Personal Care Products Council
Committed to Safety, Quality & Innovation

July 21, 2009

Division of Dockets Management
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852

RE: Comments on: Citizens Petition to the Commissioner of the Food and Drug Administration Seeking a Cancer Warning on Talc Products Docket FDA-2008-P-0309

Dear Division of Dockets Management:

The Personal Care Products Council[1] (the Council) appreciates the opportunity to comment on the above referenced Citizens Petition. Cosmetic talc is used within the personal care products industry, and thus, the request for a warning is of significant interest to the Council's members.

A 1994 Citizen's Petition to FDA similarly requested that FDA (1) immediately require cosmetic talcum powder products to bear labels with a warning such as "Talcum powder causes cancer in laboratory animals. Frequent talc application in the female genital area increases the risk of ovarian cancer" and (2) hold a hearing to allow the petitioner to present scientific evidence to support their petition. FDA did not act on this petition and did not implement the requests made by the petitioner. We believe the current request for a cancer warning also lacks scientific merit, and that a review of all of the pertinent literature supports our confidence in the safety of cosmetic talc.

The 2008 Petition cites twelve articles that are described as 'confirming' "the causal relation between genital application of talc and ovarian cancer." We disagree with the petitioner's interpretation of the data that are cited, and we believe that the available ovarian cancer epidemiology studies do not support a causative role for talc. We note that ~half of the citations

[1] Based in Washington, D.C., the Personal Care Products Council (formerly CTFA) is the leading national trade association representing the $250 billion global cosmetic and personal care products industry. Founded in 1894, the Council's more than 600 member companies manufacture, distribute, and supply the vast majority of finished personal care products marketed in the United States. As the makers of a diverse range of products millions of consumers rely on everyday, from sunscreens, toothpaste and shampoo to moisturizer, lipstick and fragrance, personal care products companies are global leaders committed to product safety, quality and innovation.

do not provide new data on talc and ovarian cancer, but rather are reviews of data on ovarian cancer incidence in general.

To address these issues further, the Council hereby submits a detailed review of the points raised in the petition, co-authored by Dr. Michael Huncharek, MD, MPH, Meta-Analysis Research Group and Associate Professor of Preventive Medicine, University of South Carolina School of Medicine, Columbia, SC; and Dr. Joshua Muscat, Ph.D., MPH, Meta-Analysis Research Group and Professor of Public Health Sciences, Pennsylvania State University College of Medicine, Hershey, PA. The review includes an assessment of each of the twelve literature references cited in the petition, with an assessment of the relevance of the study findings to support a causal association (Attachment).

This review concludes that "the weak epidemiological association is unlikely to be causal." Arguing against a causal association are lack of a clear dose-response relationship between increasing talc exposure and increasing ovarian cancer risk, with some epidemiological studies suggesting an inverse association between exposure and risk. A plausible biological mechanism is lacking to explain a causal relationship. The finding of a small increase in relative risk could be due to several potential confounding factors. A serious limitation of the epidemiology studies, many of which were not specifically designed to test the hypothesis that talc use contributes to ovarian cancer, 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).

Given the lack of evidence of a causal role for talc in ovarian cancer, we therefore respectfully ask that the Petitioners' request for a cancer warning be denied. The basis of the request lacks scientific merit and the addition of a warning label would be inappropriate and unnecessarily alarming.

Thank you for the opportunity to comment on the Citizens Petition. Please let us know if we can provide more information.

Sincerely,

John E. Bailey, Ph.D.
Executive Vice President – Science

ATTACHMENT

Comments on: Citizens Petition to the Commissioner of the Food and Drug Administration Seeking a Cancer Warning on Talc Products

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I. Introduction

On May 13, 2008, Samuel Epstein, MD, Chairman of the Cancer Prevention Coalition, submitted a Citizen's Petition to the Commissioner of the Food and Drug Administration seeking placement of cancer warning labels on talc products. The Petition requests the Commissioner of Food and Drugs to require that all talc products bear labels with a warning such as, "Frequent application of talcum powder in the female genital area substantially increases the risk of ovarian cancer."

Given the multiple implications of such warning labels, The Personal Care Product Council sought an evaluation of the validity of the scientific facts underlying this request. The Meta-Analysis Research Group was retained to provide an independent review of the relevant data. Below are the findings of this review.

II. Executive Summary

This document is in response to the recent Citizens Petition to the Food and Drug Administration (FDA) that seeks placement of a cancer warning on cosmetic talc products (2008). Dr. Samuel Epstein, Chairman of the Cancer Prevention Coalition, and other interested parties, filed this petition.

The claim refers to the first observational study (case-control) suggesting an association between use of talc powders on the female perineum (via direct dusting or dusting sanitary napkins) and increased risk of ovarian cancer, published in 1982. In this document, the authors partly base their conclusions of an association on the "…chemical relationship between talc and asbestos", the latter substance being a known human carcinogen. The claim also references a number of additional epidemiological studies conducted after 1982 that have shown a statistical link between talc dusting and ovarian cancer risk. A subset of these reports show a roughly 30-60% increased risk of ovarian cancer associated with perineal talc exposure.

Although separating causal from non-causal explanations for an observed statistical association is a difficult process, there currently exist commonly accepted guidelines by which such inferences can be made (see Hill, 1965). These scientific approaches include consideration of the strength of the association, the consistency of the finding across studies, and existence of a biological explanation of the observed phenomenon, among others. When applied to the context of a proposed talc/ovarian cancer association, we conclude that the weak statistical associations cited in the petition do not support a causal association.

Our conclusions are based on a number of statistical, methodological and biological issues. First, contrary to the assertions of Epstein et al., findings from the

cited studies are not consistent from study to study, and also differ by study design. Two meta-analyses by Huncharek et al. (2003) and Langseth et al. (2008) both show significant differences in summary odds ratios between population-based and hospital-based case control studies, with the latter showing generally null results. The Nurses Health Study, the one prospective study that examined this association, found no risk with talc dusting. Formal statistical tests for heterogeneity in both analyses support this finding. This fact suggests the existence of bias and standard approaches to meta-analysis indicate that the pooled odds ratio, in this case an OR of 1.30, is not valid in the presence of heterogeneity. Huncharek et al. (2003, 2007) suggest multiple possible sources of bias that could produce a spurious positive finding, including unaccounted effects of cancer treatment and confounding by smoking.

The assembled data also fail to show a clear dose-response relationship, i.e. increasing ovarian cancer risk with increasing talc exposure. Some epidemiological studies actually suggest an inverse association between perineal talc exposure and cancer risk. The reason for this inverse association in some studies is not known, but could be due to aspects of talc usage that are not fully understood such as the possibility that disease symptoms or cancer treatment may spur temporary talc use in case subjects.

There is no coherent biological explanation as to how talc could induce cancer of the ovary. The theories put forth to explain the statistical association between talc and ovarian cancer have changed over time with little underlying consistency. The long-standing claim that talc is chemically "similar" to asbestos and is therefore a carcinogen is a misunderstanding of the chemical and physical properties of talc.

The use of therapeutic talc for pleurodesis in patients with benign and malignant pleural effusions involves the direct application of talc to the human pleura. Clinical follow-up studies of these patients have shown no increased incidence of lung or pleural malignancies despite patient follow-up extending over decades. The above noted data are supported by the lack of positive findings among occupational cohorts exposed to talc and negative findings from various animal studies. More recently proposed mechanisms based on other biological pathways are speculative at this point. Given the lack of supporting evidence from *in vivo* and clinical research studies using human subjects, the weak and inconsistent epidemiological associations, that also lack a gradient in effect, argues against a claim of causality.

III. Overview of citations listed in the CPC Petition to the FDA

Citation: #1, National Cancer Institute. SEER Cancer Statistics Review, 2005.

SUMMARY OF FINDINGS:

The age-adjusted U.S. mortality rate from ovarian cancer in elderly white and black women (ages 65+) increased from 1975-1991, and has remained stable from 1991-2005. In contrast the SEER (Surveillance Epidemiology and End Results Program) incidence rates of ovarian cancer in elderly white women increased from 1975-1991, but has decreased since that time. In elderly black women the rates have been stable throughout this period. The age-adjusted incidence and mortality rates of younger white and black women (<65) have decreased about 30% from 1975-2005. There is a poorer survival rate among elderly women. (see Appendix re: SEER data)

Ovarian cancer is estimated to be the 5th most common form of cancer deaths among women in 2008.

ALLEGATIONS OF PETITION'S AUTHORS re: CITATION:

The authors make no claim with regard to talc causality. The data presented are intended to show that ovarian cancer is a relatively common cancer and has a poor prognosis, especially in older women.

MEASURE OF RELATIVE RISK/ODDS RATIO:

None.

RELEVANCE OF STUDY FINDINGS TO SUPPORT CAUSAL ASSOCIATION:

None. The data cited are intended to show that if talc has an effect, it is an important public health problem given the high case fatality rate from ovarian cancer in older women.

It should be noted that Epstein et al. cited mortality data that do not reflect updated SEER information showing that mortality for this disease has been stable for almost the last two decades. In addition, the incidence data show stable or decreasing rates since 1991 with incidence and mortality declining substantially among women under 65 years of age.

Citation: #2, Purdie D. et al. Reproductive and other risk factors and risk of epithelial ovarian cancer : An Australian case-control study. Survey of Women's Health Study Group. Int J Cancer 1995; 62:678-684.

SUMMARY OF FINDINGS:

Purdie conducted a population-based case-control study of 824 histologically confirmed cases and 860 controls in Australia. No response rate was given but it appears that a large number of cases could not be located or agree to be interviewed post-diagnostically. There may have been a survivor effect where the enrolled cases were more likely to have been early stage cases. This study was done to assess hormonal/reproductive factors on ovarian cancer risk. There was one question asked on talc exposure.

