	EXPOSURE RATE OF GENITAL TALC IN CONTROLS AND DEFINITION	RISK ESTIMATES		COMMENTS
Harlow et al. 1992 Boston, Massachusetts	Case-control (population-based) Cases were 235 white women diagnosed with histologically confirmed epithelial ovarian cancer from 1984-1987. Controls were 239 women matched on race, age, and residence.	Any genital: 39.3% Perineal dusting: 25.5% Data regarding perineal talc use included the method of application, as well as brands used, age at first use, total years of use, and frequency of use per month.	**Genital Talc Application**	**Odds Ratio (95% CI)**	Cases appear to be prevalent cases and interviewed after discharge. Hospital-based case interview, neighborhood controls used. The authors concluded that these data support the concept that a lifetime pattern of perineal talc use may increase the risk for epithelial ovarian cancer, but is unlikely to be the etiology for the majority of epithelial ovarian cancers. The authors discouraged the use of talc for daily genital hygiene. As this study used a case-control design, recall and/or selection bias may have affected the results. Only 60 percent of identified cases and 45 percent of identified controls were included in the analysis. A consistent dose-response trend was not observed across the number of talc applications per month, years of talc use, age at first talc use, or years since last talc use. A statistically significant linear trend was observed across censored applications. Risk estimates were adjusted for parity, education, marital status, religion, use of sanitary napkins, douching, age, and weight. Sub-analyses of years of talc use did not reveal any significant associations. Additional data not presented in "Risk Estimate" column: • A significantly elevated risk was not observed among any category of years of talc use, total applications, applications excluding use after sterilization, and women with mid-cycle pain. • A significant risk was observed among women with a regular period, women with no history of PID or ectopic pregnancy and women with ovarian tumors of endometrioid type or borderline grade.
			None	1.0 (reference)	
			Any	1.5 (1.0-2.1)	
			Talc Applications/Month		
			<5	1.5 (0.8-2.7)	
			5-29	1.2 (0.6-2.2)	
			≥30	1.8 (1.1-3.0)*	
			Age at First Talc Use		
			<20	1.7 (1.1-2.7)*	
			20-25	1.2 (0.6-2.2)	
			>25	1.6 (0.8-3.2)	
			Years Since Last Talc Use		
			Within last 6 mos.	2.3 (1.3-4.0)*	
			Between 6 mos.-10 yrs.	1.1 (0.7-1.9)	
			≥ 10 yrs.	1.4 (0.8-2.6)	
			Era of Use		
			Exclusive use after 1960	1.1 (0.6-2.1)	
			Any use before 1960	1.7 (1.1-2.7)*	
			Applications Excluding Use After Sterilization or During Nonovulatory Months		
			None	1.0 (reference)	
			<1000	1.5 (0.8-2.9)	
			1000-10,000	1.3 (0.8-2.0)	
			>10,000	2.8 (1.4-5.4)*	

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APPENDIX: ANALYTIC EPIDEMIOLOGY STUDIES
COSMETIC TALC AND RISK OF OVARIAN CANCER (Continued)

CITATION, LOCATION	STUDY TYPE, POPULATION	EXPOSURE RATE OF GENITAL TALC IN CONTROLS AND DEFINITION	RISK ESTIMATES		COMMENTS
Harlow and Weiss 1989 Washington State	Case-control (population-based) Cases were 116 white women aged 20-79 diagnosed with serous and mucinous borderline ovarian tumors during the years 1980-1985. Controls were 158 white women recruited via random digit dialing and matched to controls on age and county of residence.	Any perineal talc: 40.5% Perineal dusting: 23.4%. Subjects were asked about their perineal exposure to talc, as well as the types of powder used and various methods of application. Ever-users included women who reported using either one or more of three types of talc containing powders or cornstarch. Exposure information pertained to use prior to diagnosis (or a similar date for controls).	**Perineal Exposure to Talc** None Any **Type of Powder Used** None Cornstarch only Baby powder only Baby powder only or combined use Talc, unspecified Deodorizing powder only Deodorizing powder only or combined use	**Relative Risk (95% CI)** 1.0 (reference) 1.1 (0.7-2.1) 1.0 (reference) 0.8 (02-3.8) 0.8 (0.4-1.9) 0.9 (0.5-2.0) 1.0 (0.4-2.4) 3.5 (1.2-28.7)* 2.8 (1.1-11.7)*	Based on prevalent cases although only 5% were deceased. Subjects were asked about exposure before diagnosis. The authors concluded that the application of talc to diaphragms is not associated with increased risk of borderline ovarian tumors, but that there was a modest increase in risk among women who applied talc-containing powders to the perineum or sanitary napkin. Interviews were obtained for 68 percent of eligible cases and 74 percent of eligible controls. Data on frequency and duration of talc use were not collected. Risk estimates were adjusted for age, parity, and use of oral contraceptives. No association was found for talc-dusted diaphragm.

