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Dr.Linda J.Loretz
CTFA
1101 17th Street,N.W.,Suite 300
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Dear Dr.Loretz:

I am pleased to enclose the Critique of NTP's Draft, as discussed. Please note that the spiral-bound copy --in red for easy identification-- is intended for CTFA's in-house use as it does not contain Appendices A and B for reasons discussed. Clean copies of the Appendices (A=paper by Taubes; B=paper by Muscat and Barish) should be inserted at CTFA behind the respective Appendix cover pages before copies of the critique are distributed by CTFA. The loose-leaf copy of the critique lets CTFA make any desired number of copies. The enclosed disc (Microsoft Word on PC using Windows) facilitates easy changes if CTFA wishes to do so.

I enjoyed collaborating with CTFA on this project. Please let me know if I can be of further assistance.

Sincerely

Dr.Alfred P.Wehner

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CRITIQUE

of the Draft

Background Document for Talc Asbestiform and Non-Asbestiform

submitted by

The Cosmetic, Talc and Fragrance Association
1101 17th Street, NW
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G. Taubes, SCIENCE, **269**:164-169, 1995.

Appendix B. Epidemiology of Talc Exposure and Ovarian Cancer: A Critical Assessment.
J.E. Muscat and M. Barish. COMMENTS ON TOXICOLOGY,. **6**:327-335, 1998.

Overview

This critique is restricted to that part of the above-identified document, in the following called the Draft, which deals with non-asbestiform cosmetic talc.

Examination of the Draft reveals a seriously flawed, biased document. Specifically, this critique will show the following.

- The Draft presents discredited studies in support of the intent to list cosmetic talc in the Tenth Report on Carcinogens (RoC).
- The Draft ignores evidence that does not support, or that contradicts, the reasons given for intending to list cosmetic talc in the Tenth RoC.
- The Draft miscites literature references, i.e., references cited in support of a position on a given issue do, in fact, not support that position.
- The Draft contains misrepresentations.
- The Draft ignores the public workshop on talc, sponsored by the International Society of Regulatory Toxicology and Pharmacology (ISRTP) and the FDA (1/31 – 2/1/94, Bethesda, MD), and the conclusion by its panel of experts that cosmetic talc does not present a risk to the consumer.
- There is a heavy reliance on citing from the 1987 IARC review rather than examining the original publications.
- The Draft does not observe NTP's own criteria for Listing Agents, as printed on page i, in its pursuit to list cosmetic talc in the Tenth RoC.

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Critique and Comments

The National Toxicology Program (NTP) rationalized its intent to list cosmetic talc in its Tenth Report on Carcinogens (RoC) as follows: "Talc not containing asbestiform fibers is *reasonably anticipated to be a human carcinogen* based on consistent evidence from human epidemiological studies, which showed an increase in ovarian cancer in women who use cosmetic talc in the genital area, and evidence of carcinogenicity from a study in experimental animals" (Draft, p.i, first paragraph).

This critique will show that the weak epidemiological data are ambiguous, *inconsistent*, controversial and therefore inconclusive. They have generated but not tested the hypothesis that hygienic use of cosmetic talc is a risk factor for ovarian cancer, a disease whose etiology still is poorly understood. This critique will also highlight serious flaws in the discredited animal study cited in the Draft, a study that has been declared irrelevant for human risk assessment. Finally, this critique will examine the Draft line by line and page by page to document the statements made in this critique's Overview.

The Epidemiological Studies

For anyone wishing to understand epidemiological data and weigh their biological significance without being trained in this field, the article "Epidemiology Faces Its Limits" by Gary Taubes in SCIENCE (**269**:164-169, 1995) is required reading and reprinted in Appendix A. It is appropriately subtitled "The search for subtle links between diet, lifestyle, or environmental factors and disease is an unending source of fear – but often yields little certainty." The paper explains that, because of the softness of epidemiological data, a number of epidemiologists consider relative risk (RR) or odds ratios (OR) below 3 or even below 4 of questionable biological significance. Mantel, one of the leaders in the field of epidemiological analysis, observed that epidemiology is too blunt a tool to estimate relative risk less than 2.0.

