DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
College Park, MD 20740

APR 1 - 2014

Samuel S. Epstein, M.D.
Cancer Prevention Coalition
University of Illinois at Chicago
School of Public Health, MC 922
2121 West Taylor Street, Rm. 322
Chicago, Illinois 60612

RE: Docket Numbers 94P-0420 and FDA-2008-P-0309-0001/CP

Dear Dr. Epstein:

This letter is in response to your two Citizen Petitions dated November 17, 1994 and May 13, 2008, requesting that the Food and Drug Administration (FDA or the Agency) require a cancer warning on cosmetic talc products. Your 1994 Petition requests that all cosmetic talc 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." Additionally, your 2008 Petition requests that cosmetic talcum powder products bear labels with a prominent warning such as: "Frequent talc application in the female genital area is responsible for major risks of ovarian cancer." Further, both of your Petitions specifically request, pursuant to 21 CFR 10.30(h)(2), a hearing for you to present scientific evidence in support of this petition.

We have carefully considered both of your Petitions. We are committed to the protection of the public health and share your interest in reducing the risk of ovarian cancer. Current regulations state that cosmetic products shall bear a warning statement whenever necessary or appropriate to prevent a health hazard that may be associated with a product. FDA may publish a proposal to establish a regulation prescribing a warning statement on behalf of a petitioner if the petition is supported by adequate scientific basis on reasonable grounds.

After careful review and consideration of the information submitted in your Petitions, the comments received in response to the Petitions, and review of additional scientific information, this letter is to advise you that FDA is denying your Petitions. FDA did not find that the data submitted presented conclusive evidence of a causal association between talc use in the perineal area and ovarian cancer.

For this reason and for the additional reasons described below, FDA is denying your Petitions.

I. Discussion

The basis of your request, throughout both Petitions, can be summarized as comprising three major points:

1. Talc may be associated with asbestos.
2. Talc is a carcinogen based on the findings of a 1993 National Toxicology Program study.
3. Epidemiological studies confirm the causal relation between genital application of talc and ovarian cancer, and the protective effect of tubal ligation or hysterectomy, preventing the translocation of talc to the ovary.

As the points you raise in your Petitions concern the chemistry and toxicology of talc, the epidemiology associated with talc use, and the etiology of ovarian cancer, commensurate reviews were conducted to assess your request.

Chemistry Findings:

Asbestos is a known carcinogen and your first major point is that talc may be associated with asbestos. As evidence that talc cosmetic products contain asbestos, you first cite a 1968 survey of 22 talcum products that found fiber content averaging 19% in all 22 products. This author further concludes that "the fibrous material was predominantly talc but probably contained minor amounts of tremolite, anthophyllite, and chrysotile [asbestos-like fibers] as these are often present in fibrous talc mineral deposits …"

You then cite a follow up study from 1971-1975 that examined 21 samples of consumer talcums and powder and concluded that cosmetic grade talc was not used exclusively in these products. This study found the presence of asbestiform anthophyllite and tremolite, chrysotile, and quartz. From these two citations, one may infer that currently available talc-containing cosmetic products are presently contaminated with asbestos, a known carcinogen. Unfortunately, you did not present any original data on the chemical composition of talc currently being used in cosmetics talc products or data linking these findings to currently used talc.

It has been reported in the scientific literature that most talc products in world trade are impure as a result of the geological processes involved in the formation of talc deposits. Further, talc containing asbestos fibers such as tremolite asbestos or chrysotile are sometimes encountered. However, large deposits of high purity, asbestos-free talc do exist and talc purification techniques have been developed which can be used to improve talc quality. Thus, while it has been reported in the past that cosmetic talc has been contaminated with asbestos, it has been also reported that asbestos-free talc deposits do exist. In addition, techniques do exist for the purification of talc in order to improve its quality. You have not provided evidence that asbestos contaminated talc-containing cosmetic products are currently being marketed, since the data submitted is almost 40 years old.

Because safety questions about the possible presence of asbestos in talc are raised periodically, in 2009 FDA conducted an exploratory survey of currently marketed cosmetic-grade raw material talc and finished cosmetic products containing talc. This survey analyzed cosmetic-grade raw material talc from four suppliers out of a possible group of nine suppliers we had requested talc samples from, along with thirty-four talc-containing cosmetic products currently available in the Washington, D.C. metropolitan area for the presence of asbestos. In order to cover as broad a product range as possible, samples identified for testing included low, medium, and high priced products, along with some from "niche" markets. The cosmetic products identified as containing talc included eye shadow, blush, foundation, face powder, and body powder.

The survey found no asbestos fibers or structures in any of the samples of cosmetic-grade raw material talc or cosmetic products containing talc. While FDA found this data informative, the results were limited by the fact that only four suppliers submitted samples and by the number of products tested. They do not prove that all talc-containing cosmetic products currently marketed in the United States are free of asbestos contamination. As always, when potential public health concerns are raised, we will continue to monitor for new information and take appropriate actions to protect the public health. You may wish to see more on this survey on our website at http://www.fda.gov/Cosmetics/ProductandIngredientSafety/SelectedCosmeticIngredients/ucm293184.htm.

Toxicology Findings:

Your second major point is that talc is a carcinogen with or without the presence of asbestos-like fibers. The basis to this claim is that in 1993, the National Toxicology Program (NTP) published a study on the toxicity of non-asbestiform talc and found clear evidence of carcinogenic activity.

This NTP report concluded that cosmetic-grade talc caused tumors in animals, even though no asbestos-like fibers were found. The report made the following observations:

- There was some evidence of carcinogenic activity in non-asbestiform talc from inhalation studies in male rats based on an increased incidence of benign or malignant pheochromocytomas of the adrenal gland.
- There was clear evidence of carcinogenic activity of talc in female rats based on increased incidences of alveolar/bronchiolar adenomas and carcinomas of the lung and benign or malignant pheochromocytomas of the adrenal gland.
- There was no evidence of carcinogenic activity of talc in male or female mice exposed to 6 or 18 mg/cubic meter.

However, this study lacks convincing scientific support because of serious flaws in its design and conduct, including:

- The investigators used micronized talc instead of consumer-grade talc resulting in the experimental protocol not being reflective of human exposure conditions in terms of particle size.

- Investigators conceded that they had problems with the aerosol generation system; whereby, the target aerosol concentrations were either excessive or not maintained during 26 of the 113-122 weeks of the study.
- The study did not include positive and negative dust controls which would have permitted an "exact assessment" of the talc's carcinogenicity relative to the two control dusts.

In light of these shortcomings, a panel of experts at the 1994 ISRTP/FDA workshop declared that the 1993 NTP study has no relevance to human risk.

In addition, we reviewed relevant toxicity literature (consisting of 15 articles from 1980 to 2008), not cited in your Petitions, to determine if there was additional support at this point in time to for your suggested warning label. Scientific literature on studies of acute exposure effects, subchronic exposure effects, chronic exposure or carcinogenicity effects, developmental or reproductive toxicity, and genotoxicity effects were reviewed. As a result of the review of this relevant literature, FDA did not find enough additional support at this point in time for your suggested warning label.

Epidemiology and Etiology Findings:

Your third major point is that epidemiological studies confirm the causal relation between genital application of talc and ovarian cancer, and the protective effect of tubal ligation or hysterectomy, preventing the translocation of talc to the ovary.

After consideration of the scientific literature submitted in support of both Citizen Petitions, FDA found:

1 The exposure to talc is not well-characterized; it is not known if the talc referred to in the scientific studies was free of asbestos contamination; various consumer brands or lots of talc were not identified; and contamination of talc by asbestiform minerals or other structurally similar compounds was not ruled out.

2 Several of the studies acknowledge biases in the study design and no single study has considered all the factors that potentially contribute to ovarian cancer, including selection bias and/or uncontrolled confounding that result in spurious positive associations between talc use and ovarian cancer risk.

3 Results of case-controls studies do not demonstrate a consistent positive association across studies; some studies have found small positive associations between talc and ovarian cancer but the lower confidence limits are often close to 1.0 and dose-response evidence is lacking.

4 A cogent biological mechanism by which talc might lead to ovarian cancer is lacking; exposure to talc does not account for all cases of ovarian cancer; and

5 there was no scientific consensus on the proportion of ovarian cancer cases that may be caused by talc exposure.