ALLEGATIONS OF PETITION'S AUTHORS re: CITATION:
The petition authors cite this reference as "confirming" the findings of prior work showing a positive relationship between perineal talc use and ovarian cancer risk.

MEASURE OF RELATIVE RISK/ODDS RATIO:

The "use of talc around abdomen/perineum" was associated with a nonsignificant 1.21 [1.00-1.46] risk and a significant 1.27 [1.04-1.54] risk in nulliparous women.

RELEVANCE OF STUDY FINDINGS TO SUPPORT CAUSAL ASSOCIATION:

The question of statistical significance is ambiguous here. The crude odds ratio is nonsignificant or of borderline significance and not adjusted for confounders. The authors calculated an adjusted odds ratio in only a subset of women (e.g. nulliparous) women because the overall study was designed to examine hormonal factors, and the sample size was large enough to conduct a stratum-specific analysis to remove the confounding effects of parity. However, since talc was clearly not the main hypothesis, the adjusted odds ratio in only a subset of women makes it difficult to interpret and generalize the talc findings. Thus it may be argued that the nonsignificant crude odds ratio is the more appropriate measure. While the difference in the crude and the adjusted subsetted OR is quite small, such differences become important given that the overall "effect" of talc exposure in this study and the literature in general is small to begin with. The meta-analysis by Huncharek et al. included the adjusted odds ratio, but in retrospect the lower crude OR was probably the better measure when pooling the results. There are no data on dose-exposure response effect or latency. The association with talc cannot be considered causal in this individual study as the exposure is crudely defined, the findings based on the whole dataset are marginally significant, and there are no dose-response data.

Citation: #3, Kasper CS, Chandler PJ Jr. Possible morbidity in women from talc on condoms [letter]. JAMA 1995; 846-847.

SUMMARY OF FINDINGS:

This is an article that raises the hypothesis that talc on condoms and diaphragms may cause ovarian cancer. The original hypothesis that talc used on birth control devices may be associated with disease risk was raised in 1979 by Longo and Young (Lancet 1979;2:349-351). Kasper cites new microscopy data that supports this hypothesis, with findings demonstrating the presence of talc on condoms, with varying degrees of density/surface area depending on the brand.

ALLEGATIONS OF PETITION'S AUTHORS re: CITATION:
The petition authors cite this reference as "confirming" the findings of prior work showing a positive relationship between perineal talc use and ovarian cancer risk.

MEASURE OF RELATIVE RISK/ODDS RATIO:
None.

RELEVANCE OF STUDY FINDINGS TO SUPPORT CAUSAL ASSOCIATION:

There is no new data that confirms that talc is associated with ovarian cancer. Rather, the hypothesis that talc from other sources besides perineal dusting, is alleged to possibly cause ovarian cancer. The documentation that talc is found to be concentrated on the surface of latex condoms raises the hypothesis that condom use may cause ovarian cancer.

Kasper hypothesizes that with the large increase of condom use in the U.S. from 1985-1995, that if talc were carcinogenic to the ovaries there would be a large increase in the rates of ovarian cancer in the U.S. We previously examined the rates of ovarian cancer to determine if there have been any increases in incidence during this time period. We found no evidence for an increased SEER rate (Muscat and Huncharek. Eur J Cancer Prev. 2008;17:139-46). Using the latest data from the SEER program, it can be seen that the age-adjusted incidence rates for ovarian cancer in white women have declined by about 20% since 1985, the date of the Kasper article. These data clearly do not support the Kasper hypothesis and the claim made by Dr. Epstein and others.

Citation: #4, Cramer DW & Xu H. Epidemiologic evidence for uterine growth factors in the pathogenesis of ovarian cancer. Am J Epidemiol 1995; 5:310-314.

SUMMARY OF FINDINGS:

This was a hospital-based case-control study from two time periods that included a total of 450 cases and 454 controls from Boston. The controls were randomly selected women from the population. Controls with a history of bilateral oophorectomy were excluded.

MEASURE OF RELATIVE RISK/ODDS RATIO:

"Talc use for genital hygiene" was associated with a crude 1.6 [1.2-2.1] risk.

ALLEGATIONS OF PETITION'S AUTHORS re: CITATION:
The authors cite Cramer 'confirming' the results from Purdie.

RELEVANCE OF STUDY FINDINGS TO SUPPORT CAUSAL ASSOCIATION:

It is not clear if the OR presented is the crude or adjusted odds ratio. A calculation of the crude OR from the table reveals a 1.6 odds ratio. The table (Table 1) does not indicate that the OR is adjusted despite the methods section stating that adjustments were made. In contrast tables 2 and 4 had footnotes indicating the OR for other risk factors were adjusted ORs. There were no dose-response data provided.

Use of body powders was assessed via personal interview. Use of powder in non-genital areas was not associated with increased ovarian cancer risk (1.08[0.77-1.50]) nor was increased risk seen among those using powder to dust the perineum (1.45(0.97-2.18]), dusting sanitary napkins (1.45[0.68-3.09]) or dusting underwear 1.21[0.40-3.64]). An elevated risk of ovarian cancer was noted for the exposure categories "multiple uses, genital area", i.e. 2.15(1.30-3.57) and "any personal genital exposure", i.e. 1.6(1.18-2.15).

Only one case and three controls reported using cornstarch powders. Dose-response analysis showed an inverse relationship for both frequency of use per month or number of applications.

The authors conclude that there is a "significant association between the use of talc in genital hygiene and risk of epithelial ovarian cancer."

ALLEGATIONS OF PETITION'S AUTHORS re: CITATION:

The authors cite Cramer et al. to document that these investigators suggested institution of "formal public health warnings" in 1999 based on their interpretation of existing data, i.e. that they "confirm" the relationship between perineal talc use and ovarian cancer is causal.

MEASURE OF RELATIVE RISK/ODDS RATIO:
Risk associated with genital exposure to talc, OR=1.60(1.18-2.15)

RELEVANCE OF STUDY FINDINGS TO SUPPORT CAUSAL ASSOCIATION:

This population-based case-control study found a statistically significant association between "any personal genital exposure" to talc and risk of ovarian cancer with an odds ratio of 1.60(1.18-2.15). No clear dose-response relationship was seen. In fact, data in both tables II and III suggest an inverse dose-response.

Citation: #5, Chang et al. Perineal talc exposure and risk of ovarian carcinoma. Cancer 79:2396-2401, 1997.

SUMMARY OF FINDINGS:

Chang and Risch present the findings of a population based case-control study of ovarian cancer risk associated with perineal exposure to talc. The study population was derived from Ontario, Canada and consisted of 450 cases and 564 controls. Dusting or powdering behaviors considered included regular application of talc to the perineum after showering or bathing and dusting of talc on sanitary napkins. Similar information was recorded regarding use of cornstarch products.

Analyses were adjusted for age, oral contraceptive use, average duration of breastfeeding per pregnancy, tubal ligation/hysterectomy or family history of ovarian or breast cancer. No adjustment was made for smoking history.

Women with any regular talc exposure showed an increased risk of disease, i.e. OR=1.42(1.08-1.86) with no association seen with talc exposure via dusting of sanitary napkins, i.e. OR of 1.26(0.81-1.96). Use after bathing showed a borderline effect of 1.31(1.00-1.73). As noted in a number of other observational studies, no increasing risk of ovarian cancer with increasing talc exposure was noted.

The authors concluded that their data provide support that perineal talc use may increase the risk of ovarian cancer. They acknowledged that the lack of a dose-response needs clarification. In fact, an inverse dose-response is suggested by the data in Table 2 of the manuscript.

ALLEGATIONS OF PETITION'S AUTHORS re: CITATION:

Epstein et al. suggest that reference number five supports the findings of Purdie et al. (reference #2), the largest case-control analysis examining perineal talc and ovarian cancer risk as well as other reports cited in the petition.

MEASURE OF RELATIVE RISK/ODDS RATIO:
Any perineal talc exposure: OR=1.42(1.08-1.86)
Dusting of sanitary napkins: OR=1.26(0.81-1.96)
Talc use after bathing: OR=1.31(1.00-1.73)
>25months use of after-bath talc: OR=0.95(0.61-1.49)
>40yrs after bath talc use: OR=0.87(0.54-1.38)

RELEVANCE OF STUDY FINDINGS TO SUPPORT CAUSAL ASSOCIATION:

Chang and Risch indicate that their study results "appear to support the contention that talc exposure increases risk of ovarian carcinoma." The Discussion section of the article gives an overview of the literature and addresses some of the limitations of the available database. Although there is some

discussion in the manuscript regarding the dose-response data, Chang and Risch do not provide an explanation for the lack of a dose-response (or inverse response) in their report or others in the literature. This is clearly an important criterion for drawing causal connections so the nature of the dose-response relationship is crucial to interpretation of possible biological relationships.

Chang and Risch also make reference to the fact that asbestos and talc are "chemically related". This is an often-repeated claim in many papers dealing with talc in the medical literature. In our recent publication in the European Journal of Cancer Prevention we describe how there is little mineralogical similarity between talc and asbestos other than both being magnesium silicates (Muscat, Huncharek, 2008). Commercial talc is a soft, non-fibrous entity that is structurally unlike the forms of asbestos associated with malignant disease in humans. There are new scientific findings in this area that demonstrate different carcinogenic effects between talc and asbestos. For example, talc induces apoptosis (programmed cell death) in malignant mesothelioma cells but not in normal mesothelial tissue while asbestos induces programmed cell death in normal mesothelium (see Nasreen et al., 2000 and Broaddus et al., 1996). Talc has also been found to alter the angiogenic balance (blood vessel growth promotion versus blood vessel growth inhibition) in the pleura by inducing the production of endostatin (an inhibitor of blood vessel growth) by normal pleural mesothelial cells but not in malignant mesothelial cells, thereby creating an angiostatic, and therefore, tumor inhibitory environment (see Najmunnisa et al., 2007).