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The RRs or ORs of the (barely statistically significant) studies cited in the Draft generally have RRs or ORs around 1.5. This explains the controversy surrounding the epidemiological data linking hygienic talc use to ovarian cancer: Their interpretation is a matter of personal opinion rather than scientific proof. While Cramer and Harlow might believe in a causal link, many scientists will side with Mantel and Taubes. Hardly a case of "consistent evidence" and conclusive scientific proof.

Weak and ambiguous epidemiological data can become more meaningful if they are supported by data demonstrating consistent dose-response relationships (Wynder, 1987), by data from animal studies and by *in vitro* studies. Almost all of the NTP-cited epidemiological data show no, or inconsistent, or bizarre dose-response relationships. As this critique will show, the only animal study cited by NTP (NTP, 1993) in support of its intent to include cosmetic talc in the Tenth RoC contains serious flaws and has been declared irrelevant for human risk assessment. No other animal study has linked cosmetic talc to cancer. Several animal studies, specifically designed to investigate this point, resulted in *no* malignancies (Wehner et al, 1977a; Wagner et al, 1977; Pickrell et al, 1989). Even NTP concedes that cosmetic talc is not genotoxic and not carcinogenic *in vitro*. Thus, NTP's case rests solely on statistically weak, biologically questionable, inconsistent, ambiguous and therefore inconclusive epidemiological data, judged to be so by a panel of experts at the ISRTP/FDA workshop.

Muscat and Barish (1998) recently provided a critical assessment of the epidemiology of talc exposure and ovarian cancer which is presented in Appendix B because of its direct relevance to this critique.

Suffice it to state here that the etiology of ovarian cancer remains poorly understood; that most of the studies cited in the Draft were not designed to specifically investigate talc but several agents; that some of the agents showed a much stronger association with ovarian cancer than the weak statistical link with cosmetic talc; that, as stated before, consistent dose-response relationships generally were lacking; that dose definitions were woefully inadequate; and that none of the investigators who did find a

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weak statistical link between cosmetic talc and ovarian cancer claim in their original publications to have established causality.

Whittemore et al. (1988) found the ovarian cancer risk in women who had consumed coffee for more than 40 years to be 3.4 times that of women who had never regularly consumed coffee. This relationship is much more robust (P = 0.01) than the marginal significance of the relationship (RR = 1.40, P = 0.06) which the investigators observed for perineal talc use. Both studies failed to show dose-response relationships. Should, therefore, coffee be listed in the Tenth RoC?

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

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

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

Only when the authors stratified by histological subtype did they observe a statistically barely significant increase in risk for ever talc use for *serous invasive* cancers (RR = 1.40; 95% CI, 1.02-1.91) but not for all serous cancers (including borderline cancers), endometrioid cancers, or mucinous cancers. For women who reported ever daily use of talc, the RR of invasive serous cancer was 1.19 (95% CI, 0.98-2.26). The RRs for ever

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talc users of less than once per week and one to six times per week were 1.29 (95% CI, 0.81-2.04) and 1.49 (95% CI, 0.77-2.11), respectively (*P* for trend = 0.05).

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

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

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

For more comments on the epidemiological studies reference is made to Muscat and Barish (Appendix B) and to Wehner (1994, 1998).

Does Talc translocate from the Perineum to the Ovaries?

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

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

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

The Animal Studies

The Draft devotes four pages (pp 43-37) to the NTP-sponsored talc inhalation study in rats and mice, conducted by the Lovelace Biomedical and Environmental Research Institute (NTP, 1993). The write-up completely ignores (1) the serious flaws in the design and conduct of the experiments; (2) published critiques of the study (e.g., Oberdörster, 1995; Wehner, 1994;1998); the conclusion of the panel of experts at the ISRTP/FDA sponsored workshop on talc (1/31 – 2/1/94, Bethesda, MD) that, on account of its flaws, the results of the study are not relevant to human risk assessment. The Lovelace investigators themselves never claimed relevance of their findings to human risk assessment.