6 The conclusion of the International Agency for Research on Cancer that epidemiological studies provide limited evidence for the carcinogenicity of perineal use of talc based body powder and the IARC classification of body-powder talc as group-2B, a possible carcinogen to human beings, is persuasive, but the results of the Nurses' Health Study, a large prospective cohort study, revealed no overall association with ever talc use and epithelial ovarian cancer.

Per the etiology review, approximately 10% of epithelial ovarian cancers are associated with inherited mutations. The remaining 90% of epithelial ovarian cancers are not related to these genetic mutations are non-hereditary. They have been historically classified based on histology as borderline/low malignant potential, serous, endometrioid, mucinous, and clear-cell.

Two theories have historically dominated on the cause of epithelial ovarian cancer and these are the "incessant ovulation hypothesis" and the "gonadotropin hypothesis." In addition to these endogenous factors, the role of exogenous factors via retrograde transport of noxious substances (e.g. carcinogens, particulates such as talc and asbestos, endometriosis and infectious agents) from the vagina and uterus into the Fallopian Tubes and peritoneal cavity have been studied extensively as a possible risk factor for ovarian cancer.

While there exists no direct proof of talc and ovarian carcinogenesis, the potential for particulates to migrate from the perineum and vagina to the peritoneal cavity is indisputable. It is, therefore, plausible that perineal talc (and other particulate) that reaches the endometrial cavity, Fallopian Tubes, ovaries and peritoneum may elicit a foreign body type reaction and inflammatory response that, in some exposed women, may progress to epithelial cancers. However, there has been no conclusive evidence to support causality.

The best evidence for an association or causal relationship between genital talc exposure and ovarian cancer comes from epidemiologic data which show a statistically significant but modest increased risk of epithelial ovarian cancer, especially with serous histology, among women with a history of genital dusting with talcum powder. While the growing body of evidence to support a possible association between genital talc exposure and serous ovarian cancer is difficult to dismiss, the evidence is insufficient for FDA to require as definitive a warning as you are seeking.

Request for hearing

In addition to your request for a warning label, you also requested a hearing, under 21 CFR 10.30(h)(2), so that you can present scientific evidence in support of your petitions.

Under this regulation, FDA may deny a citizen petition request for a hearing if the data and information submitted (even if accurate), are insufficient to justify the determination urged. In consideration of your request, we conducted an expanded literature search dating from the filing of the petition in 2008 through January 2014. The results of this search failed to identify any new compelling literature data or new scientific evidence.

Since we find that the data and information are insufficient to justify the determination you request and we did not identify any new compelling literature data or new scientific evidence, FDA is also denying your hearing request.

II. Conclusion

FDA appreciates the goals of the Cancer Prevention Coalition and FDA supports the goal of reducing the rate of ovarian cancer. Although FDA is denying the Cancer Prevention Coalition's petitions for the reasons discussed above, the Agency shares your commitment to the public health.

Sincerely,

Steven M. Musser, Ph.D.
Deputy Director for Scientific Operations
Center for Food Safety
and Applied Nutrition

Drafted: J. Gasper, OCAC, 2/28/14
Comments: L. Katz, OCAC, 3/3/14
Revised: J. Gasper, OCAC, 3/4/14
Cleared: N.Sadrieh, OCAC, 3/4/14
Cleared: LMKatz, OCAC, 3/5/14
Reviewed: FHogue, OCAC: 3/614
Cleared by:Musser:3/13/14
F/T:SRussell, OCAC 3/18/14

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UIC SCHOOL OF PUBLIC HEALTH, MC 922 · 2121 W. TAYLOR ST. · CHICAGO, IL 60612 · (312) 996-2297 · epstein@uic.edu

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PETITION SEEKING A CANCER WARNING ON COSMETIC TALC PRODUCTS

May 13, 2008

Mike Leavitt
Secretary of Health and Human Services
U.S. Department of Health and Human Services

Andrew C. von Eschenbach, M.D.
Commissioner of Food and Drugs

Dockets Management Branch
Food and Drug Administration, Room 1601
5630 Fishers Lane
Rockville, MD 20852

Citizen Petition

The undersigned submits this May 13, 2008, Citizen Petition on behalf of: Samuel S. Epstein, M.D., Chairman, Cancer Prevention Coalition (CPC), and Professor emeritus Occupational and Environmental Medicine, University of Illinois at Chicago School of Public Health; Peter Orris, M.D., Professor and Chief of Service, University of Illinois at Chicago Medical Center; Quentin Young, M.D., Chairman, Health and Medicine Policy Research Group, Chicago; Rosalie Bertell, Ph.D., International Association for Humanitarian Medicine, Scientific Advisor to the International Institute of Concern for Public Health, Toronto, and the International Science Oversight Board of the Organic Consumers Association, Washington, D.C.; and Ronnie Cummins, National Director of the Organic Consumers Association.

This Petition, submitted under 21 U.S.C. 321 (n), 361, 362, and 371 (a); and 21 CFR 740.1, 740.2 of 21 CFR 10.30 of the Federal Food, Drug and Cosmetic Act, requests the Commissioner of Food and Drugs to require that all cosmetic 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."

A. AGENCY ACTION REQUESTED

This Petition requests FDA to take the following action:

(1) Immediately require cosmetic talcum powder products to bear labels with a prominent warning such as: "Frequent talc application in the female genital area is responsible for major risks of ovarian cancer."

(2) Pursuant to 21 CFR 10.30 (h) (2), a hearing which will be held at which time we can present scientific evidence in support of this Petition.

B. STATEMENT OF GROUNDS

On November 17, 1994, the Cancer Prevention Coalition and the New York Center for Constitutional Rights submitted a Citizen Petition to the Commissioner of the FDA, "Seeking Carcinogenic Labeling on all Cosmetic Talc Products." The Petition was endorsed by Quentin Young, M.D., Chairman of The Health and Medicine Policy Research Group, Peter Orris, M.D., Director of Health Hazard Evaluation, Cook County Hospital, and Professor of Medicine, University of Illinois Medical School, Chicago, Nancy Nelson, Chair of the Ovarian Cancer Early Detection and Prevention Foundation, and subsequently by Senator Edward Kennedy. In a 1997 statement to the Senate, he requested the FDA to place a cancer warning on the label of talc products, besides other products containing known carcinogens. However, over a decade later his warning remains ignored.

The 1994 Petition was supported by 15 scientific publications. These included nine, from 1983 to 1992, on the major risks of ovarian cancer from the frequent application of brand or generic talc "baby powder" to the genital area of women without any warning of the risks involved. Two of these publications also reported that the genital application of talc could result in its translocation to the ovary.

The scientific basis of the 1994 Petition was further supported by J. Mande, Acting Associate Commissioner for Legislative Affairs of the Department of Health and Human Services. On August 25, 1993, he admitted that "We are aware that there have been reports in the medical literature between frequent direct female perineal talc dusting over a protracted period of years, and an incremental increase in the statistical odds of subsequent development of certain ovarian cancers . . . (However) at the present time, the FDA is not considering to ban, restrict or require a warning statement on the label of talc containing products."

The scientific basis of the 1994 Petition was also admitted by the industry. In an August 12, 1982, article in the *New York Times*, Johnson & Johnson, the manufacturer and retailer of talc dusting powder, stated it was aware of a publication which concluded that frequent genital application of talc was responsible for a three-fold increased risk of ovarian cancer. Warnings of these risks were emphasized by the Cancer Prevention Coalition in November 19, 1994, in letters to Mr. Ralph Larsen, CEO of Johnson & Johnson, and Mr. C.R. Walgreen, Chairman and CEO of Walgreens. Johnson & Johnson was urged to substitute cornstarch, a safe organic

carbohydrate, for talcum powder products, and also to label its products with a warning on cancer risks.

In spite of the scientific evidence, and admission by Johnson & Johnson, the Petition was denied by Dr. John Bailey, FDA's Director of the Office of Cosmetics and Colors, on the basis of the "limited availability" (of Agency resources) and on alleged scientific grounds. Dr. Bailey is currently Director of the industry's Personal Care Products Council.

Evidence for the May 2008 Petition is supported by Edward Kavanaugh, President of the industry's Cosmetic Toiletry and Fragrance Association. In 2002, he admitted that talc is "toxic," that it "can reach the human ovaries," and that prior epidemiological investigations concluded that its genital application increased the risk of ovarian cancer. Further evidence for this Petition is based on 12 publications since 1995, cited below. These confirm the causal relation between genital application of talc and ovarian cancer, and the protective effect of tubal ligation or hysterectomy, preventing the translocation of talc to the ovary.