Citation: #6, Daly M, Obrams I. Epidemiology and risk assessment for ovarian cancer. Seminar Oncology 1998; 25:

SUMMARY OF FINDINGS:

This is a review article on the epidemiology of ovarian cancer. It reviews many risk factors besides talc.

ALLEGATIONS OF PETITION'S AUTHORS re: CITATION:

The petition authors cite this reference as "confirming" the findings of prior work showing a positive relationship between perineal talc use and ovarian cancer risk. However, Daly and Obrams did not publish new data, and do not offer an opinion on the causality of the association. Rather they state, "The use of talc in dusting the perineum, in feminine hygiene sprays, or on sanitary napkins, condoms, or diaphragms has been suggested as a possible risk factor for ovarian cancer. " They cite the article by Harlow that shows a 1.5 fold risk and a higher risk in long-term users (> 10 years). The 1982 Cramer article was cited as talc being significantly contaminated with asbestos. They cite the article by Heller et al, that ovarian tissue is contaminated with asbestos and that the fiber burdens were highest in women whose fathers/husbands had a history of asbestos exposure.

MEASURE OF RELATIVE RISK/ODDS RATIO:
NA

RELEVANCE OF STUDY FINDINGS TO SUPPORT CAUSAL ASSOCIATION:

Daly and Obrams did not publish new data, and state that talc has been investigated "as a possible risk factor" for ovarian cancer. This is clearly not a statement that they believe the association is causal. There is no scientific checklist for determining a causal association. The Hill postulates or variations of the Hill postulates are often used to help make assessments of causality (Hill, 1965). These postulates include strong associations, consistent associations across studies, biological plausibility, dose-response relationships and others.

Citation: #7, Green A et al. Tubal sterilization, hysterectomy and decreased risk of ovarian cancer. Int J Cancer 71:948-951, 1997.

SUMMARY OF FINDINGS:

Using a population-based case-control study design (with 824 cases), Green et al. examined the effects of tubal sterilization and hysterectomy on ovarian cancer risk. Both procedures were shown to have a protective effect ranging from a 37% to 74% risk reduction. Data on "ever" versus "never" perineal talc use were also available. The analysis showed a "modest" (authors' terminology), but significant, association between perineal talc use and ovarian cancer risk, i.e. 1.3(1.1-1.6). No dose-response was found and the authors acknowledged this fact.

The investigators also collected information on talc exposure via condom and contraceptive diaphragm use. Duration of use for both exposures showed no association with ovarian cancer risk, consistent with others in the literature recently reviewed by Huncharek and Muscat (European Journal of Cancer Prevention, 2007). The relevant raw data were not presented in the manuscript nor were odds ratios given for these associations.

Interestingly, women with either heavy or painful periods had a marginally increased risk of ovarian cancer, i.e. 1.2(0.93-1.4), 1.1(0.86-1.4) respectively. The magnitude of effect between these two groups is similar to that seen for perineal talc use in this study. The authors provide no further discussion of this finding. This raises the question as to whether there is any relationship between heavy menstruation/painful periods and talc use. It should be noted that investigators such as Paulsen et al. show that abdominal pain is reported by 53% of women with invasive epithelial ovarian cancer prior to diagnosis (Paulsen, 2005). Among the cohort studied by Paulsen et al., fourteen percent of women with ovarian cancer also reported abnormal vaginal bleeding. It is unclear at present whether these symptoms could prompt talc use, in the short term and contribute to a spurious association with ovarian cancer e.g., detection bias may account for

the talc/ovarian cancer connection due to these factors. Further data are needed to clarify this issue.

ALLEGATIONS OF PETITION'S AUTHORS re: CITATION:

The petition authors cite this reference as "confirming" the findings of prior work showing a positive relationship between perineal talc use and ovarian cancer risk. In the discussion of the paper, the authors reiterate the theory of Cramer et al. that artificial closure of the fallopian tube prevents toxins from traversing the tube and depositing on the ovary, despite the fact that this view is speculative. Nonetheless, the odds ratio of 1.3 is consistent with a number of other observational studies in the literature.

As we will discuss in our report summary, this theory is also challenged by new work suggesting that the origin of serous ovarian tumors, the most common type of ovarian carcinoma, may actually be the distal fallopian tube, i.e. the fimbria (see, for instance Crum CP et al. Clinical Medicine and Research 5(1):35-44, 2007). The decrease in ovarian cancer among women with hysterectomy/tubal ligation could be due to removal of the site of origin rather than obstruction of a physical route of passage for suspected carcinogens. The Crum et al. findings are relatively recent and have not been discussed in the medical literature in the context of the talc/ovarian cancer hypothesis. It is our feeling that this pathological information could represent an important piece of evidence that challenges the biological explanation offered for these epidemiological findings.

MEASURE OF RELATIVE RISK/ODDS RATIO:
Relative risk of perineal talc use, OR=1.3(1.1-1.6).

RELEVANCE OF STUDY FINDINGS TO SUPPORT CAUSAL ASSOCIATION:

The report by Green et al. was designed specifically to examine the impact of hysterectomy and tubal sterilization on ovarian cancer risk rather than the influence of perineal talc exposure. Talc data were collected although the raw data are not presented in the published manuscript. The weak effect shown for talc exposure is presented by the authors as supportive of the theory that interruption of the fallopian tube prevents the passage to carcinogens, including talc, from reaching their target organ, i.e. the ovary. Despite the fact that this theory is put forth in much of the relevant literature, it remains speculative. As noted previously, there does exist pathology literature that suggests the origin of epithelial ovarian tumors is actually the fimbria (distal fallopian tube). Should this be proven to be correct, it would present a challenge to the talc carcinogenesis theory.

The Green et al. data do not show a dose-response relationship with condom or diaphragm use. Other work supports this, as does our recent review in the European Journal of Cancer Prevention (Muscat, Huncharek, 2008). Talc exposure via this route is directly into the female reproductive tract in contrast to

perineal dusting. This persistent finding in the epidemiological literature also argues against the talc/ovarian cancer association being causal.

The Green et al. paper also raises another interesting point. As briefly discussed above, this study shows that women with painful or heavy menstrual periods had a marginally increased risk of ovarian cancer. There is a body of literature that documents the occurrence and nature and frequency of symptoms, including these, among patients with epithelial ovarian cancer. Compared with controls, ovarian cancer patients report a multitude of symptoms including pain, abdominal bloating and urinary frequency. In addition, some of this work provides information on the duration of these symptoms prior to diagnosis, ranging from weeks to many months. These factors could contribute to a detection bias where ovarian cancer symptoms could prompt short-term talc use. Although this suggestion is theoretically possible, it has not been addressed in the literature in the context of the talc/ovarian cancer hypothesis.

Citation: #8, Cramer et al. Genital talc exposure and risk of ovarian cancer. Int J Cancer 81:351-356, 1999.

SUMMARY OF FINDINGS:

Cramer et al. conducted a population-based case-control study involving 563 ovarian cancer cases. Use of body powders was assessed via personal interview. Use of powder in non-genital areas was not associated with increased ovarian cancer risk (1.08[0.77-1.50]) nor was increased risk seen among those using powder to dust the perineum (1.45(0.97-2.18]), dusting sanitary napkins (1.45[0.68-3.09]) or dusting underwear 1.21[0.40-3.64]). An elevated risk of ovarian cancer was noted for the exposure categories "multiple uses, genital area", i.e. 2.15(1.30-3.57) and "any personal genital exposure", i.e. 1.6(1.18-2.15).

Dose-response analysis showed an inverse relationship for both frequency of use per month or number of applications of talc. Only one case and three controls reported using cornstarch powders.

The authors conclude that there is a "significant association between the use of talc in genital hygiene and risk of epithelial ovarian cancer."

ALLEGATIONS OF PETITION'S AUTHORS re: CITATION:
The authors cite Cramer et al. to document that these investigators suggested institution of "formal public health warnings" in 1999 based on their interpretation of existing data at that time, i.e. that they "confirm" the causal relationship between perineal talc use and ovarian cancer risk.

MEASURE OF RELATIVE RISK/ODDS RATIO:
Risk associated with any personal genital exposure to talc, OR=1.60(1.18-2.15)

RELEVANCE OF STUDY FINDINGS TO SUPPORT CAUSAL ASSOCIATION:

This population-based case-control study found a statistically significant association between "any personal genital exposure" to talc and risk of ovarian cancer with an odds ratio of 1.60(1.18-2.15). No clear dose-response relationship was seen. In fact, data in both tables II and III suggest an inverse dose-response. Again, as occurs throughout much of the relevant literature, no further explanation for the inconsistent dose-response relationship is offered. The manuscript concedes that, "…it is difficult to quantify the amount of powder actually used…" In essence, they point out the crude nature of the measure of exposure. They acknowledge that a crude exposure measure could also contribute to the finding of a spurious association.

In the discussion of the paper, the authors present a pooled summary odds ratio of fourteen case-control studies in the literature at the time the Cramer et al. report was conducted. The summary OR was 1.36(1.24-1.49). Although the authors point out that this association is statistically significant the p value associated with their assessment of statistical heterogeneity was 0.085. Cramer et al. state that this p value indicates a lack of statistical heterogeneity and therefore suggest that the data show consistency.