The repeatedly mentioned flaws include:

- The study design did not include positive and, especially, negative dust controls. Inclusion of negative and positive dust control groups would have allowed unambiguous determination of relative toxicity/carcinogenicity of inhaled talc. As it is, the question remains whether the observed pulmonary lesions and other

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

- The selected target aerosol concentrations were too high. Oberdörster, one of the leading experts on pulmonary overload-related phenomena, states in his critical analysis of the Lovelace talc inhalation study that the lung cancers in female rats of the high-exposure group (16 mg/m^3) are a secondary effect as a consequence of chronic high pulmonary particle overload and its associated chronic toxicity (1995).
- If NTP intended to test cosmetic talc for biological effects, then cosmetic talc as available to the consumer should have been specified for the experiment. Instead, the investigators used micronized talc. Micronizing results in smaller particles. This, in turn, changes surface characteristics of the particles and – more important—their pulmonary deposition and clearance characteristics. More specifically, a higher percentage of particles in a given respirable aerosol cloud containing particles of a smaller mass median aerodynamic diameter (MMAD) will be deposited in the non-ciliated part of the respiratory tract than is the case for particles having a larger MMAD. The significance of this phenomenon lies in dramatically different clearance times because of different clearance mechanisms. The larger particles, deposited on the ciliated part of the respiratory tract, are cleared by the mucociliary escalator system within minutes and hours. The smaller particles, deposited in the deep lung or alveoli, are cleared by pulmonary macrophages, a process taking weeks and months. Thus, micronizing the talc resulted in a greater deep lung burden and contributed to lung overload even at the lower aerosol concentration in the Lovelace study.
- The investigators were unable to maintain target aerosol concentrations for the 18 mg/m^3 rat exposure group during 19 of the 113-122 weeks of exposure. **For seven of these weeks the rats were exposed to approximately twice the intended aerosol concentration.** Even the two intended exposure concentrations led to an impairment of lung clearance mechanisms and therefore meet the criteria for a maximum tolerated dose or maximum functionally tolerated dose.

Each of these flaws by itself raises serious questions about the validity of this study. In combination, they disqualify the study from consideration for human risk assessment, an opinion shared by the panel of experts at the ISRTP/FDP workshop and by other

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distinguished experts (see Wehner, 1998). Yet time and again, the Lovelace study is exhumed and presented without any qualifications as "evidence" for the carcinogenicity of cosmetic talc.

The concept of lung particle overload and its pathophysiological and toxicological implications, now widely accepted, was first proposed by Morrow (1988) more than a decade ago. Analysis of past chronic inhalation studies has shown that in many cases the animals had been exposed to excessively high aerosol concentrations. Excessive because large numbers of particles being deposited chronically in the deep lung overwhelm the capacity of the alveolar macrophages (AM) to clear the alveoli of the deposited particles. This condition leads to an increasing particle overload of the lung as a function of exposure time and dose. As is well known, chronic presence of (highly insoluble) particles even of low toxicity --such as TiO_2, toner, carbon black, talc and others-- induces an inflammatory tissue reaction. Chronic inflammatory processes, in turn, are recognized as potential contributing factors in the etiology of some malignant tumors. Phagocytic cells release reactive oxygen species which are genotoxic. As Morrow et al. (1996) state, "inflammatory cells (i.e. neutrophils, macrophages) when activated by various stimuli can produce genotoxic effects in both mammalian and bacterial cell systems. Thus, nongenotoxic agents when given at exposures sufficient to elicit the recruitment and activation of inflammatory cells may cause genotoxic effects and potentially the neoplastic transformation of cells." The authors further observe, " the demonstrations that inflammatory doses of particles produce mutation in the rat lung epithelial cells and that the particle-elicited rat lung inflammatory cells are themselves mutagenic indicate there are factors which can contribute to rat lung tumor responses under inflammatory conditions." Lee et al (1985) induced cancer in rats chronically exposed by inhalation to high concentrations of TiO_2, a powder frequently used in experiments as a negative control dust. Should, therefore, TiO_2 be declared a carcinogen?

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

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

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

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

The increased incidence of pheochromocytomas in the adrenal medulla in rats of both sexes in the 16 mg/m^3 exposure group remains a perplexing phenomenon that needs to be independently confirmed. There is no known mechanism by which highly insoluble, inanimate talc particles deposited in the lung can affect, via "long-distance", the adrenal medulla, with the possible exception of a nonspecific stress-related secondary effect owing to pulmonary overload, as suggested by Oberdörster.