As Dr. Andrew C. von Eschenbach, former Director of the National Cancer Institute, is aware, the mortality of ovarian cancer for women over the age of 65, has escalated dramatically since 1975, by 13% for white and 47% for black women (1). There are about 15,300 deaths from ovarian cancer each year. This makes it the fourth most common fatal cancer in women after colon, breast and lung.

A case-control study, the largest to date, confirmed the relation between the perineal use of talc and ovarian cancer (2). This has also been confirmed by other reports (3-7). In view of the strength of this evidence, "formal public health warnings" were urged in 1999 (8). An analysis of 16 pooled studies confirmed a statistically significant 33% increased risk of ovarian cancer associated with the perineal use of talc (9). A report by 19 scientists in eight nations worldwide, under the auspices of the International Agency for Research on Cancer, concluded that eight publications confirmed a 30-60% increased risk of ovarian cancer following the perineal application of talc (10). This risk has been confirmed in other reports (11, 12).

The protective effects of tubal ligation or hysterectomy, preventing the translocation of talc from the perineum to the ovary, have also been confirmed (2, 3, 4, 7).

C. CLAIM FOR CATEGORICAL EXCLUSION

A claim for categorical exclusion is asserted pursuant to 21 CFR 25.24 (a) (11).

D. CERTIFICATION

The undersigned certifies, that, to his best knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

This petition is submitted by:

Samuel S. Epstein, M.D.
Chairman, Cancer Prevention Coalition
Professor emeritus Occupational and Environmental Medicine
University of Illinois School of Public Health, Chicago

REFERENCES

1. National Cancer Institute. SEER Cancer Statistics Review, 2005 (posted 2008).

2. Purdie D, et al. Reproductive and other factors and risk of epithelial ovarian cancer: an Australian case-control study. Survey of Women's Health Study Group. *Int J Cancer* Sep 15;62(6):678-684, 1995.

3. Kasper CS & Chandler PJ Jr. Possible morbidity in women from talc on condoms [letter]. *JAMA* March 15;273(11):846-847, 1995.

4. Cramer DW & Xu H. Epidemiologic evidence for uterine growth factors in the pathogenesis of ovarian cancer. *Ann Epidemiol* July;5(4):310-314, 1995.

5. Chang S & Risch HA. Perineal talc exposure and risk of ovarian carcinoma. *Cancer* June 15; 79(12):2396-2401, 1997.

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7. Green A, et al. Tubal sterilisation, hysterectomy and decreased risk of ovarian cancer. Survey of Women's Health Study Group. *Int J Cancer* June 11;71(6):948-951, 1997.

8. Cramer DW, et al. Genital talc exposure and risk of ovarian cancer. *Int J Cancer* May 5;81(3):351-356, 1999.

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* Mar-Apr;23(2C):1955-1960, 2003.

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

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

12. Merritt 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.

C T F A

THE COSMETIC, TOILETRY, AND FRAGRANCE ASSOCIATION

June 16, 1995

E. EDWARD KAVANAUGH
PRESIDENT

Dockets Management Branch (HFA-305)
Food and Drug Administration
Room 1-23
12420 Parklawn Drive
Rockville, Maryland 20857

Re: FDA Docket No. 94P-0420/CP 1

Dear Sir or Madam:

Enclosed for filing please find comments of The Cosmetic, Toiletry, and Fragrance Association (CTFA) in response to a Citizen Petition filed on November 17, 1994 by Jill A. Cashen and Samuel S. Epstein, M.D. on behalf of the Cancer Prevention Coalition ("Petitioner"). Petitioner urges the Food and Drug Administration to require "cosmetic talcum powder" to bear warning labels such as "Talcum Powder causes cancer in laboratory animals. Frequent talc application in the female genital areas increases the risk of ovarian cancer."

As discussed in detail in the enclosed comments, CTFA believes that the Petitioner's arguments are without scientific merit. Much of the evidence relied upon by Petitioner has already been fully considered by FDA with the conclusion that there is no risk to human health posed by the use of talc in cosmetic products. New evidence further supports this conclusion. Therefore, the requested label warnings are not necessary to protect the health of consumers and would unnecessarily alarm consumers regarding the use of safe cosmetic products.

We respectfully request that the petition be denied.

Sincerely,

E. Edward Kavanaugh
President

Enclosures

1101 17TH ST., N.W., SUITE 300 WASHINGTON, D.C. 20036-4702
202.331.1770 FAX 202.331.1969
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94P-0420

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COMMENTS

OF

THE COSMETIC, TOILETRY, AND FRAGRANCE ASSOCIATION

IN RESPONSE TO

A CITIZENS PETITION

FILED WITH

THE FOOD AND DRUG ADMINISTRATION

ON NOVEMBER 17, 1994

WHICH WOULD REQUIRE CARCINOGENIC LABELLING

ON ALL

COSMETIC TALC PRODUCTS

FDA Docket No. 94P-0420/CP 1

June 1995

Table of Contents

I. INTRODUCTION

The Cosmetic, Toiletry, and Fragrance Association (CTFA)[1] is filing these comments in response to a citizens petition filed by Ms. Jill A. Cashen and Samuel S. Epstein, M.D. on behalf of the Cancer Prevention Coalition ("Petitioner") on November 17, 1994 (FDA Docket No. 94P-0420/CP 1). Petitioner urges the Food and Drug Administration (FDA) to require "cosmetic talcum powder" products to bear labels with warnings such as "Talcum powder causes cancer in laboratory animals. Frequent talc application in the female genital area increases the risk of ovarian cancer". CTFA contends that such labelling is without scientific basis and is unnecessary to protect the health of consumers.

Talc (CAS No. 14807-96-6) comprises pulverized, natural, foliated, hydrous magnesium silicates (Harvey, 1988). As a pure mineral compound, talc is mineralogically defined as hydrous magnesium silicate, with the approximate chemical formula:

$$Mg_3(Si_2O_5)_2(OH)_2$$

The largest commercial uses of talc are in industrial applications such as paint, plastics, paper, ceramics, and construction materials. Talc utilized in direct cosmetic applications accounts for a relatively small percentage of the overall talc market. In 1992, approximately 48,000 tons of talc were used in the United States for cosmetics, pharmaceuticals, and food products (American Westmin, Inc./Luzenac America, unpublished data).

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[1]The Cosmetic, Toiletry, and Fragrance Association is the national trade association representing the cosmetic, toiletry and fragrance industry in the United States. CTFA, founded in 1894, represents over 500 companies involved in the personal care products industry. CTFA's active members manufacture and distribute the vast majority of personal care products marketed in the United States. CTFA's associate member companies supply goods and services such as raw materials and packaging to the industry's manufacturers and distributors. The personal care products industry prides itself on a long history of providing safe, reliable products to meet the diverse needs and personal tastes of the American consumer.

Pharmaceutical tableting and various food applications account for approximately 8% of direct consumer uses of talc products; the greatest proportion (approximately 92%) is used in cosmetic applications. Used for decades in a wide variety of cosmetic and other applications, talc has proven to be among the safest of all consumer products. The talc industry has adopted stringent quality assurance standards set by the Food Chemical Codex, the United States Pharmacopeia and the Cosmetic, Toiletry and Fragrance Association. The focus of all three specifications is similar in that they place limits on certain extractable elements and other potential chemical contaminants. Only relatively pure talc products are capable of meeting these specifications.

Petitioner contends that labelling of cosmetic talc products is required in order to adequately warn consumers of the risk of ovarian cancer. However, the available literature and the experience of manufacturers provides no evidence that cosmetic talc, when used as intended, presents any health risk to the consumer. All current available safety information on cosmetic talc has been thoroughly reviewed (Wehner, 1994). Moreover, a panel of experts at a workshop organized by FDA and the International Society of Regulatory Toxicology and Pharmacology (ISRTP) convened to review the latest toxicological and epidemiological studies on talc concluded that the "probability of human risk [from talc] is likely non-existent under customary conditions of use "and that "while some weak association between talc exposure and ovarian tumors has been reported, it [is] not sufficient warning for concern" (Carr, 1995).