The above evaluation of statistical heterogeneity is incorrect in that the threshold p value used in pooled analyses of observational studies, as opposed to randomized clinical trials, is conventionally 0.10 (see Petitti, 2000). The justification for using a much more conservative p value when analyzing epidemiological studies is that they are inherently more variable than randomized trials. Therefore, a p value of 0.085 is consistent with statistical heterogeneity and suggests that the data should not be pooled since the outcome measures across studies vary by a degree greater than would be expected by chance alone. As Huncharek et al. pointed out in their later meta-analysis, clear differences exist between case-control and cohort studies examining the talc/ovarian cancer association. It is essential to seek explanations for these differences (as per Petitti, for instance) rather than ignore the heterogeneity and calculate a pooled estimate of effect. Essentially, Cramer et al. demonstrate that the database they analyzed was not suitable for calculating a pooled odds ratio although they characterize the data as "consistent."

In their Discussion, Cramer et al. also state, "Talc, as a chemical relative of asbestos, appears able to induce histologic changes that are similar to those of asbestos…" As we've pointed out throughout this document and in our recent review article (Muscat, Huncharek, 2008), this is a factual inaccuracy that is repeated in the relevant literature with great frequency. The only similarity between talc and asbestos is that they are both magnesium silicates. Beyond that, the two mineral types share no similar properties. There is a large mineralogical literature detailing the nature of the structure of both asbestos and talc that clearly outlines this fact. The medical literature also contains abundant

information on fiber carcinogenesis. It is largely the morphologic structure of asbestos and other fibers that dictates their toxicity and not their chemical composition. The 3:1 "aspect ratio" of fibers is important in induction of disease and this is independent of chemical composition (see Stanton, 1981). It should be pointed out that many non-fibrous types of asbestos are NOT carcinogenic. Therefore even within the group of asbestos minerals, only a subset of fibrous particles of specific sizes is toxic. A "real-world" example of the composition versus structure issue is the clear difference between diamond and graphite. Both are composed of carbon yet each is distinctly and profoundly different. Diamond is the hardest substance known while graphite is very soft, non-crystalline and brittle. Graphite is also a good conductor of electricity etc. Again, the primary point of importance is that similarity in chemical composition of minerals does not imply similarity in other properties, including biological activity.

Citation: #9, Huncharek M et al. Perineal application of cosmetic talc and risk of invasive epithelial ovarian cancer: A meta-analysis of 11,933 subjects from sixteen observational studies. Anticancer Res 23:1955-1960, 2003.

SUMMARY OF FINDINGS:

This paper presents the results of a meta-analysis designed to evaluate the relationship between perineal dusting with talc and risk of developing ovarian cancer. The rationale for this study was two-fold; (1) Although a possible association between talc use on the female perineum and increased risk of ovarian cancer was first proposed in 1982, the existing literature is inconsistent and the validity of this association is unclear, and (2) meta-analysis provides a systematic, reproducible and transparent method for analyzing large, complex data-sets and appeared well suited to exploring the scientific basis of this proposed association.

Using accepted meta-analytic techniques, data from sixteen observational studies (one cohort and 15 case-control) enrolling 11,933 subjects were statistically pooled. Nine of the sixteen reports showed non-statistically significant odds ratios or relative risks with the one cohort study demonstrating no association between talc use and ovarian cancer. Initial pooling of all 16 reports yielded a summary relative risk of 1.33(1.16-1.45) suggesting a possible positive association, although sensitivity analyses and consideration of causal criteria argued against a causal association.

The assertion by the authors that the use of the summary relative risk statistic of 1.33 is not an appropriate measure to characterize this association is based upon several important findings of the meta-analysis. First, differences in outcome were seen between hospital-based versus population-based case-control studies, i.e. 1.19(0.99-1.41) versus 1.38(1.25-1.41 respectively. This suggests the possible influence of selection bias on study results and/or a "treatment effect" due to short-term talc use by some subjects secondary to treatment induced side effects. Among subjects in population-based studies, there may exist a time

interval between diagnosis and study interview. In this interval some patients may have undergone treatment with modalities such as surgery, radiation and/or chemotherapy. Short-term talc use could be prompted by side effects from treatment such as skin irritation, abdominal bloating etc. The population-based reports may therefore have a larger proportion of prevalent cases versus case-control studies that are more likely to undergo surgery and radiation therapy. Since the majority of women with ovarian cancer present with advanced disease at the time of diagnosis, a larger proportion of subjects in population-based studies may have more limited disease since survival times for advanced ovarian cancer are quite poor (i.e. 5 year survivals under 10%).

Second, demonstration of a dose-response relationship is important for establishment of causal associations. The present data set does not suggest that risk increases with increased exposure and a number of the observational studies show greater disease risk among those in the lowest exposure categories. This may be partially explained by the "treatment effect" phenomenon referred to above. Another possible explanation as discussed in prior portions of this report, is bias secondary to talc use due to disease symptoms. Nonetheless, the lack of a positive dose-response between agent and cause argues against a causal association. The authors conclude, "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."

ALLEGATIONS OF PETITION'S AUTHORS re: CITATION:

Epstein et al. note, "An analysis of 16 pooled studies ***confirmed*** (added) a statistically significant 33% increased risk of ovarian cancer associated with the perineal use of talc." Essentially, the petitioners erroneously indicate that the meta-analysis supports an association between perineal talc dusting and ovarian cancer risk, when, in fact, the report clearly states the contrary conclusion, i.e. "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."

MEASURE OF RELATIVE RISK/ODDS RATIO:
Summary relative risk for association OR=1.33(1.16-1.45) pooling all 16 studies
Summary relative risk for hospital based studies, OR=1.19(0.99-1.41)
Summary relative risk for population based studies, OR=1.38(1.25-1.52)

RELEVANCE OF STUDY FINDINGS TO SUPPORT CAUSAL ASSOCIATION:

The petition's use of the Huncharek et al. meta-analysis as supporting evidence for a causal association between talc and ovarian cancer is inconsistent with the stated findings of the report, as outlined in both the "Abstract" and "Discussion" sections. As above, the summary relative risk initially obtained by pooling data from all sixteen observational studies (1.33[1.16-1.45]) is of questionable validity

since differences in outcomes were seen across study designs. The one cohort study by Gertig et al. showed negative results while the available case-control differed in outcome depending upon the source of study controls (hospital derived versus population). Studies using hospital derived controls showed no increased risk while those employing population-based controls were consistent with a 38% increased risk of disease.

As discussed in the manuscript, short-term use of talc prompted by symptoms caused by treatment could also bias the population based case-control studies. The proportion of ***prevalent*** cases enrolled in the study, time from diagnosis and stage of disease at diagnosis, could all contribute to this "treatment effect" and explain the inverse dose-response seen in many studies.

The above discussion clearly points out the fact that the Huncharek et al. meta-analysis of existing data does not support a causal association between talc and ovarian cancer. The authors of the petition mis-interpret the pooled analysis.

Citation: #10, Baan R et al. Carcinogenicity of carbon black, titanium dioxide and talc. The Lancet Oncology 7:295-296, 2006.

SUMMARY OF FINDINGS:

Citation number 10 is a summary of the recent IARC proceedings during which the carcinogenicity of talc was considered, along with carbon black and titanium dioxide. The summary notes that the one available cohort study (Gertig et al.) failed to show any association between talc use and ovarian cancer risk. Nonetheless, the summary document states that, "Although the cohort study did not lend support to an association, the case-control studies showed a high degree of consistency: the eight ***more informative studies*** (added) reported a 30-60% increase in risk…." The authors acknowledge that the body of available evidence does not provide evidence of a dose-response relationship.

ALLEGATIONS OF PETITION'S AUTHORS re: CITATION:

Epstein et al. cite reference 10 as further support of epidemiological findings of a 30-60% increased risk of ovarian cancer among women using perineal talc and that this report was produced under the auspices of IARC.

MEASURE OF RELATIVE RISK/ODDS RATIO:

Citation #10 is a review article and therefore does not present a measure of association derived from a statistical analysis. As above, Baan et al. cite the fact that the IARC deliberations concluded that the "more informative" epidemiological studies suggest a 30-60% increased risk of ovarian cancer among subjects using talc products on the perineum/genitals.

RELEVANCE OF STUDY FINDINGS TO SUPPORT CAUSAL ASSOCIATION:

This citation provides a very brief summary of the recent IARC proceedings during which the carcinogenicity of talc was considered. The 2B rating suggests that talc is a possible human carcinogen, at least with regard to ovarian cancer although the IARC summary points out that inhaled talc is not classifiable as a human carcinogen (category 3).

Based on our experience as observers to the relevant IARC proceedings, there are a number of issues that appear to contradict the IARC conclusions. IARC's analysis of the human epidemiological literature is based on the "eight more-informative studies" rather than on the total available epidemiological data. The total epidemiological data do NOT show a "high degree of consistency", as characterized by IARC. For example, the one cohort study on this topic clearly showed no increased cancer risk from talc dusting. The case-control study results differ by design as pointed out by Huncharek et al. (see above) and as seen in the report by Langseth et al. (below). That is, hospital-based studies showed results different from those found via population-based analyses. Neither Epstein nor Baan acknowledge these differences but rather characterize the data as "highly consistent".

Additionally, neither Epstein et al. nor Baan et al. take into consideration the lack of a dose-response relationship in the majority of the epidemiological studies, which would be considered evidence against the suspected association being causal. Huncharek et al., in contrast, addressed this issue and offered possible explanations for this finding based on methodological considerations. All of the above issues suggest the possible influence of bias on the various study results although these issues are not addressed in any substantive way by either set of authors. It is also problematic that neither Baan et al. nor IARC considered the meta-analysis of Huncharek et al. and it's findings.

