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THE COSMETIC, TOILETRY, AND FRAGRANCE ASSOCIATION

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E. EDWARD KAVANAUGH
P R E S I D E N T

Dr. Kenneth Olden
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Dear Dr. Olden:

The Cosmetic, Toiletry, and Fragrance Association (CTFA) appreciates the opportunity to submit further information on talc not containing asbestiform fibers following NTP's deferral on the decision to list in the Report on Carcinogens. The enclosed information is submitted in response to the offer of collaboration which you extended in your July 9 letter.

In an attempt to clarify issues that were raised in the initial Draft Background Document (DBD), in discussions at the RoC Subcommittee meeting, and in your letter of July 9th, we have completed an updated review and analysis of the literature. Our findings include some 90 studies, articles, and commentaries, more than 50 of which (the ones preceded by an asterisk) are not referenced in the initial DBD. While not all of the additional references may meet NTP criteria for use in a DBD, we believe that they provide useful information relevant to the subject matter.

A summary of our findings from this further review, including the literature references, is contained in the Attachment to this letter.

Our review during the 10th RoC proceedings, together with this additional literature review, indicates that the scientific literature on which the initial RoC nomination for non-asbestiform talc was based was incomplete, and that findings in the DBD are unsupported on certain key points. Re-analysis of the pertinent literature further supports our confidence in the safety of cosmetic talc. While we do not intend to represent that our literature research is totally exhaustive at this point, we do believe it is balanced and that it raises or highlights significant points that deserve further attention as NTP reviews this matter.

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Again, CTFA appreciates the opportunity to provide input on talc. We continue to be open to further discussion, including meeting with you at your convenience. Please let us know if there is additional information that we can provide.

Sincerely,

A handwritten signature in black ink, appearing to read "G. N. McEwen, Jr.", with a stylized flourish at the end.

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

A Supplemental Analysis of Cosmetic Talc Issues and Literature Evidence Regarding Ovarian Cancer Risk

Cosmetic talc vs. asbestos

In 1976, CTFA promulgated a specification for cosmetic talc to ensure that it is free of asbestos. As a practical matter, that specification is self-enforcing. Asbestos has been listed as a known human carcinogen, is highly regulated, and no consumer products company would knowingly run the risk of asbestos being present in its product, even in minute quantities. This is a matter both of public perception and potential litigation exposure. Therefore, both suppliers and end users go to great lengths to assure that the CTFA specification is met. In some cases, cosmetic talc producers augment the quality assurance process by utilizing additional detection precautions such as transmission electron microscopy.

The literature clearly does not support the statements that were originally made in the DBD, and in many of the epidemiologic studies, that talc has a mineralogical and chemical similarity to asbestos, and that this similarity supports the biological plausibility of the findings of weak associations in the epidemiologic studies of ovarian cancer. (E.g., DBD at 24, 28.) This was a central point of dispute by the commenters in the RoC Subcommittee meeting. Dr. A.P. Wehner has commented, "Talc is as similar to asbestos as graphite is to diamond." [*84] Krause and Ashton, by way of explaining that chemical composition does not in any way by itself determine the properties of a substance, have used the metaphor that "a pearl [calcium carbonate] is not a piece of chalk [calcium carbonate]." [*49] Rather, the biological effects of a substance are determined by a combination of chemical composition, morphology, and molecular structure. [*Id.*] Zazenski et al. have clearly explained and illustrated the great dissimilarities between pure talc and asbestos in terms of morphology, chemical structure, and surface properties. [92,*93] When considered in its totality, pure talc bears little to no resemblance to asbestos. The idea that talc is like asbestos, repeated many times in the literature (and the DBD) without critical examination, has done considerable harm to the industry.

The dissimilarities between pure talc and asbestos are borne out by the extensive literature on the biological effects of the substances. Asbestos has long been listed (since the 1st RoC in 1980) as a known human carcinogen, and has shown clear carcinogenic action in both humans and animals. Asbestos is known to induce pleural and respiratory system cancers. While its exact carcinogenic mechanism has not been determined and probably involves several different effects, it has demonstrated cancer promotion activity in experimental animals and *in vitro*, including induction of chromosomal changes (aneuploidy) and cell transformation. [*4,*5, 79,*80] These biological effects of asbestos have been attributed to its fibrous structure and dimensions, as well as properties such as fiber durability and physiochemical surface properties. [*Id.* and *52] Such properties differentiate asbestos from pure talc and talc associated with calcite, dolomites, etc.

There is also epidemiologic evidence for a relationship between asbestos exposure and ovarian cancer. [*1,*6, 24,*47,*78,*90] This evidence is consistent with the other epidemiologic and mechanistic evidence concerning asbestos carcinogenicity.