By contrast, the Draft deals with the Battelle study (Wehner et al, 1977a) in only 8 ½ lines. That chronic inhalation study in hamsters showed no harmful and certainly no carcinogenic effects of cosmetic talc under rational exposure conditions.

Wehner et al (1977a) exposed the hamsters to a respirable talc aerosol concentration of approximately 8 mg/m^3 for 3, 30, or 150 minutes/day, 5 days/week for 30 days, or for 30 or 150 minutes/day either until they died naturally or for a maximum of 300 days. Exposure was followed by observation until 90% of the animals had died. The hamsters received cumulative exposures ranging from about 15 to more than 6000 $mghr/m^3$.

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Estimates based on a pulmonary deposition and clearance study with neutron-activated talc (Wehner et al., 1977b) indicate that from 0.05 to 6 µg talc, depending on the length of exposure, was deposited in the hamster lungs at each exposure. Estimates based on infant-dusting experiments (J. N. Sivertson, personal communication, 1976) show that the weekly hamster exposures, expressed in mghr/m^3, exceeded the average weekly infant exposures by some 30 to 1700 times, depending on the hamster exposure group. Deposition of talc particles in the lungs of the exposed animals was demonstrated by X-ray fluorescence and by X-ray diffraction. At death, the lungs, trachea, larynx, liver, one kidney, stomach, uterus, one ovary, or one testis, and all tissues showing gross lesions were collected for histopathological examination. The talc exposures did not affect body weight, survival *or, with the exception of increased focal alveolar hyperplasia, the type, incidence or degree of histopathological changes in the exposed groups compared with sham-exposed controls.*

The Draft on page 48 refers to IARC 1987a (apparently nobody at NTP read the original publication, Wehner et al, 1977a) whose "Working Group noted the inadequate duration of the study." The IARC statement is inaccurate. Wehner et al started exposing the hamsters at the earliest age possible, 7 weeks, given that they had to be at least 4 weeks old to survive being shipped across the country, followed by a mandatory 3-week quarantine period. The hamsters were then exposed for up to 300 days, i.e., the majority of their life span. After the end of exposures the hamsters were maintained for observation for an additional 150 days to allow for any exposure-related lesions with a long latency period to develop. The observation period was terminated after 90% of the animals had died, a generally accepted and scientifically sound standard procedure for experimental protocols. Transposed roughly to a human scale, human subjects would receive exposures from age 7 to age 50, followed by observation to age 75 by which time 90% of the subjects had died.

The positive response of the Syrian golden hamster to a variety of carcinogens has been reported by a number of investigators (Dontenwill, 1970; Dontenwill and Mohr, 1961; Herrold and Dunham, 1963; Mohr, 1970; Mohr, Wieser and Pielsticker, 1966; Montesano and Saffiotti, 1968; 1970; Smith, 1974). Montesano, Saffiotti, and Shubik (1970) used this species extensively as an animal model for the study of the pathogenesis of lung cancer and found it "markedly susceptible to various respiratory carcinogens and conveniently refractory to chronic pulmonary infections."

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Pickrell et al. (1989) investigated the relationship between the aerosol concentration of talc and the resulting lung burdens and histological lesions. Rats were exposed to 0, 2.3, 4.3, and 17 mg talc/m^3 for 6 hours/day, 5 days/week, for 4 weeks. Lung burdens were 0, 0.07, 0.17 and 0.72 mg talc/g lung, respectively. Mice were exposed to 0, 2.2, 5.7 or 20.4 mg talc/m^3, which resulted in lung burdens of 0, 0.10, 0.29 and 1.0 mg talc/g lung. Histological changes consisted of a modest increase in talc-containing free macrophages within alveolar spaces in both rat and mouse groups exposed to the highest concentration of talc.