In summary, there is no evidence to suggest that cosmetic-grade talc is a human carcinogen. Specifically, CTFA will show that:

- the contention that cosmetic-grade talc contains asbestos is unsupportable;
- talc is a rat carcinogen only under conditions which produce particle overload

and related chronic toxicity;

- consumer exposure to respirable talc particles is several orders of magnitude lower than exposures which result in rat lung tumors;
- evidence for the role of intrinsic and extrinsic risk factors in the etiology of ovarian epithelial cancer is inconclusive;
- epidemiological evidence supports only a weak statistical association between perineal talc use and ovarian cancer, the significance of which is not considered scientifically or medically meaningful; and
- statistical arguments are unsupported by evidence of a plausible biological mechanism by which talc could cause ovarian cancer.

In short, there is no scientific justification to support the Petitioners contention that cosmetic talc products should bear labels warning that "[t]alcum powder causes cancer in laboratory animals" and that "[f]requent talc application in the female genital area increases the risk of ovarian cancer".

II. THERE IS NO EVIDENCE TO SUGGEST THAT COSMETIC-GRADE TALC IS A HUMAN CARCINOGEN

A. The Contention that Cosmetic-Grade Talc Contains Asbestos is Unsupportable

Petitioner contends that talc used in cosmetic applications contains asbestos. This contention is based on outdated and erroneous evidence which FDA has previously refuted. Petitioner quotes early mineralogical research done by Cralley *et al* (1968) and Rohl *et al* (1976) which sought to identify asbestos contamination in cosmetic talc. During the early 1970's FDA became concerned that

cosmetic talc contained significant amounts of asbestos. However, in response to an earlier Citizens Petition "... FDA considered all analytical results to be of questionable reliability. This assessment proved to be correct because many questions were subsequently raised about results reported in the literature in the early 1970's" (letter from FDA Acting Associate Commissioner for Regulatory Affairs, 1986). In denying the Petition, FDA noted "we find that there is no basis at this time for the agency to conclude that there is a health hazard attributable to asbestos in cosmetic talc" (*Id*).

The erroneous association between talc and asbestos is an extremely unfortunate one. Precipitated in large part by the use of overly broad definitions of asbestos and nonspecific analytical techniques (Rohl, 1974; Rohl and Langer, 1974; Krause and Ashton, 1978; Parmentier and Gill, 1978), the idea that asbestos is commonly and intimately associated with talc is simply incorrect. As a retrograde mineral, talc may be found in association with chrysotile in serpentinites and other hydrous minerals. However, the geologic conditions under which talc and asbestos form are dissimilar. Many talc-bearing rocks form from ultramafic rocks, the central core of which is composed of serpentinite surrounded, successively, by shells of talc-carbonate rock and talc-bearing steatite (steatite is synonymous with soapstone). Usually a thin wall schistose rock, composed essentially of chlorite, separates the steatite from the country rock. The serpentinite is composed mostly of non-fibrous serpentine minerals (lizardite and antigorite), but small amounts of chrysotile asbestos may also occur within the serpentinite. The talc-carbonate and steatite shells which surround the serpentinite core contain abundant talc but do not contain asbestos. Careful mining procedures enable the serpentinite core to be avoided and thus possible contamination of talc ore with asbestos is obviated. Confirmation of the absence of asbestiform minerals in the finished talc product is established using x-ray diffraction, optical microscopy and electron microscopy techniques (CTFA,

1990).

B. Talc is a Rat Carcinogen Only Under Conditions Which Produce Particle Overload and Related Chronic Toxicity

Petitioner contends that "[t]alc is a carcinogen, with or without the presence of asbestos-like fibers". In support of this contention, Petitioner relies on the results of studies published by the National Toxicology Program (NTP). Petitioner's reliance is misplaced in that NTP showed talc to be a rat (but not a mouse) carcinogen, and only under circumstances indicative of a secondary mechanism involving particle overload and resultant chronic toxicity. In 1992, NTP reported the results of 2 year inhalation studies designed to determine the effect of talc in experimental animals (NTP, 1993); male and female F344/N rats and B6C3F$_1$ mice were exposed to target aerosol talc concentrations of 0, 6, or 18 mg/m^3 for 6 hours/day, 5 days/week, for 2 years. NTP concluded that:

> *Under the conditions of these inhalation studies, there was* ***some evidence of carcinogenic activity*** *of talc in male F344/N rats based on an increased incidence of benign and malignant pheochromocytomas of the adrenal gland. There was* ***clear evidence of carcinogenic activity*** *of talc in female F344/N rats based on increased incidences of alveolar/bronchiolar adenomas and carcinomas of the lung and benign and malignant pheochromocytomas of the adrenal gland. There was* ***no evidence of carcinogenic activity*** *of talc in male or female B6C3F$_1$ mice exposed to 6 to 18 mg/m^3.*

Since its publication, the findings of NTP have been criticized by several experts in the field of inhalation toxicology with regard to both study design and conduct. Most notably these studies were the subject of a joint ISRTP/FDA scientific workshop held in 1994 (*Talc: Consumer Uses and*

Health Perspectives; January 31/February 1, 1994) which discussed the relevance of the NTP findings with regard to consumer exposure and consumer safety. Criticisms of the study made at the workshop may be summarized as follows:

Test Article/Particle Size: The NTP study has questionable relevance with regard to prediction of human risk due to consumer exposure since the talc sample utilized in the NTP study was of a kind which is used in industrial applications, and was not a product that would be used in a cosmetic powder application because of its extreme fineness (Zazenski et al., 1995). The test material used by NTP is an industrial grade product typically used in specialty coatings and high performance polymeric applications. The median particle size of the NTP talc sample was approximately 1.2 microns and had a top size of approximately 10 microns. In contrast, typical commercial loose talc powder has a median particle size of approximately 10 microns and a top size of approximately 45 microns (Zazenski et al., 1995).

Exposure Levels Resulted in Lung Particle Overload: The major criticism of the NTP study is the failure to include exposure levels which did not lead to lung particle overload. The concept of "particle overload" in chronic inhalation studies with highly insoluble particles of relatively low toxicity is now widely accepted (Morrow, 1988). Typically, exposure concentrations are relatively high and result in retained particulate lung burdens which are also high. Such retained lung burdens lead to a sequence of inflammatory responses, altered particle-clearance/retention and altered morphology, leading to chronic disease states including fibrosis and the induction of benign/malignant tumors (see Oberdörster, 1995).

Highly insoluble particles deposited in the lower respiratory tract are removed by two important mechanisms (see Oberdörster, 1995). The mucociliary escalator removes particles

deposited in the conducting airways; particles deposited in the alveolar region are phagocytosed by alveolar macrophages (AM) which then migrate towards the mucociliary escalator and are removed (Schlesinger, 1985, Oberdörster, 1988; Snipes, 1989). When deposition rate in the alveolar region exceeds the AM-medicated clearance rate, alveolar retention halftime is considerably increased (often irreversibly) and results in excessive accumulation of particles in the lung. One further consequence of excessive accumulation is increased translocation of particles to the pulmonary interstitium which eventually results in the induction of pulmonary fibrosis (Adamson et al., 1989; Bowden et al., 1989), activation of macrophages and release of cytokines resulting in increased epithelial cell proliferation (Driscoll et al., 1990).

Based on the actual talc burdens of exposed rats (ie., as measured by NTP), Oberdörster (1995) has estimated that the pulmonary retention halftimes of the retained talc particles range between 250 and 300 days, ie., is markedly longer than the normal retention halftime for highly insoluble particles in rat lungs of ~70 days. Oberdörster has concluded that these results are indicative of lung particle overload. Oberdörster has also shown that the talc-exposed mice exhibited a marked increase in pulmonary retention halftime for talc particles with increasing lung burdens (i.e., a severe retardation of normal AM-mediated particle clearance) compared to a normal retention halftime in mice lungs. In summary, the lung particle clearance was impaired in both rats and mice in the NTP study, resulting in altered accumulation kinetics of talc particles chronically inhaled at concentrations of 6 and 18 mg/m^3. The rat tumor response is thus very likely a secondary effect of the particle overload phenomenon ie., due to altered lung clearance kinetics resulting in excessively high lung burdens leading to chronic inflammatory and cell proliferative processes (Oberdörster, 1995). Conceivably, the difference in tumor response between male and female rats may be merely

temporal since hyperplasia and an interstitial fibrosis was observed in both sexes. Oberdörster attributes the lack of pulmonary tumors in mice to the fact that rat lung tumors associated with a high pulmonary particle load appears to be a very species-specific response to non-fibrous particles (Oberdörster, 1995).