Overall, although the Baan et al. report is held as support for a causal association, the document provides evidence of flaws not only in the pertinent epidemiological evidence itself but also in its erroneous interpretation as causal. It is our opinion that the IARC review of available data on the talc/ovarian cancer association failed to consider the flaws on the relevant database in its entirety. IARC also did not consider the observational data in the context of the criteria recognized as necessary for drawing causal inferences.

Citation: #11, Langseth et al. Perineal use of talc and risk of ovarian cancer. J Epidemiol Community Health 62(4):358-360, 2008.

SUMMARY OF FINDINGS:

Reference number 11 is a short review article outlining some of the major limitations of the data linking perineal talc use and ovarian cancer. The article also makes some methodological suggestions for future studies in this area.

Langseth et al. cite several aspects of the theory supporting a causal association. These include citing references that suggest talc particles applied to the perineum can migrate to the ovary, that hysterectomy and tubal ligation appear to decrease the risk of ovarian cancer by "removing the pathway by which carcinogenic substances (in this case talc) can reach the ovaries", that the possible mechanism via which talc exerts its carcinogenic effect is inflammation, and finally, that the lack of a demonstrated dose-response may be secondary to the "crudeness of the exposure metric used."

ALLEGATIONS OF PETITION'S AUTHORS re: CITATION:
Epstein et al. cite the Langseth article as supporting the findings of the IARC Monograph 93, i.e. that perineal talc exposure increases ovarian cancer risk 30-60% based upon the eight observational studies cited by IARC.

MEASURE OF RELATIVE RISK/ODDS RATIO:
As in above section.

RELEVANCE OF STUDY FINDINGS TO SUPPORT CAUSAL ASSOCIATION:
As a review, the paper provides no new data to support a causal association. Nonetheless, the authors tend to emphasize aspects of the literature that provide supporting information for the theories put forth by Cramer et al.

Figure 1 in the manuscript is instructive, though, on the difficulty the authors have in substantiating the causal claim. The Figure provides a pooled analysis of available observational studies up to the time of publication of the present review. It's important to note that the pooled OR for population-based studies shows a significant effect (1.40[1.29-1.52]) while pooling the hospital-based analyses gives a null results, i.e. OR of 1.12(0.92-1.36). These results are consistent with the prior meta-analysis published by Huncharek et al. although Langeth et al. largely ignore the above noted problems. Alternative explanations are also plausible that could account for an attenuated effect among hospital-based studies. For instance, hospital derived controls may be more likely to use talc powders over the short-term secondary to their specific hospital admission diagnoses.

The differences in outcome based on study design require explanation and none is offered. In addition, Figure 1 also provides a p value for a test for data heterogeneity, i.e. p=0.036. A p value of this magnitude indicates the presence of heterogeneity, meaning that the differences in outcome across studies are not due to chance alone. In general, such a finding precludes statistical pooling (see Petitti, 2000) since the studies are not measuring effects of similar magnitudes. The appropriate task in this context is to attempt sensitivity analyses to explain the observed heterogeneity. A pooled odds ratio in the face of heterogeneity is simply not a valid parameter.

Also, in the final portion of the manuscript, Langeth et al. point out, "The current body of experimental and epidemiological evidence is insufficient to establish a causal association between perineal use of talc and ovarian cancer risk." They

also attempt to "explain away" the lack of a dose-response by attributing it, possibly, to the use of a "crude exposure metric", i.e. years of use. Again, this feature of the data cannot be ignored and the crude nature of the exposure measure can, just as readily, account for spurious findings of a positive association in some reports.

Overall, despite the fact that this short review attempts to provide a narrative justification for a talc-ovarian cancer relationship, it serves to point out the many shortcomings of the data base and the numerous sources of flawed reasoning employed in its interpretation.

Citation: #12, Merrit MA et al. Talcum powder, chronic pelvic inflammation and NSAIDS in relation to risk of epithelial ovarian cancer. Int J Cancer 122:170-176, 2008.

SUMMARY OF FINDINGS:

Citation number twelve derives from the Australian Ovarian Cancer Study Group and is a population-based case-control study of 1,576 women with both invasive and borderline ovarian malignancies. The study was designed primarily to address the question as to whether chronic pelvic inflammation is a risk factor for epithelial ovarian cancer.

Although "ever" use of talc was associated with a small increased risk of ovarian cancer, 1.17(1.01-1.36), there was no evidence of increased risk with increased exposure. Regarding inflammatory processes and disease risk, no increased risk of ovarian tumors was associated with pelvic inflammatory disease, endometriosis, human papillomavirus infection, mumps infection or genital herpes, although the latter showed an association with serous tumors, i.e. OR=1.65(1.01-2.69). Neither aspirin nor NSAID use was consistently associated with a decreased risk of ovarian cancer, providing additional evidence against inflammation as a biologically important mechanism in ovarian carcinogenesis.

Another important limitation of this study that should be noted is the relatively low response rates for cases and controls. Only 47% of eligible controls participated, as did only 65% of potential cases.

The authors conclude that, "…on balance, chronic inflammation does not play a major role in the development of ovarian cancer."

ALLEGATIONS OF PETITION'S AUTHORS re: CITATION:

The petition cites Merritt et al. as another observational study supporting a positive association between perineal talc use and ovarian cancer risk. Again, this isolated finding is not put in the context of limitations and inconsistencies regarding such issues as dose-response.

MEASURE OF RELATIVE RISK/ODDS RATIO:
For "ever use" talc/ovarian cancer risk: OR=1.17(1.01-1.36)
For talc use at other body sites: OR=1.01(0.84-1.20)

RELEVANCE OF STUDY FINDINGS TO SUPPORT CAUSAL ASSOCIATION:

As seen previously, Epstein et al. isolate the weak positive association shown between "ever" use of talc and ovarian cancer risk from the limitations of the existing data, including the lack of support Merritt et al. provides for the theory underlying talc carcinogenicity, i.e. inflammation. Merritt et al., along with two prior negative meta-analyses on anti-inflammatory medication use in this context, provides cogent evidence against the proposed biological mechanism for the talc/ovarian cancer association. This is even more convincing in that none of the other conditions associated with pelvic inflammation, such as pelvic inflammatory disease (PID) or endometriosis were related to increased risk. Since biological plausibility is a necessary component of causal inference, Epstein et al. ignore a major weakness of their argument and simply concentrate on the odds ratio of 1.17 for "ever" use of perineal talc as the basis for a causal relationship.

IV. Talc and ovarian cancer risk: A critique of post-1995 data

Introduction

Above, we reviewed literature citations included in the petition to the FDA by Epstein et al. The petition cites some of the relevant literature published since 1995. We also searched electronic databases in order to determine if other citations exist that were not cited either by Epstein et al. or by Huncharek et al. in their 2003 meta-analysis. No additional observational studies relevant to the issue of ovarian cancer causation were located.

The issues articulated by Epstein et al. in relation to the possible carcinogenicity of talc are not uncommon when dealing with interpretation of results derived from observational studies. In an article published twenty years ago, Feinstein provided an insightful and cogent explanation for the myriad problems that plague the process of causal inference as it applies to non-experimental data (Feinstein, 1988). As he points out, most people learn about science by studying experimental methods. These methods largely include direct intervention by the experimenter on whatever entity is under study, whether it be an animal species such as rats or mice, specific chemical compounds, sub-atomic particles etc. The scientist, in this context, directly manipulates the study subject/object using established principles of experimental science. In the context of human studies, the experimental design that has come to represent the "gold standard" of cause-effect relationships is the randomized clinical trial. Unfortunately, in epidemiological research, issues of feasibility and ethical considerations preclude randomization of healthy human subjects to receive potentially harmful exposures to various substances, including those that represent possible carcinogenic hazards. Therefore, the epidemiologist must substitute observational methods to study cause-effect relationships that preclude direct

intervention with, and/or manipulation of, study subjects (i.e. experiments). Because of this fact, criteria for establishing cause-effect relationships are inherently different when utilizing epidemiological methods versus experimental ones.

In 1965, Hill published a landmark article articulating standards for drawing causal inferences from observational data. His rationale for this stemmed from the realization that the urgency of many public health problems demands action despite the fact that existing knowledge might be imperfect (Rothman, 1986). The "Hill Criteria" as they've become known, are not simply a "checklist" of requirements that must be met in order to determine cause-effect relationships. Rather, they represent a theoretical framework to guide one's thinking when attempting to decide whether a body of data meets a basic threshold necessary to distinguish causal from non-causal associations. These criteria include, (1) strength of association, (2) consistency (i.e. repeated observation of an association in different populations under different circumstances), (3) specificity (a given cause leads to a specific effect), (4) temporality (cause must precede effect), (5) biological gradient (dose-response), (6) plausibility (biological plausibility), (7) coherence (i.e. that a given cause/effect relationship for an association does not conflict with what is known of the natural history and biology of the disease in question), (8) experimental evidence (to support the observational findings), (9) analogy.

While the Hill criteria do not provide a complete solution to the dilemma of causal inference in epidemiology, their importance lies in establishing at least a general framework for the process. The proposed talc/ovarian cancer association represents an illustrative example of the utility of this framework. Below we discuss the points raised by Epstein et al. in this context and show that the conclusion that the proposed talc/ovarian cancer association is causal is not supported by existing data.

Overview

The possibility that perineal talc exposure could be associated with development of ovarian cancer was initially derived from a case-control study published in 1982 (Cramer, 1982). Since that time, a number of additional reports have addressed this question with most showing odds ratios ranging between 1.0 and 2.0. Although this has prompted some to suggest that these estimates of effect provide support for a cause-effect relationship between this exposure and disease outcome, several important caveats must be considered.

