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THE COSMETIC, TOILETRY, AND FRAGRANCE ASSOCIATION

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E. EDWARD KAVANAUGH
PRESIDENT

Dr. C. W. Jameson
National Toxicology Program
Report on Carcinogens
MD EC-14
P.O. Box 12233
Research Triangle Park, NC 27709

RE: Call for Public Comments on 8 Nominations, Proposed for Listing in or Delisting From the Report on Carcinogens, Tenth Edition (66 Federal Register 13334): Talc Not Containing Asbestiform Fibers

Dear Dr. Jameson,

The Cosmetic, Toiletry, and Fragrance Association[1] (CTFA) appreciates the opportunity to provide comments on the above referenced topic. Talc not containing asbestiform fibers is used within the personal care products industry, and thus, the review for possible listing in the 10th Report on Carcinogens is of significant interest to CTFA members.

The definition of talc, which was a point of considerable debate at the Board of Scientific Counselors (BSC) meeting in December, is addressed in these comments. Because a valid conclusion regarding carcinogenesis cannot be reached without a clear understanding of the substance being evaluated, a clarification of the definition of talc is provided herein. Also included in these comments is a very brief summary of the substantial comments submitted to NTP prior to the BSC meeting. The previous comments are included in this comment by reference.

NTP cited both ovarian cancer epidemiology studies and an NTP rat chronic inhalation study as the basis for proposing the listing of "talc not containing asbestiform fibers" in its 10th Report on Carcinogens. Detailed comments addressing these issues were submitted prior to the December meeting and again, are included by reference. The comments and the discussion at the meeting, as recorded in the meeting transcript, make it clear that much consideration was given to both of these

[1]CTFA is the U.S. national trade association representing the personal care products industry. CTFA is comprised of about 300 active members that produce the vast majority of the cosmetics distributed in the U.S. and many over-the-counter drugs designed for dermal application. The association also has about 300 associate members that provide raw ingredients and supplies and services to the industry. Many of CTFA's members are international companies that do business in foreign countries as well.

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issues before the BSC voted 7-3 in favor of not listing "talc not containing asbestiform fibers" in the 10th Report on Carcinogens. This is in contrast to a statement in the Federal Register notice that the ovarian cancer studies were not considered.

- **At the BSC meeting, the motion which passed by a vote of 7-3 was "not to list talc not containing asbestiform fibers." "Talc" and "asbestiform" definitions are presented here.**

A clear understanding of the definition of the material being evaluated is fundamental to reaching a valid conclusion as to its carcinogenicity. Technical comments by experts in the field of mineralogy were submitted to NTP for the purpose of clarifying the definitions of talc and asbestiform fibers.[2] Consistent with those submissions, the following definitions of "talc" and "asbestiform", as those mineralogical terms are defined and understood by professionals in the geological sciences, are presented:

Talc (CAS Registry Number: 14807-96-6)

Talc [$Mg_3Si_4O_{10}(OH)_2$] is a hydrous magnesium silicate consisting theoretically of 31.7% MgO, 63.5% SiO2 and 4.8% H_2O. Pure talc is a translucent mineral with a Mohs hardness of 1 and is considered the softest and least abrasive of minerals. Commercial high quality grades of talc offer fine particle sizes in the range of 1-20 μm, a very hydrophobic surface, organophilic in nature, tremendous slip as a result of its lamellar (platy) crystal formation, heat stability up to 900°C, are inert in most chemical reagents and are typically utilized in ceramic, paper, plastic, paint, roofing, rubber, cosmetic and pharmaceutical applications.[3]

Asbestiform

The term "asbestiform" describes a mineral habit; it is a way something grows in nature, and is applied to an array of minerals. Asbestiform is a material with the geometry of a fiber or matted mass that is easily split into long, thin flexible fibers. The American Society for Testing and Materials (ASTM) definition of asbestiform is as follows:

> "Asbestiform mineral fiber populations generally have the following characteristics when viewed by light microscopy: (1) many particles with aspect ratios ranging from 20:1 to 100:1 or higher (greater than 5 μm in length); (2) very thin fibrils generally

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[2] See comments submitted by Dr. Ann Wylie, Professor, University of Maryland; and John Addison (John Addison Consultancy) and Dr. Arthur M. Langer (Professor, The City University of New York). Presentations by Dr. Wylie and Mr. Addison, and by Dan Crane, OSHA, at the BSC meeting, also provided clarification/corrections.

[3] Pooley, F.D. and Rowlands, N. (1977) Chemical and Physical Properties of British Talc Powders. In: Walton, W.H. and McGovern, B., eds., Inhaled Particles, Vol. IV, Part 2, Oxford, Pergamon Press, pp. 639-646.

less than 0.5 μm in width; and (3) in addition to the mandatory fibrillar crystal growth, two or more of the following attributes: (a) parallel fibers occurring in bundles, (b) fibers displaying splayed ends, (c) matted masses of individual fibers, and (d) fibers showing curvature."