For talc, on the other hand, putting aside for the moment the issue of the ovarian cancer epidemiologic studies, there is a distinct lack of evidence of carcinogenic activity. Talc is recognized as a fibrotic and sclerosing agent (at a high enough dose) in the lungs, bronchia, and pleura, and has been implicated as causing granulomas in the peritoneum when introduced via surgeons' gloves (in the past). In clear contrast to asbestos, however, pure talc has not been associated with human respiratory, pleural, or peritoneal cancers. Nor has its use in pharmaceuticals been associated with cancer in the gastrointestinal

tract or other organs. To the contrary, pure talc has been accepted in the medical community for decades as a highly effective agent for therapeutic pleurodesis (*i.e.*, with no indication of carcinogenic activity) of malignant pleural effusion and pneumothorax with no observed risk of cancerous activity. [*65,*86] Additionally, talc has not been shown to have potential carcinogenic activity in animal or *in vitro* experiments. While it has been hypothesized that talc fibrosis in the ovaries due to use of talc on condoms could lead to ovarian cancer [*46], there have been no observations of ovarian fibrosis associated with ovarian cancer.

Evaluation of the Ovarian Cancer Epidemiologic Studies

Several of the generally accepted Bradford Hill evaluation factors for judging the credibility of a causal relationship appear to have received insufficient attention to this point. With regard to strength, the statistical associations observed have been weak, generally well under 2.0, with the majority of findings lacking statistical significance. Also, a number of commenters, as well as study authors themselves, have observed the distinct absence of a clear dose-response trend in most of the studies. Dr. Ernst Wynder, one of the founding practitioners of epidemiology in the U.S., and a colleague (Muscat JE) commented specifically on this point, noting that lack of a clear dose-response is particularly significant in the case of consistently weak associations, since it is likely to indicate presence of a consistent bias. [*54]

The potential for recall bias in case-control studies is well recognized. [*Id.*] Muscat and Wynder [*id.*] have pointed out that in the talc-ovarian cancer case-control studies there is very wide variability in the percentage of controls reporting use of talc for perineal dusting, and that this indicates a lack of reliability in the subject's recall and reporting. In the ten case-control studies of U.S. subjects, we found that the percentage of controls reporting perineal dusting ranged from <5% to 46%. This is in line with the range found by Muscat and Barish of approximately 3% to 50%. [*53] The subjects' consistent reporting of slightly more use of perineal dusting than controls, despite this wide variation in reported use, raises a very strong suspicion of consistent recall bias. The conclusion in the DBD (at iii and v) that bias is unlikely is not supported. The failure of Cramer et al. to find a trend of higher reported usage in the more recent studies, given as a reason for such a conclusion (DBD at 28), does not address this point made by Barish Muscat, and Wynder. The high amount of publicity surrounding the allegations of asbestos in talc in the 1970s and subsequent epidemiologic study reports provides a very plausible basis for such a recall bias.

In addition to the lack of strength, lack of dose-response trend, and likelihood of bias, we also believe the Hill factors of consistency and biological plausibility require more attention.

Consistency

The discussion in the DBD and the RoC Subcommittee meeting focused almost exclusively on the consistency among a majority of epidemiologic study findings with regard to use of powders in the perineal area, although the RG1 and RG2 findings of consistent association appeared to also include use of talc on sanitary napkins and diaphragms. (At iii and v.) Such a conclusion regarding those other modes of exposure is not supported. The study results were far from consistent for talc on sanitary napkins, talc on diaphragms, and talc on condoms. All of these modes of exposure would more plausibly expose the ovaries to talc than external dusting. (The translocation issue is discussed below.)

For talc on sanitary napkins, nine studies reported results. Four reported results below the null (non-significant) [87, 14, 25, 91], and five reported increases ranging from 1.3 to 4.8 (one result significant, one barely significant) [12, 17, 19, 69, 56]

For talc on diaphragm or cervical cap, eight studies reported results or conclusions. Three reported results at or below the null (non-significant) [36, 27, 56], one relied on two previous studies for considering the risk to be non-significant [19], one reported a RR of 3.0 (non-significant) [69], one a RR of 1.5 (non-significant) [87], one a RR of 1.2-1.6 (non-significant) [17], and one a RR of 1.1 (non-significant). [34]

For talc on condoms, four studies reported results or conclusions. Two of these studies reported no elevation in risk [17, 27], one relied on previous studies in considering that there was no significant risk [19], while one reported a non-significant RR of 1.6. [69]

Considering all modes of exposure examined in the studies, there was pronounced inconsistency in the findings.