Effects of this magnitude are often characterized as "weak effects" and although the exact definition of a weak effect is debatable, most epidemiologists would consider associations of less than 2.0 to fall within this general category. Hill and others argue that strong associations are more likely to be causal than weak associations since, "..if they were due to confounding or some other bias, the biasing association would have to be even stronger and would therefore presumably be evident" (Rothman, 1986). As Rothman points out, weak associations are more likely to be explained by undetected biases.

Measures of association of this magnitude are often difficult to interpret. This is based on the fact that the investigator cannot directly manipulate the levels of exposure of interest or extraneous factors that could affect study findings. Attempts to control for external factors are accomplished by statistical manipulations of collected data. However, this process depends on the accuracy and completeness of data collection. Further, the correct choice and interpretation of both statistical models and statistical findings can also be contentious.

It is important to point out that although an association is weak, this does not rule out a causal connection. Nonetheless an example of a factor that could confound the weak effect shown for perineal talc is smoking. It's now recognized that smoking is a risk factor for a number of solid tumors including lung (with OR's on the order of 5.0 versus non-smokers) and esophageal cancer. Evidence exists that smoking may also be related to at least some types of ovarian tumors, in particular, those of the mucinous histology. The current literature contains a number of reports showing a doubling or tripling of mucinous ovarian cancer risk among smokers (Green, 2001)(Pan, 2004). Since Rosenblatt et al. reported that smokers are more likely to engage in perineal talc dusting compared with non-smokers, an imbalance in smokers across case and control groups in epidemiological studies of the talc/ovarian cancer association could contribute to a spurious positive association (Rosenblatt, 1998).

Consistency of an effect could contribute to a causal claim despite a finding of a weak association. Epstein et al. characterize the talc/ovarian cancer relationship as being "confirmed" by multiple scientific publications as well as by review of available evidence by the International Agency for Research on Cancer (IARC). They state that, "…IARC..concluded that eight publications confirmed a 30-60% increased risk of ovarian cancer following the perineal application of talc". Despite the claims of the petitioners, a review of available evidence shows that the epidemiological evidence is NOT consistent across studies or across study types. For instance, Table 1 in Huncharek et al. (2003) shows several inconsistencies in the database. Clearly, not all studies showed a positive, statistically significant association, even among the case-control reports that make up the bulk of the database. In addition, there was relatively wide variation in the magnitude of measures of association.

Interestingly, up to the date of filing of the petition by Epstein et al., only one cohort study had been published, i.e. Gertig et al. (2000) showing no association between perineal talc use and ovarian cancer risk. Given the conflicting findings of case-control studies, Huncharek et al. employed meta-analytic techniques to explore possible sources of variability among these reports. Their rationale for doing so was that if meta-analyses showed that the patterns of low relative risks or odds ratios are consistent across all relevant studies in different populations, these weak associations are less likely to be due to confounding or other biases. If a statistical test for heterogeneity shows effects of different magnitudes across studies, sensitivity analyses can be employed to determine the source of

observed variability and thereby identify biases due to study design, case-control selection etc.

Huncharek et al. initially pooled data from fifteen case-control and one cohort analysis, yielding a summary relative risk (RRs) of 1.33 (1.16-1.45). Although this suggests a statistically significant positive association between perineal talc use and ovarian cancer, risk sensitivity analyses demonstrated clear differences in outcome based on study design. That is, hospital-based case-control studies showed no evidence of an effect (1.19[0.99-1.41]) in contrast to those reports using population-derived controls (1.38[1.25-1.52]). As discussed in the earlier portion of this report, these findings suggest bias and bring the validity of the initial pooled RRs into question. The Huncharek report provides some possible explanation for the observed differences, as was outlined previously, and indicates that study outcomes are not consistent.

Further supporting the findings of this meta-analysis is the more recent and updated pooled data provided by Langseth et al. (2008) cited by the Epstein petition. These authors pooled data from twenty relevant epidemiological studies. Again, although the calculated summary relative risk obtained from pooling data from all 20 reports gives a statistically significant RRs (pooled odds ratio) of 1.35(1.26-1.46), the statistical test for data heterogeneity yielded a p value of 0.036. A p value of this size (i.e. less than 0.10) is indicative of significant heterogeneity and, as per convention (see Petitti) precludes statistical pooling, i.e. the pooled summary estimate of effect is not valid given that the data are heterogeneous. This shows that the available data are not consistent and therefore makes a causal association less likely.

One of the more persistent findings among the epidemiological studies examining this suspected association is the lack of a dose-response relationship. Table 2 of the Huncharek et al. meta-analysis displays dose-response data for those included studies providing such information. Many of the reports do not show increased risk with increasing exposure. The even more problematic finding in terms of establishing a causal association is that a number of studies suggest that risk decreases with increased exposure, (e.g. see Chang and Risch above or Cook et al., 1997).

Few authors directly address the above noted lack of evidence of a dose – response. Huncharek et al. (2003, Petition reference #9) and Huncharek and Muscat (2007), in contrast, offer a number of possible explanations for an inverse dose response. As outlined above, treatment for ovarian cancer may induce specific symptoms that could prompt short-term talc use. For instance, some early stage patients may undergo radiation therapy, which causes skin irritation. Such side effects could result in some patients using talc products to address these side effects. Talc is often recommended to keep skin folds in the perineum dry and prevent skin breakdown secondary to radiation. In addition, symptoms of the disease process itself could cause some women to use talc to counter these symptoms. Paulsen et al. (2005) and Golf et al. (2004) document that a number of symptoms are quite common among ovarian cancer cases versus

control patients. For instance, Golf et al. (2004) show that increased abdominal size is over seven times more common among cases versus controls while abdominal bloating is 2.5 times more common. The combination of bloating, increased abdominal size and urinary symptoms were found in almost half of all ovarian cancer patients but in only 8% of controls. Also of interest are the findings of Green et al. (1997, Petition reference #8) that increased ovarian cancer risk was seen among patients with painful periods or excessive vaginal bleeding. Again, such symptoms could prompt talc use and lead to a spurious association with talc. Although there are no firm data in the existing literature to definitively establish that these factors lead to increased short-term use of talc, the scenarios are plausible and could explain the inverse dose-response seen in a number of epidemiological studies.

The majority of reports largely ignore the counter-intuitive findings although Cramer et al. (Petition reference #4) attribute the dose-response inconsistencies, possibly, to the "crudeness" of the exposure measurement used. What is not acknowledged is that this same problem of imprecise exposure estimates could also explain a spurious *positive* association of talc and ovarian cancer, especially in light of the inconsistent outcomes across reports. In summary, the failure to show a coherent and consistent relationship between talc exposure and ovarian cancer risk argues against a causal association.

An additional limitation of the existing literature dealing with the proposed talc/ovarian cancer association is the lack of any known biological mechanism via which talc particles could induce ovarian tumors. This represents probably the most troublesome aspect of arguments in support of this proposed causal association. It is also interesting to note, that biologically theories put forth to explain how talc may cause neoplastic transformation have changed over time as various proposed mechanisms have met with criticism in the developing literature.

Initially, Cramer et al. (1982) and others sought to draw an analogy between talc and fibrous asbestos, the latter being a known and well-described carcinogen. The biological effects of asbestos have been elucidated over the last 50-60 years via a multitude of epidemiological, in vitro and in vivo studies (Huncharek, 1986). Specific asbestos types are recognized as both animal and human carcinogens and, due to this fact, this commodity is banned from use in the United States. A number of investigators initially implicated talc products as possible carcinogens since prior to the early 1970's, some talc products contained small amounts of asbestos fibers (Rohl, 1976). Clearly, such products could possibly represent a carcinogenic risk secondary to the asbestos contamination. It should be pointed out that this in no way implicates talc as a toxin since the problematic constituent of such products was the asbestos fibers, not talc.

Since the early 1970's, the relevant industries voluntarily eliminated asbestos contamination from talc products. Because of this, the "anti-talc" argument shifted to implicate talc itself as a carcinogenic risk based on its "chemical similarity" to talc. It is interesting, and confusing, as to why talc is thought by

some to be carcinogenic based on the fact that there is some common chemical constituents of talc and asbestos.

Both commercial talc and the group of minerals known as asbestos are magnesium silicates. Beyond that fact, the two substances share no common characteristics. The work of Stanton (1981, referenced below) and others shows that the carcinogenic ability of fibrous asbestos is due to its structure, not its chemical composition. While talc and asbestos are both magnesium silicates, they are structurally distinct and belong to different mineral groups and subgroups, as detailed by Muscat and Huncharek (2008). Amphibole asbestos minerals are inosilicates while talc is a member of the silicate subclass phyllosilicate and group clay or montmorillonite/smectite. While serpentines, including serpentine asbestos (chrysotile), are also phyllosilicates, serpentine minerals belong to the kalolinite-serpentine group. The asbestos varieties of serpentine are structurally different from other members of the serpentines in that their brucite layers and silicate layers bend into tubes that produce fibers. Non-fibrous serpentine does not have carcinogenic properties and it is clear that the physical structure of serpentine asbestos (and amphibole asbestos) is responsible for its disease-causing potential, not its atomic constituents. It simply does not follow that one should assume talc is carcinogenic simply because it is a silicate. Structure dictates toxicity/carcinogenicity, not chemical composition.

Earlier in this report, we use the analogy of graphite and diamond as an example of two substances that are chemically identical yet are vastly different in their physical properties. The contrast between commercial talc and any of the varieties of fibrous asbestos is just as stark. Clearly, the "asbestos analogy" used to support the possible carcinogenicity of talc is not supported by existing data.