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

Neither the studies by Wehner et al, Pickrell et al, nor Wagner et al showed any signs of malignant pulmonary neoplasms. The latter three studies demonstrate in three animal models --hamsters, rats, and mice-- that, even at talc aerosol concentrations far exceeding those encountered by human consumers (Aylott et al, 1979; Russell et al, 1979), cosmetic talc is not carcinogenic, just as the studies by Lee et al (1985) and others show that under conditions of lung overload any dust --even titanium dioxide-- can indeed cause cancer.

Summary and Conclusions

NTP provides two rationales for its intent to include cosmetic talc in the Tenth RoC. These are (1) results of certain epidemiological studies, and (2) the NTP-sponsored inhalation study in rats and mice, conducted at Lovelace.

Little is known about the etiology of ovarian cancer.

The results of the epidemiological studies are inconsistent, ambiguous, controversial, and generally fail to demonstrate dose-response relationships. They must, therefore, be considered inconclusive. They have generated but not tested the hypothesis that hygienic use of cosmetic talc is a risk factor for ovarian cancer.

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Those studies having shown weak, statistically barely significant links between hygienic talc use and ovarian cancer (but did not prove causality) report RRs or ORs generally around 1.5. Many epidemiologists consider epidemiology too blunt a tool to estimate risk ratios less than 2.0 or even less than 3. Several epidemiological studies showed no association.

The Lovelace study has been discredited by flaws in design and execution. Administered aerosol concentrations resulted in lung overload in all exposure groups of both sexes and species, most likely accounting for the observed malignancies. The study has been declared irrelevant for human risk assessment and therefore should not be cited by NTP as evidence for listing cosmetic talc as a human carcinogen. Other inhalation studies in three species have shown no carcinogenic effect of cosmetic talc.

NTP's own guidelines for listing an agent as "Reasonably Anticipated to be Human Carcinogens" (Draft, p. i) require for an agent showing "less than sufficient evidence of carcinogenicity in humans or laboratory animals" to meet the following criteria: (1) The agent must belong to a structurally related carcinogen, or (2) There must be "convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans."

It can hardly be disputed that the evidence against cosmetic talc in humans and laboratory animals is "less than sufficient." As to (1) above, talc is as similar to asbestos as diamond is to graphite. As to (2), cosmetic talc is recognized even by NTP to be neither genotoxic nor carcinogenic *in vitro*.

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

Perhaps the most powerful and convincing proof that cosmetic talc is *not* carcinogenic can be found in the results with pleurodesis. Pleurodesis is the deliberate therapeutic creation of a fibrous adhesion between the visceral and parietal layers of the pleura. It is performed surgically by inserting talc into the pleural canal to treat recurrent spontaneous pneumothorax and other conditions. There is not a single report in the scientific literature suggesting that inhalation of cosmetic talc causes lung cancer or

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mesothelioma in consumers. Pleurodesis has not caused any such lesions in approximately 200 patients up to 40 years after the procedure (Chappell et al, 1979; Weissberg and Kaufman, 1986).

Finally and last but not least, after thorough examination of all available evidence, the panel of experts at the ISRTP/FDA – sponsored workshop concluded that cosmetic talc, when used as intended, does not present a risk to the consumer. No new evidence has been presented since the workshop that would require a revision of that conclusion. Several case-control studies published since the workshop do not present new findings. Wherever a link existed between hygienic talc use and ovarian cancer, it was weak and statistically barely significant, with RRs or ORs about 1.5, i.e., of the type dealt with at the workshop with all their shortcomings such as lack of dose-relationships.

Given the wealth of well-documented evidence reviewed in this critique, NTP's case for wanting to list cosmetic talc in the Tenth RoC should collapse.

In the following section of this critique, a page by page scrutiny of NTP's Draft is presented, highlighting its many flaws and misstatements.