Biologic plausibility

As discussed above, there is a notable lack of mechanistic evidence for the carcinogenicity of talc supporting the findings in the case-control studies of ovarian cancer; and the mechanistic evidence argues strongly against biologic plausibility. The absence of consideration of this point in connection with the epidemiologic data in the DBD is surprising in view of the NTP emphasis on consideration of mechanistic data in the last several years. Most of the discussion in the DBD focused on the biologic plausibility of whether talc can translocate from the external perineal region to the ovaries, not whether there is mechanistic evidence supporting the biologic plausibility that exposure of the ovaries to talc will cause cancer.

In considering the issue of translocation, there are basically three components: (1) Observations of the presence of talc in the ovaries or ovarian tumors; (2) findings from controlled experiments designed to test for translocation; and (3) findings of reduced risk of ovarian cancer in epidemiologic studies of subjects who had undergone tubal ligation or hysterectomy. We will address each of these briefly.

(1) The observations by Henderson et al. in 1971 of talc particles embedded in ovarian tumors led to the hypothesis that talc might be related to ovarian carcinogenesis, although Henderson et al. did not propose such a hypothesis. [42, 43] They also reported finding even larger quantities of talc in healthy ovaries. A more recent study showed the presence of talc particles in the ovaries of all of both supposedly unexposed and perineally exposed subjects, although some of the "unexposed subjects appeared to have been exposed during diapering." [40] Asbestos fibers have also been found in ovarian tumors and malignant peritoneal mesotheliomas of women who had no recorded asbestos exposure history. [41,*38]

(2) Experiments attempting to test the hypothesis that talc or other particles can translocate from the vagina to the ovaries have produced conflicting results, and experimenters who have found no translocation have offered explanations for the opposing findings. [82,*21, 23,*62,*77]

(3) A number of epidemiologic case-control studies have consistently found a reduced risk of ovarian cancer in women who have undergone tubal ligation or hysterectomy and had been exposed to cosmetic talc. However, at least one study has also found significantly reduced risk in cases that had not reported being exposed to cosmetic talc. [*31] Some have hypothesized that such surgical procedures block external environmental agents such as talc or asbestos from entering the ovaries. However, this has not been the sole, or even the preferred hypothesis. It has also been hypothesized that, since there is now a considerable body of evidence indicating that ovarian cancer risk is influenced by hormonal and ovulatory factors, reduced risk from such procedures could be due to disruption of ovulation and certain hormone levels. [*15,*70] It has also been noted that such procedures could result in incidental removal of cancerous tissue. [*75]

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Thus, it seems clear that some talc particles, as well as asbestos fibers, can reach the human ovaries; however, how this occurs is still unclear. It has not been established that talc particles can reach the human ovaries through vaginal translocation as a result of perineal exposure, and there is some evidence that talc, as well as other mineral particles of low toxicity and low solubility, can be transported to various internal organs through the human body's systemic circulation. [85,*11] Of course, the mere presence of talc in the ovaries does not indicate that it is a cause of ovarian cancer, and there is not a biologically plausible explanation for cancer causation by pure talc.

Historical contamination of cosmetic talc with asbestos

Two studies, one in 1968 and one in 1976, reported finding fibrous-like materials and asbestos in off-the-shelf consumer talc products. [16, 68] In the latter study, half the brands had detectable asbestos. This occurred at a time when evidence was accumulating concerning the human carcinogenicity of asbestos. Although there were doubts concerning the validity of the studies [*48,*49], and given the lack of previous awareness of the dangers of asbestos, it is quite possible that there was in fact asbestos contamination in some brands of cosmetic talc powders prior to 1976. Recognizing this, CTFA promulgated its specification for cosmetic talc in 1976, which required a complete absence of detectable asbestos in cosmetic talc.

A review of the epidemiologic studies on ovarian cancer and talc exposure shows that a large portion of the exposures in all of the studies must have occurred prior to 1976. In addition, none of those studies were able to characterize the composition of the powders or identify brands. Thus, in addition to the analytical weaknesses discussed previously, the exposures might have involved exposure to asbestos, making the studies essentially lacking in utility and data quality for the purpose of evaluating the safety of present-day cosmetic talc.

Conclusion

Present-day cosmetic talc must be assumed to be free of asbestos, consistent with the CTFA specification and absent evidence to the contrary. It is simply a marketplace requirement. The current biologic evidence is overwhelming that pure cosmetic talc is not a risk factor in inducing cancer. Epidemiologic findings concerning ovarian cancer and cosmetic talc are extremely weak, equivocal, and cannot be considered relevant to present-day cosmetic talc. Consequently, at present we do not see any way to define cosmetic talc in a manner that would support a RoC listing nomination.

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