Given the dissimilarities between talc and asbestos with regard to their fibrous shapes, the weak but increased associations in the epidemiological studies could be attributed to other mechanisms, assuming that the statistical associations are unbiased and not due to confounding. Asbestos fibers in the lung initiate an inflammatory and scarring process, and it has been proposed that ground talc, as a foreign body, might initiate an inflammatory response (Ness, 1999). Pelvic inflammatory diseases, however, such as endometriosis, peritonitis, tubo-ovarian abscess formation etc., have not been associated with an increased risk of ovarian cancer. A meta-analysis of studies of anti-inflammatory drug use found no reduction in ovarian cancer risk (see Muscat, Huncharek , 2008). In fact, the Merritt et al. study (2007) cited by Epstein et al. also showed no relationship between inflammation and ovarian cancer risk.

Most recently, Cramer et al. proposed that the talc/ovarian cancer association might be explained by the induction of Anti-MUC1 antibodies (Cramer, 2005). This idea has been debated on statistical grounds where talcum powder applied to the perineum was associated with increased Anti-MUC1 expression but the correlation was also observed when talc powder was applied to other body parts. More importantly, the simple observation that talc elevates immunoglobulin protein levels in blood, possibly via heat shock proteins, seems to

have no known direct relevance for ovarian cancer since Anti-MUC1 is associated with other cancers and because there is no known role of heat shock proteins in ovarian cancer risk.

Some of the most important biological data supporting the non-toxic nature of talc comes from the clinical use of talc in treating both malignant and benign pleural effusions in humans (i.e. pleurodesis). This is a common procedure in the United States and elsewhere and talc slurry is applied directly to the pleura (via chest tube placement) to induce obliteration of the pleural space by scarring and prevent the re-accumulation of fluid secondary to tumor or benign causes. Multiple long-term clinical studies, as reviewed by Muscat and Huncharek (2008), have not shown a single case of cancer secondary to direct talc application to the human pleura. In an earlier part of this report, we also detailed recent data showing that talc has demonstrated anti-tumor properties secondary to the induction of endostatin when used in pleurodesis. In fact, pleurodesis patients treated with talc are known to experience longer survival times than those treated with other sclerosing agents. This is likely due to the tumor-inhibitory effects of talc, as suggested by a number of investigators.

Finally, other human data, such as the demonstration that inhaled talc in mining and milling operations is not associated with increased pulmonary tumors and the likelihood that talc could selectively induce ovarian cancer and not lung cancer at exposure concentrations orders of magnitude lower than that experienced in occupational settings argues against its toxicity.

Although the process of drawing causal inferences from scientific data is complex, application of accepted standards, as noted above, to the talc/ovarian cancer relationship clearly indicates that the available epidemiological and other evidence does not support a causal connection. The weak association shown in a sub-set of observational studies can potentially be explained by numerous alternative hypotheses, as detailed throughout this document. Given the lack of supporting evidence from in vivo, in vitro and clinical research studies using human subjects, the weak epidemiological association is unlikely to be causal.

V. Review of Cancer Prevention Coalition website

There are a number of factual errors on the CPC website. The page containing answers to specific questions begins with a description of talc. The first sentence implies that talc contains "fibers" that are "similar" to asbestos, that are not "separated" from mined talc. This implies to the lay reader that all talc preparations contain particles of "asbestos like" fibers. This could be mis-understood by the public as implying that all talc contains potentially cancer-causing particles, contrary to established fact.

Under the section explaining "Why is talc harmful", it is stated that talc has been shown to cause tumors of the ovary. It is also stated that talc shares dangerous similarities to the "potent carcinogen", asbestos, without further elaboration. In

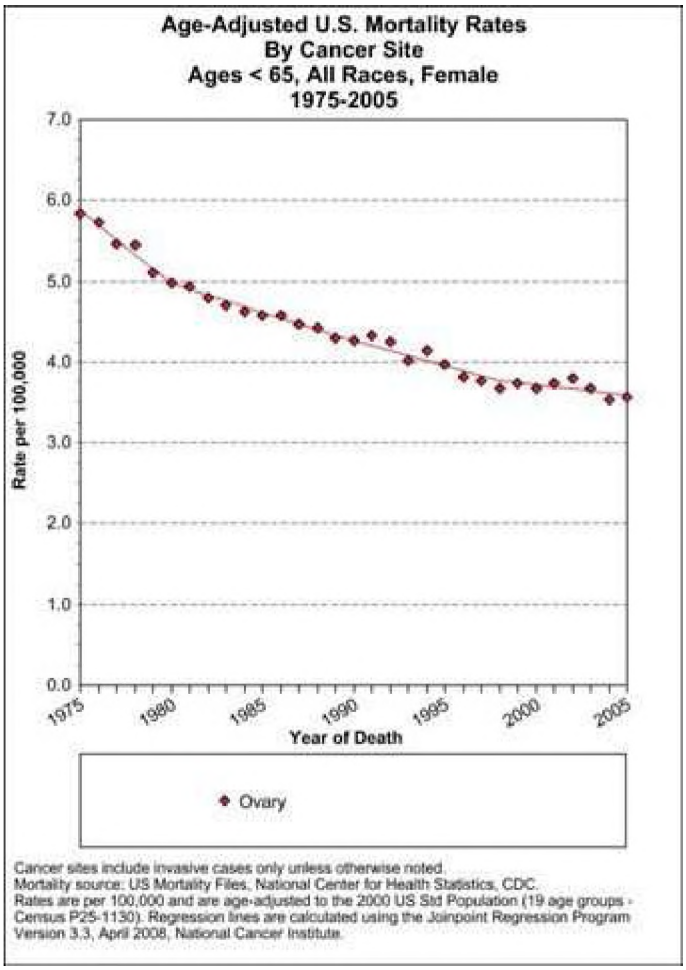
their discussion of what type of talc exposures are dangerous, the site plainly states that talc is a carcinogen and that there exists a strong link between frequent use of talc in the genital area and ovarian cancer. They also go on to state that talc should not be used on children since it carcinogenic.

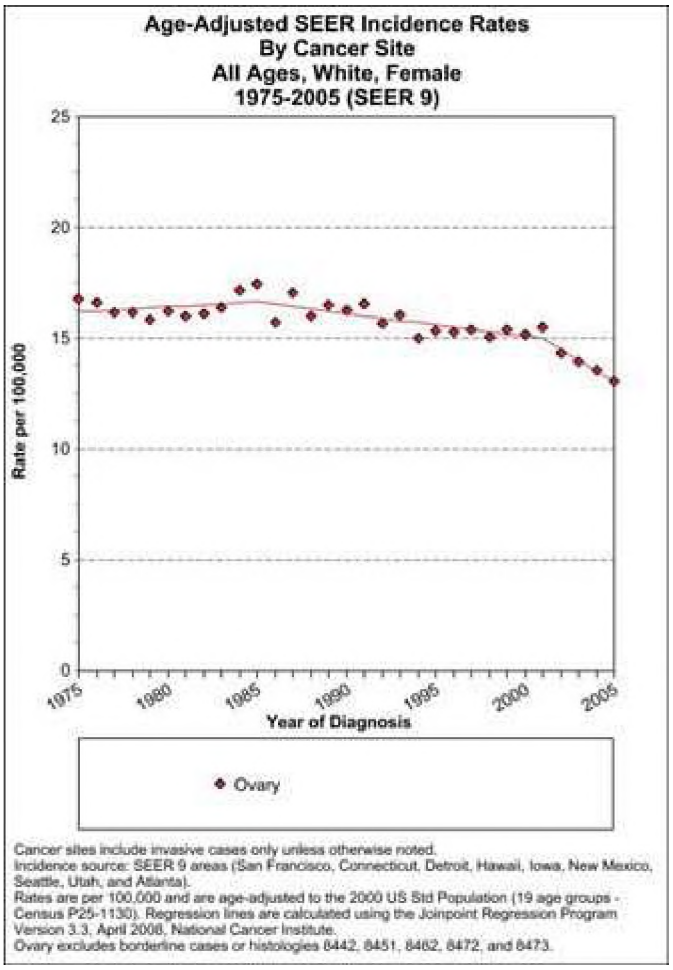
In the last paragraph of the "Risks of Talcum Powder" page, they urge consumers not to purchase talc products and to write to the FDA to express concerns regarding talc's toxicity.

Clearly, the CPC website contains multiple errors of fact and mis-representations. All of these are addressed in the earlier portions of this report.