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Scrutiny of the NTP Draft

page i

"There is less than sufficient evidence of carcinogenicity in humans or laboratory animals" for cosmetic talc. Talc platelets are as distinctly different from asbestos fibers as graphite is from diamond (Zazenski, 1998; Wehner, 1998). Talc is neither genotoxic (Endo-Capron et al, 1993) nor carcinogenic *in vitro*.

page iii, 1st paragraph

The last sentence in the first paragraph is a misstatement. As has been repeatedly documented and reviewed in this critique, the "evidence" against talc is not "consistent." In the case of the human epidemiological studies, it is inconsistent, ambiguous, controversial and therefore inconclusive. In the case of the Lovelace study it is discredited and irrelevant for human risk assessment.

page iii, 2nd paragraph

The second half of the paragraph contains a misstatement, is misleading and provides incomplete information. In addition to crystalline silica and talc dust, the workers studied by Thomas and Stewart (1987) "may also be exposed to ....soda ash, borate minerals, fluorspar, phosphate minerals, pigments and numerous substances used in glasses, including antimony, chromium, copper, iron, titanium and many others." This information should have been included in the Draft when referring to evidence of increased lung cancer mortality and/or morbidity in ceramics industry workers, as reported by Thomas and Stewart.

Wergeland et al (1990) is a miscited reference. It is just the opposite of being "consistent with other reports" on increased mortality/morbidity. Rubino et al (1976), Leophonte et al (1991) and Wergeland et al (1990), investigating workers exposed to pure talc, found no such increases.

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page iii, 3rd paragraph

The study by Gertig et al (2000) has been reviewed in this critique. It remains to be said that only one subtype of ovarian cancer, invasive serous ovarian cancer, barely reached statistical significance. It occurred in 76 women in a study population of 76,630 women (RR = 1.4, 95% CI = 1.0 – 1.9), i.e., ~1/1000 of the test population. The last sentence of the paragraph expresses a highly questionable conclusion.

The study by Wong et al (1999) did not show a significant risk for invasive serous ovarian cancer. In fact, the authors conclude unequivocally: "A significant association between the use of talcum powder and the risk of developing epithelial ovarian cancer is not demonstrable, even with prolonged exposure."

page iv, 1st paragraph

The last sentence, while technically true, is misleading. The Lovelace study was seriously flawed and is irrelevant for human risk assessment.

page iv, last 4 lines

Talc is ubiquitous. Exposure to talc particles therefore might have been recent, inadvertent and unnoticed.

page 1, 1st paragraph

The reference Wehner 1994 is cited among "human and experimental animal carcinogenicity studies of talc...that suggest an association between exposure to non-asbestiform talc (including cosmetic talc) and cancer risk in humans." The referenced paper, a review, does no such thing.

page 12, 2.6

It should be noted here that the talc aerosol exposure measurements are given in $\mu g/m^3$, that the respirable fraction of the total aerosol concentration cited is considerable smaller, and that ACGIH's TLV TWA is 2 mg/m^3, i.e., two orders of magnitude greater than the total aerosol concentrations reported here.

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page 23, lines 8 – 10

See comment to page iii, second paragraph.

page 24, 1st full paragraph

If talc, a recognized fibrogenic agent, were indeed the cause of ovarian inflammation, *where is the ovarian fibrosis* that one would expect to develop long before ovarian cancer would develop if talc were also carcinogenic? There is no ovarian fibrosis reported in the literature.

page 24, 2nd paragraph

As pointed out repeatedly in this critique and elsewhere (Zazenski et at, 1995; Zazenski, 1998), cosmetic talc is distinctly different from asbestos in important surface characteristics and physicochemical properties.

As will be shown in the critique of Section 6, the cited studies have *not* demonstrated particle migration through the fallopian tubes.

page 25, last paragraph

Note the appropriate term "suggest" in the first sentence. Suggest, yes, but "prove", definitely not. Note also the inconsistencies conceded in lines 6 and 7 of that paragraph.

page 26

Section 3.2.3 highlights the inconsistencies in ovarian cancer incidence among different histological subtypes of ovarian cancer and hygienic talc use.

page 27, 3.2.5, 1st paragraph

The last sentence refers to positive associations observed in 14 of 16 case-control studies. This account includes statistically non-significant data. Later on page 28, under 3.2.6 Summary, the Draft concedes that among the 16 studies only 8 (barely) reached statistical significance. Again, in the interpretation of these data it must be considered that (1) these data were barely statistically

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significant, (2) the RRs or ORs were in the gray area of dubious biological significance, i.e., below RRs/ORs of 2, (3) that dose-response relationships were lacking, and (4) that even those studies published after the ISRTP/FDA workshop were of the same type and produced the same ambiguous and inconsistent data as those examined at the workshop and found wanting.