Exposure Levels Exceeded the MTD: The highest dose in carcinogenicity studies is generally designed to be equivalent to the maximum tolerated dose (MTD). Although this principle has become increasingly subject to criticism, high-dose testing at the MTD remains the practice of NTP. In general, the MTD is estimated following a careful analysis of data from appropriate subchronic toxicity tests. The need to consider a broad range of biological information when selecting the MTD has become increasingly clear. For example, data concerning changes in body/ organ weight, clinically significant alterations in hematologic, urinary and clinical chemistry measurements, as well as more definitive toxic, gross or histopathologic endpoints can be used to estimate the MTD.

For chronic inhalation studies with highly insoluble particles of low cytotoxicity, the phenomenon of particle overload and the question of exceeding the MTD are intimately interrelated. Recommendations of a NTP Workshop on Maximal Aerosol Exposure Concentrations in Inhalation Studies (Lewis *et al.*, 1989) included "[the] chronic study should *not* (emphasis supplied) be performed at the highest technologically feasible concentration, three concentrations should be used of which only the highest should show some interference with lung defense mechanisms, i.e., clearance impairment; and the two lower concentrations should show no interference with clearance and particle accumulation". Based on these criteria, the MTD was clearly exceeded in the studies conducted by NTP on talc.

In the NTP study, talc-induced lung tumors were not detected in male rats, female mice or

male mice. In rats, the principal toxic lesions associated with inhalation exposure to talc included chronic granulomatous inflammation, alveolar epithelial hyperplasia, squamous metaplasia and squamous cysts, and interstitial fibrosis of the lung. These lesions were accompanied by impaired pulmonary function. While the talc burden in the lungs of males and females was similar, the degree of chronic toxicity and inflammation was substantially higher in females. In mice, inhalation exposure to talc produced some chronic inflammation. In contrast to rats, alveolar epithelial hyperplasia, squamous metaplasia, and interstitial fibrosis were not observed. Overall, markedly less talc-induced lung toxicity was produced in mice than in rats. In summary, it is apparent that an increase in lung tumors was seen only in the test animals that clearly exhibited the highest degree of chronic lung toxicity, (ie., the female rats exposed to 18 mg/m^3 talc). Similarly, the increased incidence of pheochromocytomas is most likely attributable to the stressful conditions (eg., as a result of physiological, metabolic or endocrine changes) to which the test animals were exposed. In addition, the F344/N rat is known to have a high background incidence of pheochromocytomas (NTP, 1993). The relevance of these responses with regard to extrapolation to humans is thus highly suspect (Goodman, 1995).

The unmistakable conclusion from these observations is that the MTD was exceeded in the female rats exposed to the high dose, and that talc is not expected to cause lung tumors under conditions of exposure that fail to result in marked chronic lung toxicity (Goodman, 1995). In contrast to Petitioner's characterization of the results of the NTP study, clear evidence of carcinogenic activity of talc was seen *only* in female rats (not male or female mice) exposed to the high dose of talc and *only* under circumstances in which there was evidence of particle overload and marked chronic lung toxicity. In summarizing it's assessment of the NTP study, the panel of experts at the

ISRTP/FDA workshop *Talc: Consumer Uses and Health Perspectives* characterized the positive results in female F344/N rats as "likely experimental artifact...[a] non-specific generic response of dust overload of the lungs, and not a reflection of a direct activity of talc. Given the gross differences of rodent and human lungs, the lung clearance capabilities of humans and the possible conditions of customary human exposures, the NTP bioassay results in F344/N rats cannot be considered as relevant predictors of human risk" (Carr, 1995).

C. Consumer Exposure to Respirable Talc Particles is Several Orders of Magnitude Lower Than Exposures Which Result in Rat Lung Tumors

Although Petitioner would require warning labels to the effect that "[t]alcum powder causes cancer in laboratory animals", the implication is that talc exposure constitutes human risk of cancer. Such an implication is unwarranted since consumer exposure to talc is considerably lower than exposures which result in rat lung tumors. Consumers are exposed to talc during the application and use of body powders. In this regard, human exposure occurs principally via the dermal route, but primary concern has focused on exposure via the respiratory tract. Talc miners and millers are exposed to long-term, relatively high concentrations of airborne talc; the results of human cohort studies involving cosmetic grade talc miners and millers thus provide a useful basis against which pulmonary risk to consumers may be estimated (Scansetti et al., 1963; El-Ghawabi et al., 1970; Rubino et al., 1976; Gamble et al., 1982; Wegman et al., 1982; Leophonte et al., 1983; Wergeland et al., 1990). These studies show that a pneumoconiosis (talcosis) risk does exist but only when respirable talc dust levels are significantly greater than worst-case consumer exposures (described below) and exposure is over an extended period of time (several years).

While there may be disagreement over the amount of exposure required to induce

pneumoconiosis, such studies suggest that talc poses a low to moderate pulmonary risk in an industrial setting. For example, in a mortality and morbidity study of Italian talc miners and millers, radiographic abnormalities consistent with pneumoconiosis were found among talc workers after an average duration of exposure for 22 years, with an average respirable dust concentration of approximately 11 mppcf (Rubino, et al., 1976); in contrast, in a study involving French talc workers, no cases of pneumoconiosis at a level of 15 mppcf were reported (Leophonte, et al., 1983). Although it is difficult to reliably convert respirable particle count data (mppcf) into respirable gravimetric data (mg/m^3), such levels typically fall into the 1-2 mg/m3 range (e.g., in a study of Vermont talc miners and millers (Boundy et al., 1979), pneumoconiosis was observed when respirable dust levels ranged from 0.5 to 2.9 mg/m3). Despite the incidence of pneumoconiosis at high industrial exposure levels it is important to note that an excess prevalence of lung cancer in talc mining populations has not been observed (Selevan et al 1979; Leophonte et al., 1983; Wergeland et al., 1990; Rubino et al., 1976).

Electrostatic, Van der Waal's and valance charges present on the particulate surfaces of a dry powder such as talc result in substantial particle-to-particle agglomeration, thereby increasing effective mass, diameter, and settling velocity (Carta et al., 1981; Gajewski, 1990). These factors are important with regard to influencing the respirability of dry particles. Two studies have been conducted to evaluate exposures to respirable particles during application of talc as an adult body powder and as a baby powder (Russell et al., 1979; Aylott, et al., 1979). In both studies, respirable particles ($\leq$ 10 microns) were collected usig a cyclone particle fractionation system operating at an air flow rate of 1.7-1.9 liters/minute. Adult exposure was assessed during normal face/body powdering practices by placing cyclone collection units on shelves at appropriate face height, or by positioning a cyclone attached to a headband near the nose (i.e., in the subjects breathing zone). To

evaluate the exposure of babies to talc, sampling units were placed on the changing table near the infants' (or doll's) heads during normal powdering practices (i.e., while changing a diaper). Talc was dispensed using common twist-top, sprinkle-type containers, or in the case of face powder, powder puffs. Exposure of adults to respirable particles during application of talc ranged from 0.48 to 2.03 mg/m^3, while the exposure to babies ranged from 0.19 to 0.21 mg/m^3. When these numbers are extrapolated to 8-hour time weighted average exposures, they range from <0.001 to 0.005 mg/m^3 (Zazenski et al., 1995). For comparison purposes, the current OSHA/ACGIH permissible industrial exposure limit for talc is 2.0 mg/m^3 as an 8 hour time-weighted average (ACGIH, 1992), i.e., the industrial permissible limit is approximately 350 times greater than the worst case consumer use of cosmetic grade talc.

Based upon the determinations reported in the literature, human exposure to respirable talc particles during normal product use are approximately 2,000-20,000 times lower than those used to expose rats and mice in inhalation studies conducted by the NTP (Zazenski et al., 1995). Although a direct comparison of the dosimetry of inhaled materials between rodents and humans is far from simple (Dahl et al., 1991), such a broad difference in exposure level is quite striking. The incidence of tumors resulting from massive exposures such as those involved in the NTP talc inhalation study are more likely to reflect a particle overloading effect in the experimental animals (Morrow, 1988; Morrow, 1992; Oberdörster, 1988) than any genotoxic effect associated with the test material (Endo-Capron et al., 1993).