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APPENDIX: ANALYTIC EPIDEMIOLOGY STUDIES
COSMETIC TALC AND RISK OF OVARIAN CANCER (Continued)

CITATION, LOCATION	STUDY TYPE, POPULATION	EXPOSURE RATE OF GENITAL TALC IN CONTROLS AND DEFINITION	RISK ESTIMATES		COMMENTS
Hartge et al. 1983 Washington, DC	Case-control (hospital-based) Cases were 135 women with pathologically confirmed primary epithelial ovarian cancer identified from 1974-1977 in Washington, DC metropolitan hospitals. Controls were 171 women treated at the same hospitals for conditions other than gynecologic, psychiatric, or malignant diseases or pregnancy. Controls were frequency-matched to cases on age, race and hospital.	Any perineal talc: 35.7% Subjects were asked questions regarding the use of talc (no use vs. any) and the method of application.	**Talc Use** No talc mentioned Any talc mentioned **Diaphragm-related Talc Use** No diaphragm used Diaphragm used, no talc Diaphragm, with talc **Body Talc Use** No body talc Some body talc "All over" Genital Legs only Not genital Unknown where	**Relative Risk (95% CI)** 1.0 (reference) 0.7 (0.4-1.1) 1.0 (reference) 1.6 (0.7-3.7) 0.8 (0.4-1.4) 1.0 (reference) 0.8 (0.5-1.2) 0.7 (0.4-1.2) 2.5 (0.7-10.0) NA 0.8 (0.3-2.5) 0.3 (0.1-1.2)	Hospital-based interviews of newly diagnosed cases and hospital controls. No overall association was found with perineal talc dusting. Data on frequency and duration of talc use were not collected; consequently, dose-response information is not available. No information is provided on response rates. Little methodologic information is supplied.

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APPENDIX: ANALYTIC EPIDEMIOLOGY STUDIES
COSMETIC TALC AND RISK OF OVARIAN CANCER (Continued)

CITATION, LOCATION	STUDY TYPE, POPULATION	EXPOSURE RATE OF GENITAL TALC IN CONTROLS AND DEFINITION	RISK ESTIMATES		COMMENTS
Ness et al. 2000 Delaware Valley	Case-control (population-based) Cases were 767 women aged 20-69 diagnosed with epithelial ovarian cancer within 6 months prior to the interview. Controls were 1367 women from the community. Ages were similarly distributed for cases and controls.	Genital/rectal: 16.0% Any perineal: not able to calculate. Women were asked if they used talc at least once per month for 6 months or more prior to 6 months before the interview. The types of use and duration of use for each type of use were recorded.	**Type of Talc Use** Never Feet, etc. Genital/rectal Sanitary napkin Underwear Diaphragm/cerv cap Male partner **Talc Use (Genital/Rectal and Feet)** Never <1 year 1-4 years 5-9 years 10+ years	**Odds Ratio (95% CI)** 1.0 (reference) 1.4 (1.1-1.6)* 1.5 (1.1-2.0)* 1.6 (1.1-2.3)* 1.7 (1.2-2.4)* 0.6 (0.3-1.2) 1.0 (0.7-1.4) 1.0 (reference) 2.0 (1.0-4.0) 1.6 (1.1-2.3)* 1.2 (0.8-1.9) 1.2 (1.0-1.5)	Cases diagnosed 6 months before the interview. Random population-based controls. Talc exposure information obtained for prior to diagnosis and for at least 6 months. The participation rate was 88% for cases, and 72% for controls. The dose-response trend with increasing duration of use was inverse. Risk estimates were adjusted for age, number of pregnancies, family history of ovarian cancer, race, oral contraceptive use, tubal ligation, hysterectomy, and breast-feeding. A nonsignificant protective effect was observed with talc-dusted diaphragm