page 28, 3.2.6

Evidence for causality has never been established. What has not been established cannot be weakened. What is weakened further is the weak case for listing cosmetic talc in the Tenth RoC. The invoked biological plausibility is highly questionable because of (1) the repeatedly emphasized differences between talc platelets and asbestos fibers, and (2) the ambiguity of data on talc translocation from the perineum to the ovaries. Sample contamination has never been ruled out. The cited reference, Wehner 1994, does not support biological plausibility in this case.

page 29, 3rd paragraph

See comments to page iii, second paragraph

page 29, bottom line

Suggests, but far from proves, given the inconsistence, ambiguity, controversy, lack of dose-response relationships, etc., as repeatedly documented in this critique and elsewhere.

pages 43-47

These pages describe the Lovelace study which is reviewed above in this critique.

page 46, center paragraph

Note that Hamilton et al (1984) injected 100 µl of a suspension containing 100 mg/ml Italian talc into the bursae of Sprague-Dawley rats. The animals were then

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serially sacrificed 1,3,6,12 and 18 months after treatment and examined. As is stated in the Draft, "Evidence of frank neoplasia was not found in any animals." In the case of human ovarian cancer the controversy rages over whether or not talc particles can translocate from the perineum to the ovaries in sufficient numbers and to stay there long enough to cause cancer. Here, the talc was injected directly into the ovarian bursa of perhaps the animal model most responsive to carcinogens, the female rat, to remove all doubt about talc being able to reach the ovaries. What happened? *No* malignant (or benign) tumors were caused by the agent NTP wants to list in the Tenth RoC.

page 47, 4.1.1.3

The study by Wehner et al, receiving short thrift in the Draft, was a life-span study, terminated only after 90% of the animals had died as pointed out earlier in this critique. With the exception of a 15% increase of focal alveolar hyperplasia in the exposed animals compared with the control group, there were no deleterious effects of the chronic talc exposures.

Wagner et al (1977) exposed rats to a mean respirable aerosol concentration of 11mg/m^3 of Italian talc for up to one year and did not observe any malignant neoplasms.

page 52

The table shows no mesothelioma in 48 Wistar rats following intrapleural implantation of Italian talc.

page 56, 4.3

The Summary again refers to the discredited Lovelace study which is irrelevant for human risk assessment, as documented in this critique. At the end of the first paragraph, the Draft states:

> "The lungs of the male and female rats and mice showed signs of marked toxicity, characterized by inflammation, focal fibrosis, and hyperplasia, suggestive of impaired clearance. Although no definite determination was

made, the lung burden data suggested that clearance was not significantly impaired."

The last sentence contradicts the first. It also contradicts the analysis by Oberdörster (1995), one of the most respected experts on pulmonary overload, who found that pulmonary overload did, in fact, occur in all exposure groups. As documented earlier in this critique, pulmonary overload can and does cause malignant tumors.

pages 57/58

The Draft agrees that cosmetic talc is not genotoxic.

page 65, center paragraph

Talc is ubiquitous in the environment. The talc particles found in these lung tissues and lavage fluid might have been inhaled with ambient air long after occupational or other exposures, or they could be sample contamination during sample collecting and processing (see Lee et al, 1995).

In the following paragraph reference is made to the pulmonary deposition, translocation and clearance study with neutron-activated talc in hamsters by Wehner et al (1977b), citing IARC (1987a). The Draft states, "The IARC Working Group noted that the unusually short clearance time may relate to limitations in the sensitivity of the detection methods and the large size of particles." This erroneous statement betrays remarkable ignorance of the subject on part of IARC. First of all, the observed clearance time is not "unusually short." Its biphasic course (quick mucociliary clearance + slower alveolar clearance) falls well within the expected range which is similar for several species tested. The study was conducted at Battelle Pacific Northwest Laboratories. That laboratory, internationally recognized as a leader in this field, has been specializing for five decades in work with radioactive materials, including plutonium, using cutting-edge techniques and state-of-the-art equipment. The original publication (Wehner et al, 1977b) clearly shows that pulmonary clearance was uneventfully monitored from the time of deposition (mean 33.08µg; SD 31.06; SEM 15.53) to