As previously noted, the talc sample utilized in the NTP study was not a product that would be used in a cosmetic powder application because of its extreme fineness (SECTION II. B). Further, the NTP talc aerosol was exposed to Kr-85 gamma radiation immediately prior to its introduction

into the exposure chambers containing the experimental animals. Use of ionizing radiation was intended to neutralize the electrical charge imparted on the talc particles during aerosolization. Charge neutralization tends to decrease agglomeration and results in deposition of particles in the deep lung of exposed animals. Thus, while selection of an ultra-fine product combined with procedures designed to maximize particle dispersion may be entirely appropriate from a toxicological perspective, such an artificial environment has questionable relevance with regard to actual human exposure from commercial cosmetic talc products under use conditions.

SECTION II. SUMMARY

The issues raised by Petitioner with regard to asbestos contamination of cosmetic-grade talc have previously been addressed by FDA. In 1986, FDA concluded that there was no health hazard attributable to asbestos in cosmetic talc. Since that time no new evidence has arisen which would suggest a conclusion to the contrary; moreover, appropriate selection of mine site, careful mining procedures and the utilization of modern beneficiation techniques have further safeguarded against asbestos contamination. Accordingly, CTFA believes that FDA's response to the issue of asbestos contamination raised by Petitioner should be no different than its response in 1986.

With regard to Petitioner's assertion that talc is an animal carcinogen, the NTP chronic inhalation study has been subject to severe criticism. The test material used by NTP was characterized by an extremely small particle size and is not characteristic of material used for cosmetic talc applications. Further, the exposure levels chosen by NTP clearly exceeded the MTD for talc and were such that exposure resulted in impairment of lung clearance mechanisms and a condition known as particle overload. Because any highly persistent particulate compound of low cytotoxicity has

carcinogenic potential, particularly in rats, when chronically inhaled at such high concentrations, the classification of such particles with respect to pulmonary carcinogenicity must be carefully evaluated. In the absence of any evidence of a toxic or genotoxic effect *per se*, the only reasonable conclusion which may be drawn from the studies conducted by NTP is that the carcinogenic effect of talc is a secondary phenomenon which does not occur in the absence of chronic toxicity which is itself a result of particle overload.

In summary, the application of the results of the NTP study with regard to human risk assessment are highly questionable. Consumer exposure to respirable talc particles is several orders of magnitude lower than exposures which result in rodent tumors. There is no evidence of chronic toxicity following consumer exposure to talc, thus use of the lung tumor endpoint in female rats as the basis of extrapolation to human risk is inappropriate. Clearly, Petitioner's request that FDA require warnings such as "[t]alcum powder causes cancer in laboratory animals", with it's implicit message that talc may cause human risk of cancer, is both misleading and may cause consumers unnecessary concern. As such, Petitioner's request should be denied.

III. THERE IS NO CONVINCING EVIDENCE TO SUPPORT THE CONTENTION THAT FREQUENT TALC APPLICATION IN THE FEMALE GENITAL AREA MAY INCREASE THE RISK OF OVARIAN CANCER

A. Evidence For The Role Of Either Intrinsic Or Extrinsic Risk Factors In The Etiology Of Ovarian Epithelial Cancer Is Inconclusive

The etiology of human ovarian epithelial cancer is not clearly understood. Ovarian tumors of epithelial origin, which include serous, mucinous, endometrioid, clear cell and undifferentiated adenocarcinomas and the Brenner tumor, are responsible for the majority of ovarian malignancies

(Cannistra, 1993; Slotman and Roa, 1988). The purported extrinsic and intrinsic risk factors which contribute to the incidence of epithelial cancer of the ovary have been the subject of numerous reviews (Shoham, 1994; Kelsey et al., 1994; Dietl and Marzusch, 1993; Parazzini et al., 1991; Baylis et al., 1986; Heintz et al., 1985). While a number of scientists have attempted to identify various extrinsic risk factors, including environmental (e.g. tobacco and talc), infectious disease (e.g. mumps, rubella), and dietary intake (e.g. lactose, animal fat, alcohol, caffeine) as potential etiologic agents, the data are inconclusive. At best, some studies have demonstrated a relationship between dietary factors and the incidence of ovarian epithelial cancer: in particular, an increased risk for ovarian cancer has been reported for women who consume diets which are high in animal fat (Shu et al., 1989; Mori and Miyake, 1988; La Vecchia, et al., 1987) and lactose (Cramer, 1989; Cramer et al., 1989).

Research investigating intrinsic risk factors has provided evidence which suggests that reproductive history and molecular factors are strongly linked to carcinogenesis of the ovarian epithelium. It is well documented that suppression of ovulation, either by pregnancy or by oral contraceptive use, decreases the risk for developing ovarian cancer (McGowan et al., 1979; Wu et al., 1988; Mori et al., 1988; Booth et al., 1989). Ovulation is a physiologic process which is mediated by hormones (gonadotropins) and results in repeated ruptures in the surface epithelia of the ovary. Following ovulation, a repair process takes place whereby there is an increase in epithelial cell mitotic activity. The reduced risk afforded by pregnancy or by oral contraceptive use is postulated to be meditated by the subsequent decrease in circulating gonadotropins and/or the suppression of ovulation (Whittemore, et al., 1992). Evidence supporting the etiologic role of ovulation has been provided by *in vitro* studies demonstrating that the repeated cell division of ovarian surface epithelial

cells results in a malignant transformation (Godwin et al., 1993).

Molecular events associated with the initiation of ovarian cancer have recently been reviewed (Berek and Martinez-Maza, 1994; Godwin et al., 1993). Genetic mutations are molecular events which can lead to tumor formation. Studies assessing family history have reported a genetic predisposition to ovarian cancer (Patel and Obrams, 1993; Hartge et al., 1989) which appears to be inherited on an autosomal dominant gene (Slotman and Rao, 1988). Specific loss of a gene at the 6*q* chromosomal loci has been identified in ovarian tumors (Lee et al., 1990); additionally, genetic alterations on chromosomes 1,3, 14 and 17 have been identified in certain ovarian carcinomas (Daly, 1992). Mutations can result in chromosome alterations and the subsequent inactivation of a particular gene. Studies conducted by Hoffman and colleagues (1993) have demonstrated a reduced expression of a cell adhesion molecule (E-cadherin) in an *in vitro* model of ovarian epithelial carcinogenesis. Genetic alterations can also lead to the overexpression of a gene. Proteins encoding certain chemical messengers (cytokines), such as IL-6 (interleukin 6), M-CSG (macrophage colony stimulating factor) and TNF (tumor necrosis factor) have been found to be increased in epithelial ovarian cancer cells (Malik and Balkwill, 1991).

In summary, the events which lead to development of ovarian epithelial cancer are not clearly understood. A variety of intrinsic and extrinsic risk factors may be involved. However, in light of the fact that cancer is a disease which evolves at the molecular level, it is likely that research investigating the molecular aspects of ovarian cancer may provide important insight how such risk factors relate to incidence. It is significant in this respect that a thorough review of the toxicology of talc reveals no evidence of any genotoxicity (Wehner, 1994).

B. Epidemiological Evidence Suggests Only a Weak Statistical Association Between Perineal Talc Use and Ovarian Cancer, the Significance of Which is Not Considered Scientifically or Medically Meaningful

Although several studies on the possible association between perineal talc use and ovarian cancer have been published, any evidence of such an association remains equivocal. At most, the statistical association is weak and in the absence of evidence of a plausible biological mechanism (SECTION III. C) is insufficient to warrant public health concern. There have been seven case-control studies and one cohort study that have been published containing information regarding the risk of ovarian cancer in women using talc in their perineal region (Cramer et al., 1982; Hartge et al., 1983; Whittemore et al., 1988; Booth et al., 1989; Harlow and Weiss, 1989; Harlow et al., 1992; Rosenblatt et al., 1992; Hankinson et al., 1993). Talc exposure was the primary focus in only four of these studies (Cramer et al., 1982; Hartge et al., 1983; Harlow and Weiss, 1989; Harlow et al., 1992).