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APPENDIX: ANALYTIC EPIDEMIOLOGY STUDIES
COSMETIC TALC AND RISK OF OVARIAN CANCER (Continued)

CITATION, LOCATION	STUDY TYPE, POPULATION	EXPOSURE RATE OF GENITAL TALC IN CONTROLS AND DEFINITION	RISK ESTIMATES		COMMENTS
Purdie et al. 1995 Australia	Case-control (population-based) Cases were 824 women aged 18-79 years with histologically confirmed cases of primary epithelial ovarian cancer identified from 1990-1993. Controls were 860 women drawn at random from electoral rolls, stratified by age and geographic location.	Subjects were administered a detailed questionnaire about reproductive and contraceptive history, as well as other factors of interest.	**Talc Use** No use On abdomen/perineum	**Relative Risk (95% CI)** 1.0 (reference) 1.27 (1.04-1.54)*	NOTE: All of the data in this study appear to have been re-analyzed subsequently in Green et al. 1997 As this study used a case-control design, recall and/or selection bias may have affected the results. There is some evidence of recall bias: interviews were conducted for 90 percent of eligible cases, but only 73 percent of eligible controls. Furthermore, while most cases were interviewed in a clinical setting, all controls (and only some cases) were interviewed in their homes. Data on frequency and duration of talc use were not collected; consequently, dose-response information is not available. The reported risk estimate was adjusted for parity.

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APPENDIX: ANALYTIC EPIDEMIOLOGY STUDIES
COSMETIC TALC AND RISK OF OVARIAN CANCER (Continued)

CITATION, LOCATION	STUDY TYPE, POPULATION	EXPOSURE RATE OF GENITAL TALC IN CONTROLS AND DEFINITION	RISK ESTIMATES		COMMENTS
Rosenblatt et al. 1992 Baltimore, Maryland	Case-control (hospital-based) Cases were 77 women diagnosed with ovarian cancer from 1981-1985. Controls were 46 women matched by age and race.	Any genital fiber: 88%. Subjects were asked about the manner and frequency of their talc use.	**Genital Talc Bath** No Yes **Use of Talc on Sanitary Napkin** No Yes	**Odds Ratio (95% CI)** 1.0 (reference) 1.7 (0.7-3.9) 1.0 (reference) 4.8 (1.3-17.8)* *Sanitary napkin or other sanitary product.	Cases newly diagnosed. Hospital-based controls. The dose-response odds ratios are calculated incorrectly. Recalculating length of fiber use relative to never users, the crude OR is: <37 years: 0.62 >37 years: 1.2 The very high exposure rate in the controls raises questions on the validity of this data. It is difficult to understand how there was a lack of available matching controls at Johns Hopkins hospital. Since control matching was partially unsuccessful, the authors performed a secondary matching. Further, questionnaire data was administered by telephone and directly. No information was given regarding how the percentages of the two methods in the control group, and this methodology was not taken into account statistically. Combined with the low response rate in cases (55%), the methodology is highly flawed. Data on frequency and duration of talc use were not collected. The risk estimate for exposure to a genital talc bath does not appear to have been adjusted for any potential confounding factors.

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APPENDIX: ANALYTIC EPIDEMIOLOGY STUDIES
COSMETIC TALC AND RISK OF OVARIAN CANCER (Continued)

CITATION, LOCATION	STUDY TYPE, POPULATION	EXPOSURE RATE OF GENITAL TALC IN CONTROLS AND DEFINITION	RISK ESTIMATES		COMMENTS
Tzonou et al. 1993 Athens, Greece	Case-control (hospital-based) Cases were 189 women less than 75 years of age who underwent surgery for a histologically confirmed common malignant epithelial ovarian tumor from 6/1989-3/1991. Cases were residents of greater Athena. Controls were 200 hospital visitors less than 75 years of age who were visiting patients in the same wards as the cancer patients at the same time.	Any perineal exposure: 3.5%. Subjects were asked to report the frequency of use (over an extended period before the onset of the present disease for cases, or a comparable period before the interview for controls) of talc in the perineal region (no, yes).	**Talc Application in the Perineum** No Yes	**Relative Risk (95% CI)** 1.0 (reference) 1.05 (0.28-3.98)	Cases and controls interviewed in the hospital. The authors concluded that although the number of talc users is in general small and the respective confidence intervals fairly large, there is clearly no evidence of an increased risk associated with the perineal application of talc. Interviews were conducted with 90 percent of eligible cases and 94 percent of eligible controls. Data on frequency and duration of talc use were not collected. The reported risk estimate was adjusted for a number of possible confounders although adjustment with such a low exposure rate might not be meaningful.