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near-background levels 132 days after exposure. No lack of sensitivity interfered with these measurements. Last but not least, the "large" particle size was very similar to that used by Wehner et al (1977a) in their talc inhalation study in hamsters, which, in turn, is very similar to that of cosmetic talc used by the consumer. It is the particle size that should have been used in the Lovelace study!

page 66, 2nd full paragraph, 2nd line

Wehner (1994) considers findings describing translocation of talc under normal anatomical and physiological conditions from the perineum to the ovaries rather questionable until contamination by ubiquitous environmental talc during sample collecting and processing has been ruled out (see Lee et al, 1995). Heller et al (1996) investigated ovarian asbestos fiber and talc particle burdens in a limited number of subjects (13 exposed and 17 with no history of known exposure). They reported large numbers of asbestos fibers in approximately 70% of the asbestos-exposed group, but also in 35% of the controls. They also found talc particles in 85% of the talc-exposed group, *but most astonishingly also in 100% of the controls*, casting doubt on the procedures and findings. The lack of a trend argues against a biological effect. As Wynder (1987) points out, in epidemiological studies of weak association, dose-response trends are especially important to demonstrate causality. This paper also cites, as so many others do, references that do not support what they are supposed to support (Egli and Newton, 1961). The paper also fails to cite references that do not support the view of the authors, suggesting either unfamiliarity with relevant technical literature or bias of the authors.

Chang and Risch (1997) observed an overall OR of 1.42 (CI 1.08-1.86). Their data show a consistent *inverse* dose-response relationship as shown in the following excerpt of their Table 2.

After-bath talc use(months)	Adjusted OR	95% CI
<10	1.836	1.24-2.73
10-25	1.128	0.74-1.72
>25	0.95	0.61-1.49

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Years of after-bath talc use	Adjusted OR	95% CI
<30	1.697	1.08-2.64
20-40	1.455	0.96-2.15
>40	0.865	0.54-1.38

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

page 66, 3rd full paragraph

Egli and Newton (1961) keep being cited to this date in support of particle translocation despite repeatedly published evidence (most recently, Wehner, 1998, pp. 348-350) convincingly suggesting that the authors misinterpreted their contaminated samples as showing carbon black particle translocation. Egli and Newton, medical practitioners with no training in science, failed to include examination of filter and liquid blanks as negative controls in their experimental protocol. For more details on this subject reference is made to Wehner et al, 1985 and 1986.

page 66, last paragraph

Henderson et al (1986) did *not* demonstrate "that talc particles could migrate from the vagina...to the ovaries in rats." The last sentence of that paragraph contradicts the first one, stating, "Talc particles were *not* found in the ovaries of rats within 48 hours of *intravaginal* (emphasis added) exposure." If anything, Henderson et al have demonstrated the difficulty – in their experiment the impossibility – for inanimate, insoluble particles with no locomotion of their own and inability to react to chemotactic stimuli, to breach the formidable barrier of an intact cervix. It is much more plausible for such particles to reach the ovaries when instilled in the uterus, perhaps assisted by the hydrostatic pressure exerted during instillation.

page 67, 6.1.2

The section Possible Mechanisms presents a reasonable overview which is much weaker than NTP's position throughout most of the Draft. The last two sentences state:

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"Under the conditions of the Oberdörster scenario, exposure to non-asbestiform talc that does not result in marked chronic lung toxicity would not likely cause tumors (Goodman, 1995). Estimates of human exposure to talc particles under normal conditions of use (normal face or body powdering by adults; diapering use for infants) were well below concentrations expected to result in lung toxicity (Zazenski et al, 1995)."

This falls far short of meeting NTP's guidelines for listing cosmetic talc in the Tenth RoC as "reasonably anticipated to be a human carcinogen." (see p. iii, bottom of first paragraph).

Q. E. D.

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Appendix A

Epidemiology faces its Limit

Gary Taubes

Appendix B

Epidemiology of Talc Exposure and Ovarian Cancer: A critical Assessment

Joshua E. Muscat and Melanie Barish