Cramer *et al* (1982) investigated whether there is an association between exposure to certain hydrous magnesium silicates (including talc), and the incidence of ovarian cancer. Population-based matched controls were randomly selected, and stratification and logistic regression were used to accommodate confounders. Overall, 42.8% of cases and 28.4% of controls reported exposure to talc, via direct application to the perineum, by dusting sanitary napkins, or both. The unadjusted odds ratio (OR) of ovarian cancer for any perineal exposure as opposed to no perineal exposure was 1.89 (95% CI 1.27-2.82). Adjustment was then made for parity and menopausal status. Women who used talc on both the perineum and sanitary napkin had an adjusted OR of 3.28 (95% CI 1.68-6.42) and for any exposure, 1.61 (95% CI 1.04-2.49). The reduction in risk from 1.89 to 1.61 for perineal talc exposure due to logistic regression is largely unexplained and may be due to residual confounding.

No dose-response or duration data were reported. While a major strength of the study is the use of neighborhood controls, the nonparticipation rate among controls was relatively high (260/475=55%).

Hartge *et al* (1983) investigated the association between talc use and the risk of ovarian cancer but reported no significant finding. The cases were women with pathologically confirmed primary epithelial ovarian cancer, while the hospital based controls had non-gynecological conditions (psychiatrically disturbed women, pregnant women, and women with other malignancies were excluded). Controls were frequency matched on age, race and hospital. For the group of women who did not use talc versus the group of women who did, the unadjusted OR of ovarian cancer was 0.776 (95% CI 0.47-1.20). Although no attempt was made to control for potential confounding variables, this nonsignificant odds ratio was unaffected by adjustment for parity, race and age.

Lifetime consumption of coffee, tobacco and alcohol were the principal exposure factors studied by Whittemore *et al* (1988). Women diagnosed with ovarian cancer in the San Francisco Bay area between 1983-5 provided the cases for this study. Matched controls from two groups, hospital and population, were obtained. The hospital controls were selected from the same hospitals as the cases, whereas the population controls were selected using random digit dialing. All controls were matched to cases on age, race, and having at least one ovary. Logistic regression was used to adjust for confounders. While this study examined other potential risk factors as well as talc exposure in relation to ovarian cancer, the study did not find evidence of an association between genital talc exposure and an increased risk of ovarian cancer. While women who reported regular use of talc on the perineum showed a marginally significant increase in relative risk, no other differences were noted between cases and controls when considering other types of perineal talc exposure either alone or taken in combination. The unadjusted OR of ovarian cancer for any perineal exposure as opposed

to no perineal exposure was 1.19 (95% CI 0.85-1.66). Adjusted for parity, the OR was 1.40 (95% CI 0.98-1.99). Other odds ratios also failed to produce significant associations. Several sources of bias were identified, including failure to interview all eligible cases, the potential pitfalls in combining hospital and population controls, confounding by differential talc use among women with characteristics predictive of ovarian cancer and random error in reported talc use tending to attenuate relative risk estimates. The study raises the possibility that a hormonal factor that may place women at a higher risk for the disease may also promote their use of talc.

Booth *et al* (1989) studied various potential risk factors for ovarian cancer including infertility, oral contraceptive use, parity, age at menopause, and genital talc use. Women with a diagnosis of ovarian cancer and treated at a London cancer hospital were each age matched to two hospital controls at 15 other hospitals. Non-participation rates were not provided, and one hospital providing more than 25% of the cases provided no controls. In addition, cases were generally older and in a higher social class than controls. All odds ratios were adjusted for social class in six categories. Maximum likelihood estimates of the odds ratios with the corresponding 95% confidence intervals were obtained. Logistic regression was used to test for trends. The results were inconclusive since weekly talc use showed a higher OR of ovarian cancer (2.0) than did daily use (1.3), (95% CI 1.3-3.4 and 0.8-1.9, respectively). Furthermore, there was no significant difference between cases and controls who used talc in conjunction with a diaphragm. The unadjusted OR of ovarian cancer with regard to talc use was a statistically nonsignificant 1.29 (95% CI 0.92-1.81). Overall, the study does not support the hypothesis that use of perineal talc increases the risk of ovarian cancer.

Harlow and Weiss (1989) investigated whether application of perineal talc application is

associated with an increased risk of serous and mucinous borderline ovarian tumors. Cases (residents of three urban, western Washington state counties diagnosed as having a serious or mucinous borderline ovarian tumor) were identified from the corresponding population-based cancer reporting system. Controls were population-based and located through random digit dialing. Women who reported any perineal use of dusting powders had an adjusted OR of 1.1 (95% CI 0.7-2.1) for borderline ovarian tumor. The adjustment was for age, parity, and use of oral contraceptives but not for other possible confounders. Women using deodorizing powder with or without baby powder (the only powder reported by women using a second powder) showed an increased risk of borderline tumor development, OR of 2.8 (95% CI 1.1-11.7). The elevated risk of borderline ovarian cancer among women who specifically used deodorizing powders may have been due to chance or applicable only to borderline but not malignant tumors.

Harlow *et al* (1992) investigated whether the use of talc increases the risk for epithelial ovarian cancer. Between July, 1984, and September, 1989, cases were diagnosed with borderline or malignant epithelial ovarian cancer at 10 different Boston metropolitan hospitals. Population controls were age matched and were all Caucasian. The influence of confounders and effect modifiers was assessed through stratification and logistic regression. Overall, 49% of cases and 39% of controls reported exposure to talc, yielding an OR of 1.5 (95% CI 1.0-2.1) for ovarian cancer. Among women with perineal exposure to talc, the risk was significantly elevated in subgroups of women who applied it directly as body powder (OR of 1.7; 95% CI 1.1-2.7). Women with an intact genital tract (and who had at least 10,000 applications while ovulating) showed an OR of 2.8 (95% CI 1.4-5.4). Although this study seemingly suggests a small increased risk of epithelial ovarian cancer due to lifetime use of perineal talc, the association is still not entirely clear. One important potential

confounder that was not accounted for in this study was oral contraceptive use. More controls used oral contraceptives than cases, and oral contraceptive use was associated with less reported talc exposure. Thus, use of oral contraceptives is a possible strong confounder that, if properly considered, could eliminate any observed effect.

Rosenblatt *et al* (1992) studied the relationship between "fiber" exposure (Note: these investigators mischaracterize talc as "fiber"; other exposures include asbestos and fiberglass) and epithelial ovarian cancer. Controls, who were hospital-based and free of gynecological and malignant conditions, were matched to cases by age, race and date of diagnostic admission. Due to the strict inclusion criteria, controls could not be found for each case. Thus although 140 new cases were located and 108 were successfully interviewed, only 77 cases were entered into the study. The OR (adjusted for number of live births) was 1.0 (95% CI 0.2-4.0) for women reporting any genital "fiber" use versus those women who were not so exposed; the unadjusted OR was 0.84 (95% CI 0.27-2.63). An increased risk of ovarian cancer was observed for women who used talc on their sanitary napkins with an OR of 4.79 (95% CI 1.29-17.79). However, among the remaining eight odds ratios, none was statistically significant. While there seems to be an elevated risk of ovarian cancer in women who used talc on sanitary napkins, this finding is not supported by other studies (eg., Harlow *et al.*, (1992) did not report an elevated risk in this category).

The most recent study in which an indirect comparison of ovarian cancer incidence in talc users versus nonusers can be made was reported by Hankinson *et al* (1993). The purpose of this study was to assess whether tubal ligation and hysterectomy affected subsequent risk of ovarian cancer based upon the hypothesis that such procedures could prevent translocarion of talc to the ovaries. In reporting a finding of no association between talc use and an increased risk of ovarian

cancer the authors found that tubal ligation was "highly protective in women who reported never using talc". Such a finding tends to discount the talc translocation hypothesis discussed in SECTION III.C, below).

In reviewing evidence of the proposed association of talc exposure and ovarian cancer, the panel of experts at the ISRTP/FDA workshop *Talc: Consumer Uses and Health Perspectives* found that the "epidemiologic data are conflicting and remain equivocal" (Carr, 1995). The panel noted the problems connected with the epidemiology of weak associations and the fact that any properly designed study to determine the association between perineal talc use and ovarian cancer must account for other possible risk factors. These other factors include (but are not necessarily limited to) age, oral contraceptive use, number of term pregnancies, menopausal status, and other, environmental factors such as smoking status, alcohol and caffeine consumption. Other confounding variables, such as vulvovaginal diseases and obesity may also be causally related to ovarian cancer (Rosenblatt et al., 1992). In such instances (where talc use is associated with such conditions because of the degree of comfort it imparts to those affected), any statistical association between talc use and ovarian cancer may be merely coincidental.