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APPENDIX: ANALYTIC EPIDEMIOLOGY STUDIES
COSMETIC TALC AND RISK OF OVARIAN CANCER (Continued)

CITATION, LOCATION	STUDY TYPE, POPULATION	EXPOSURE RATE OF GENITAL TALC IN CONTROLS AND DEFINITION	RISK ESTIMATES		COMMENTS
Whittemore et al. 1988 Northern California	Case-control (population and hospital-based) Cases were 188 women aged 18-74 diagnosed with primary epithelial ovarian cancer from 1/83 to 12/85 at one of seven hospitals. Of the 539 controls, 280 were hospitalized women and 259 were women selected from the general population via random digit dialing. Controls were matched to cases on age, race and additional criteria.	Perineal dusting; 41%.	**Type of Talc Use** None Perineum only Sanitary pads only Diaphragm only Any two of above All three of above **Years of Talc Use** None 1-9 10+ **Applications of Talc Per Month** None 1-20 20+	**Relative Risk (95% CI)** 1.00 (reference) 1.45 (0.81-2.60) 0.62 (0.21-1.80) 1.50 (0.63-3.58) 1.36 (0.91-2.04) 0.35 (0.04-2.94) 1.00 (reference) 1.60 (1.00-2.57) 1.11 (0.74-1.65) 1.00 (reference) 1.27 (0.82-1.96) 1.45 (0.94-2.22)	As this study used a case-control design, recall and/or selection bias may have affected the results. The most salient biases of this study include the failure to interview all eligible ovarian cancer patients and a completely random sample of controls, as well as the potential pitfalls of combining the two control groups. A significant trend was not observed with increasing duration or frequency of use. All risk estimates were adjusted for parity. In addition, the risk estimates stratified by type of talc use were also adjusted for oral contraceptive use. No association was found with talc-dusted diaphragm.

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APPENDIX: ANALYTIC EPIDEMIOLOGY STUDIES
COSMETIC TALC AND RISK OF OVARIAN CANCER (Continued)

CITATION, LOCATION	STUDY TYPE, POPULATION	EXPOSURE RATE OF GENITAL TALC IN CONTROLS AND DEFINITION	RISK ESTIMATES		COMMENTS
Wong et al. 1999 New York	Case-control (hospital-based) Cases were 499 patients with epithelial ovarian cancer treated at Roswell Park Cancer Institute from 10/1982-10/1995. Controls were 755 patients who were treated for non-gynecologic malignancies during the same period. Controls were frequency matched to cases on age at diagnosis.	Ever use: 48.7%. Subjects were asked about their method of talc application, and the duration of use.	**Talc Use by Site** Never used Sanitary napkin Genital or thigh area Both **Duration of Talc Use** None 1-9 yr. 10-19 yrs. ≥20 yrs. **No History of Surgical Interruption of Genital Tract** Nontalc user Talc user **History of Tubal Ligation or Hysterectomy** Nontalc user Talc user **No History of Hysterectomy within 5 Years of Diagnosis** Nontalc user Talc user	**Odds Ratio (95% CI)** 1.0 (reference) 0.9 (0.4-2.0) 1.0 (0.8-1.3) 1.1 (0.7-1.7) 1.0 (reference) 0.9 (0.6-1.5) 1.4 (0.9-2.2) 0.9 (0.6-1.2) 1.0 (reference) 1.2 (0.8-1.6) 1.0 (reference) 0.8 (0.5-1.2) 1.0 (reference) 0.9 (0.4-2.2)	Incident cases were interviewed in the hospital. Response rate was 93 percent of cases and 92 percent of controls. A dose-response trend was not observed with increasing duration of use. The reported risk estimates were adjusted for parity, oral contraceptive use, smoking history, family history of epithelial ovarian cancer, age at menarche, menopausal status, income, education, geographic location, and history of tubal ligation or hysterectomy. The authors note that the current study was limited to the use of talc on the perineum or sanitary napkin and did not address potential talc exposure from condom and diaphragm use. There were no significant associations between talc use and specific histologic subtypes of ovarian cancer.

* Denotes statistically significant *increase* in risk.
▼ Denotes statistically significant *decrease* in risk.