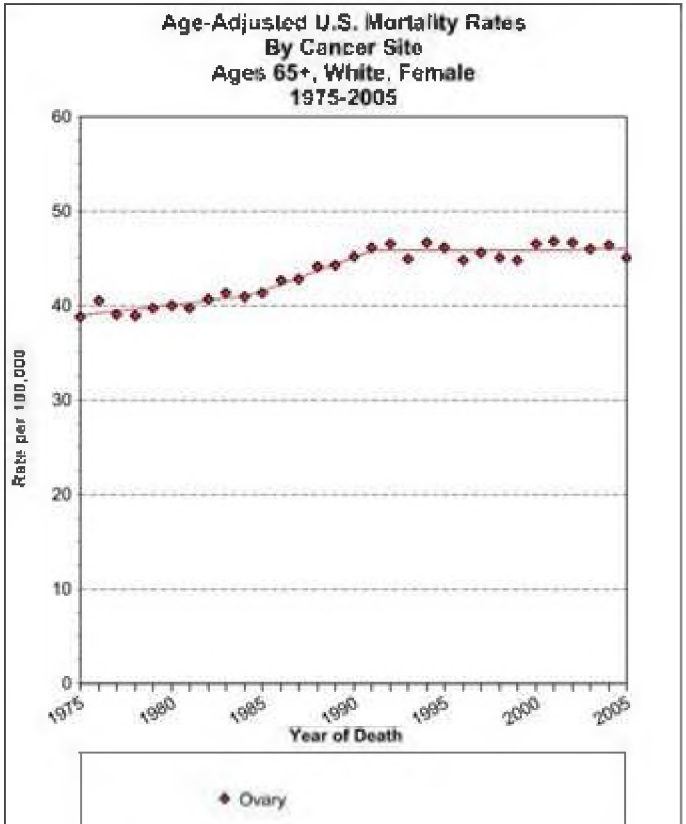
VI. Appendix

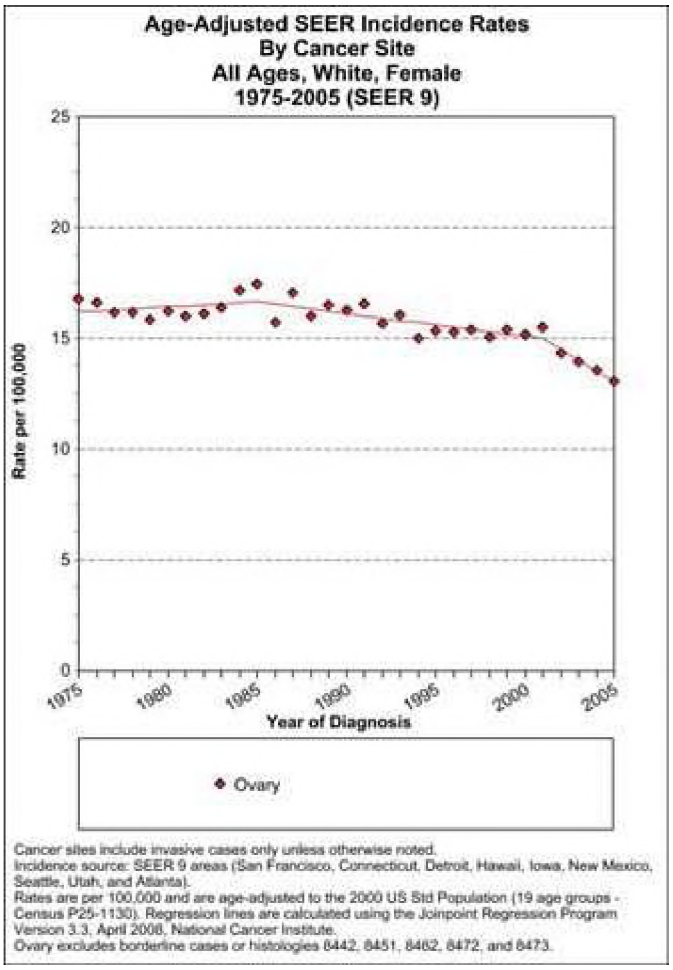
Relevant SEER data




Age-Adjusted SEER Incidence Rates
By Cancer Site
All Ages, White, Female
1975-2005 (SEER 9)
Rate per 100,000
25
20
15
10
5
0
1975
1980
1985
1990
1995
2000
2005
Year of Diagnosis
Ovary
Cancer sites include invasive cases only unless otherwise noted.
Incidence source: SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta).
Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130). Regression lines are calculated using the Joinpoint Regression Program Version 3.3, April 2008, National Cancer Institute.
Ovary excludes borderline cases or histologies 8442, 8451, 8462, 8472, and 8473.

Cancer sites include invasive cases only unless otherwise noted.
Mortality source: US Mortality Files, National Center for Health Statistics, CDC.
Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130). Regression lines are calculated using the Joinpoint Regression Program Version 3.3, April 2008, National Cancer Institute.


Age-Adjusted U.S. Mortality Rates
By Cancer Site
Ages 65+, White, Female
1975-2005
Rate per 100,000
60
50
40
30
20
10
0
1975
1980
1985
1990
1995
2000
2005
Year of Death
Ovary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By Cancer Site
All Ages, White, Female
1975-2005 (SEER 9)
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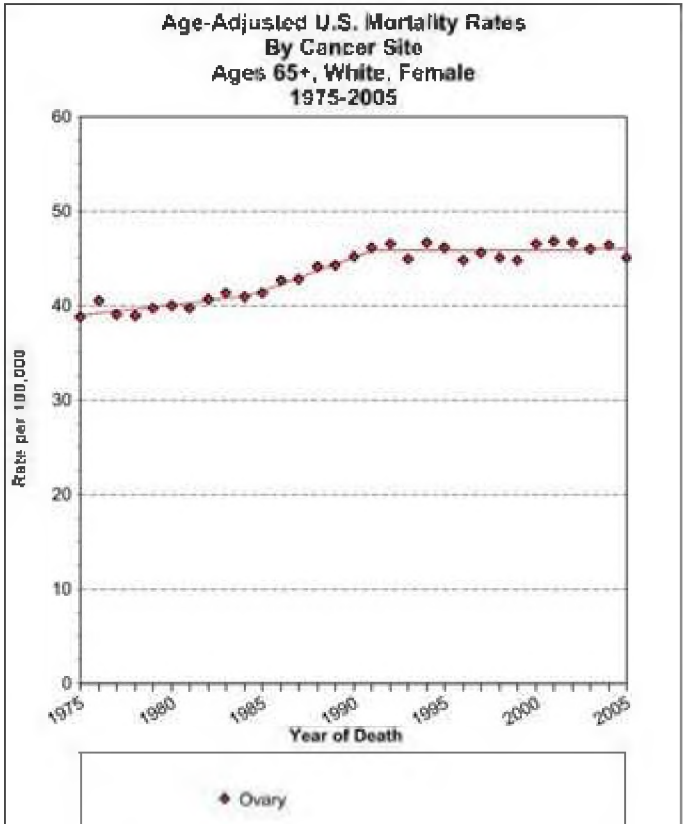
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By Cancer Site
Ages 65+, White, Female
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2005
Year of Death
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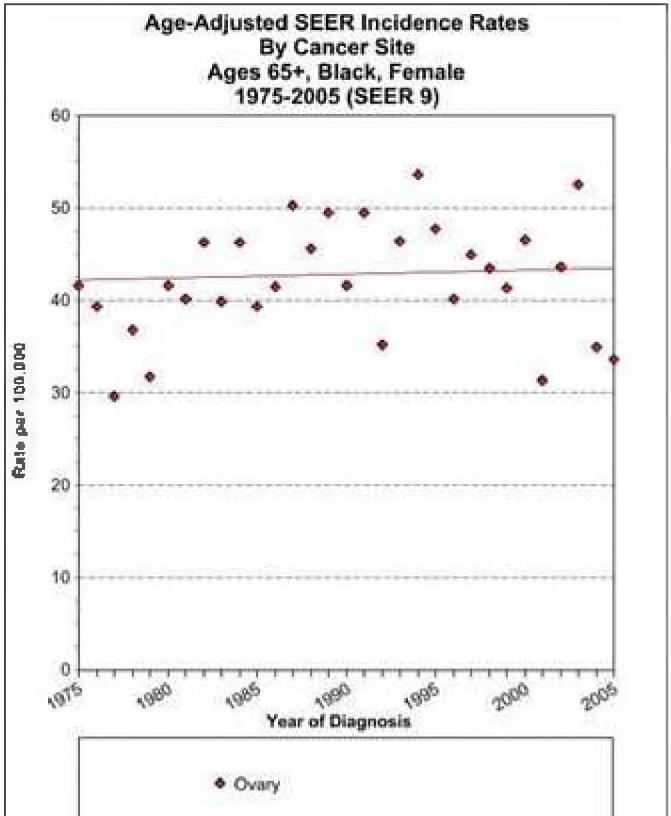
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By Cancer Site
Ages 65+, Black, Female
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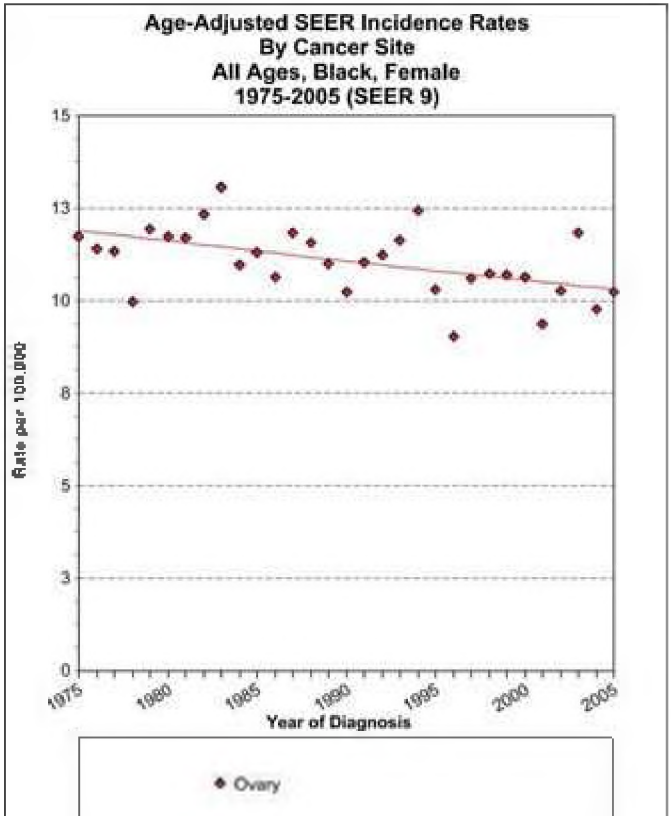
Age-Adjusted SEER Incidence Rates
By Cancer Site
All Ages, Black, Female
1975-2005 (SEER 9)
Rate per 100,000
15
13
10
8
5
3
0
1975
1980
1985
1990
1995
2000
2005
Year of Diagnosis
Ovary

VII. Cited Literature

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