In summary, the results of epidemiological studies are inconsistent and ambiguous. Any reported association between perineal talc use and ovarian cancer is weak and statistically barely significant. The biological significance (and hence public health significance) of any such weak association remains obscure.

C. Statistical Arguments are Unsupported by Evidence of a Plausible Biological Mechanism by Which Talc Could Cause Ovarian Cancer

As previously described (SECTION III. B), several investigators have proposed that, based

on weak epidemiological evidence, chronic perineal use of talc, including direct application or application to under garments, sanitary napkins or diaphragms, may increase the risk of ovarian cancer. In order for this to occur, talc particles (which have no inherent locomotive capability) would have to migrate from the perineum to the ovaries of exposed individuals. In order to try to identify such a potential translocation process, several studies have been conducted in various species, including humans. Many of these studies are so fraught with problems as to render the results of such studies ambiguous.

Egli and Newton (1961) have claimed that half an hour following vaginal deposition of carbon black particles, translocation occurred from the vagina to the oviducts in two of three female patients. The results of this study are subject to considerable doubt since the investigators failed to utilize either solution or filter blanks as negative controls. Wehner *et al* (1985) subsequently conducted a similar study in cynomolgus monkeys and found no difference in the number of carbon black particles in the blanks compared to the oviduct rinse solution.

In a study conducted by De Boer (1972), carbon black particles were deposited in the uterus, cervical canal, or vagina of over 100 patients prior to abdominal surgery. Subsequent evaluation showed that when deposited in the uterus, carbon black particles translocated to the oviducts and beyond; particles placed in the cervical canal migrated to a lesser extent. Translocation from the vagina occurred in only 2 of 37 patients: in both cases the patients were placed in the Trendelenburg position, resulting in a negative intra-abdominal pressure. Such negative pressure was considered by the investigator to have been sufficient to draw up material from the vagina, especially when the patient was anesthetized and had a relaxed cervix.

Translocation studies have also been performed in laboratory animals. Henderson *et al*

(1986) injected a suspension of talc particles into the cervical canal of 8 female ex-breeder Sprague-Dawley rats. A group of four animals was sacrificed 5 days later, while the remaining 4 animals received additional installations 6 and 15 days following initial treatment. Two of these animals were further administered the talc suspension at 22 and 30 days; six other animals received intra-vaginal injections of talc particles. Subsequent evaluation showed that all animals receiving intrauterine deposition of talc (and 2 of 6 receiving intra-vaginal administration) resulted in the detection of talc particles in the ovaries. Wehner (1994) has suggested that the hydrostatic pressure of the saline solution enhanced the potential for translocation under such conditions. In contrast Phillips *et al* (1978) found no radiolabel in the ovaries of rabbits given either single or multiple intra-vaginal doses of ^{3}H-labelled talc.

An attempt to quantify the amount of talc supposedly found in human ovarian tissue (normal ovaries, cystic ovaries, and ovarian adenocarcinomas) has been made by Henderson *et al* (1979). According to these investigators, normal ovarian tissue contained up to 55,100 particles of talc per gram of wet weight of tissue, while cystic ovaries and ovarian adenocarcinomas contained up to 24,300 particles. However, because talc is ubiquitous, especially in a laboratory or surgical setting, it is difficult to determine if the talc observed in such clinical specimens is due to a specific exposure or contamination. In order to specifically and clearly evaluate the potential for translocation of talc from the vagina to the ovaries, Wehner *et al.* (1986) used neutron- activated talc with subsequent gamma-ray analysis in order to rule out contamination. These investigators used cynomolgus monkeys since the physiological and anatomical characteristics of this species resembles the human female more closely than any other readily available laboratory animal (cynomolgus monkeys have an estrous cycle of 28 days and menstruation lasts 2-7 days). Neutron-activated talc was deposited

in the vagina for 30 consecutive working days (45 calendar days); thus exposure occurred through at least one menstrual cycle. Oxytocin was administered once per week during the study to induce the type of uterine contractions thought to occur during coitus and which may enhance the translocation process. The vagina/cervix, uterus, oviduct, ovaries and peritoneal lavage fluid of exposed animals were subsequently examined. Talc was observed only at the site of administration (vagina/cervix) and none was found in the ovaries.

In the carcinogenicity studies conducted by NTP (see SECTION II. B) male and female F344/N rats and B6C3F1 mice were exposed to target aerosol concentrations of 0,6 and 18 mg/m^3 talc for 6 hours daily, 5 days per week, for two years. Such conditions resulted in exposure via inhalation, oral and dermal (including perineal) routes. Initial tissue examination found no exposure-related lesions in either rat or mouse ovaries (NTP, 1993). Subsequent histological examination of the ovaries and ovarian bursa from rats confirmed this finding and demonstrated no material consistent with the appearance of talc in any animals from any group (Boorman and Seely, 1995).

In summary, available histologic and physiologic studies provide no concrete basis to conclude that talc can plausibly migrate to the ovaries from the perineal region. In the absence of such biological evidence, conflicting and equivocal evidence of a weak statistical association between perineal talc use and ovarian cancer is insufficient to "raise concern at level sufficient to warrant regulatory or public health measures" (Carr, 1995).

SECTION III. SUMMARY

Although several possible intrinsic and extrinsic risk factors have been suggested, the etiology of ovarian epithelial cancer is presently unknown. Critics of the supposed association between talc

and ovarian cancer highlight the reported weak associations and the numerous confounding variables (e.g., interview case/control comparisons, failure to adequately address key independent risk factors, etc.) which characterize much of the epidemiological research in this area. Further, experimental studies in which neutron-activated talc was repeatedly introduced into the vagina of cynomolgus monkeys, failed to demonstrate translocation to the cervix, uterus or ovaries. The results of these studies in monkeys suggest that any increased risk of ovarian cancer following perineal exposure to talc is biologically implausible. A causal association between perineal talc application and ovarian cancer is improbable.

IV. CONCLUSIONS

In January 31- February 1, 1994, a workshop organized by FDA and the International Society of Regulatory Toxicology and Pharmacology (ISRTP) was convened to provide a forum for an updated discussion of the origins, manufacture, characterization, toxicology and epidemiology of talc.[2] The principal focus of the meeting was on the latest toxicologic and epidemiologic studies and their significance with regard to the safe uses of talc in consumer products.

At the conclusion of the workshop, a panel of independent experts were able to reach a series of unanimous conclusions. With regard to the NTP talc bioassay in rodents, the panel found that "because of the extreme doses and the unrealistic particle sizes of the talc employed, because of the negative results in mice and male rats, because of the lack of tumor excess at the low doses, and because of the clear biochemical and cytological markers of excessive toxicity in female rats, the

[2]These conclusions are in large part based upon an Executive Summary which prefaced a series of papers published as the proceedings of the FDA/ISRTP Conference, *Talc: Consumer Uses and Health Perspectives* (Carr, 1995).

positive talc bioassay results in female F344/N rats are likely the result of experimental artifact and a non-specific, generic response of dust overload of the lungs, and not a reflection of a direct activity of talc. Given the gross differences of rodent and human lungs, the lung clearance capabilities of humans and the possible conditions of customary human exposures, the NTP bioassay results in F344/N female rats cannot be considered as relevant predictors of human risk" (Carr, 1995).

With regard to the proposed association of talc exposure and ovarian cancer, the panel found that "epidemiologic data are conflicting and remain equivocal". "Diet, parity, contraceptive use, ovulatory frequency, familial predisposition, age to menarche and menopause amongst other factors [are] associat[ed] strongly (and plausibly) with ovarian cancer incidence" (Carr, 1995). These possible confounders, as well as control selection biases, etc., interviewer and interviewee biases, as well as other factors, may well explain the conflicting results that have appeared in the literature. In summary "...epidemiologic studies have provided weak and conflicting risk signals for [the] association [between talc use and ovarian cancer], and it is unlikely that further studies may prove adequate to raise concern at a level sufficient to warrant regulatory or public health measures " (Carr, 1995).

In conclusion, there is no basis to Petitioner's request that cosmetic talc products should bear warning labels to the effect that talcum powder causes cancer in laboratory animals or that "[f] requent talc application in the female genital area increases the risk of ovarian cancer". When used as intended, talc presents no health risk to the consumer. Accordingly Petitioner's request for warning labels on talc-containing cosmetic products should be denied.

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