The definitions presented above have been concurred with by Mr. Dan Crane, Occupational Safety and Health Agency, and Mr. John Addison, former Head of the Mineralogy Section at the Institute of Occupational Medicine, Edinburgh.

The NTP background document contained erroneous information which prevented a valid assessment of the carcinogenicity of talc. Upon review of the transcript from the BSC meeting, it is clear that clarification of the mineralogy, morphology and terminology of the mineral "talc" and the mineral habit "asbestiform" was critical to the final vote on the listing of talc in the 10th Report on Carcinogens. It should be noted that the correct information regarding the terms "talc" and "asbestiform" was not available to the RG1 and RG2 committees, which explains the inconsistent recommendations regarding the listing of talc.

- **The documents previously submitted to NTP addressing the basis of the nomination show conclusively that the listing of talc not containing asbestiform fibers in the 10th Report on Carcinogens is not scientifically justified.**

  In response to the NTP draft report, CTFA and others submitted detailed comments addressing the basis of the proposed listing. Arguments against listing talc not containing asbestiform fibers as "reasonably anticipated to be a human carcinogen" are briefly summarized here:

  - The epidemiologic evidence does not support a causal association between talc use and ovarian cancer.[4] The dose-response pattern among talc users is inconsistent, and overall shows an inverse trend for both duration of use and frequency of use.[5] A plausible biological mechanism is lacking to explain a causal relationship. The majority of these studies were not specifically designed to test the hypothesis that talc use contributes to ovarian cancer.

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[4] Three reviews of the epidemiology studies re: talc and ovarian cancer were submitted by CTFA. The reviews were authored by Dr. Kenneth Rothman, (Professor, Department of Epidemiology and Medicine, Boston University), Dr. Harris Pastides (Dean, School of Public Health, University of South Carolina), and Dr. Jonathan Samet (Chairman, Department of Epidemiology, Johns Hopkins University); Dr. Samuel Shapiro, Emeritus Director, Boston University of Public Health; and Joshua Muscat, M.P.H., American Health Foundation.

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

The finding of a small increase in relative risk could be due to several potential confounding factors. Because these studies were largely retrospective studies and the applications of concern had occurred many years earlier, the composition of the material being used was not known and could have contained constituents and/or contaminants other than talc. A serious limitation of the data is that the true exposure of ovarian tissue to talc is by necessity unknown, and can only be poorly estimated using proxy measures (i.e., self-reporting of talc use in the perineal area). Additionally, use of talc-dusted diaphragms, which would clearly result in female reproductive tract exposure to talc, did not result in an increased relative risk of ovarian cancer (meta-analysis resulted in a summary odds ratio of 0.79).[6]

The Federal Register notice states in relation to the BSC meeting outcome for talc not containing asbestiform fibers that "(T)he Subcommittee did not consider the ovarian cancer studies in the evaluation of talc not containing asbestiform fibers because it was unclear if the talc used in these studies might have been contaminated with asbestos." That statement does not accurately reflect the entire discussion. While the issue of possible asbestos contamination was raised, issues such as dose-response and biological plausibility were considered and debated at length, as can be verified by the meeting transcript [7] (for example, see pages 351-352).

It is therefore clear that Subcommittee members did consider the ovarian cancer studies, and that questions about the interpretation of the epidemiology studies were not limited to questions about the presence of asbestos in talc. It is very important that this information is not lost as this nomination goes forward.

- The 1993 NTP chronic rat inhalation study was cited as evidence for the listing of talc not containing asbestiform fibers in the 10th Report on Carcinogens. However, the high dose used in this study resulted in an overloading of the rat lungs with talc particles, overwhelming lung clearance mechanisms. This ultimately resulted in the the formation of lung tumors in females (only) at the highest dose (only). The tumor response is consistent with that observed in rats exposed by inhalation to high levels of other low toxicity, poorly soluble particles and is not relevant to human talc exposure. These conclusions are discussed at length in submissions to NTP which were made prior to the BSC meeting.[8]

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[6] See epidemiology review by Joshua Muscat, point #1, Testing the talc hypothesis using different epidemiologic measures. Submitted to NTP by CTFA.

[7] Condensed Transcript, National Toxicology Program (NTP), Board of Scientific Counselors Report on Carcinogens (RoC) Subcommittee Meeting, December 14, 2000

[8] See comments submitted by Dr. Donald Dungworth, Professor (emeritus), University of California, Davis (submitted by CTFA); and by Dr. Günter Oberdörster, Professor, University of Rochester (submitted by Colipa, the European Cosmetic, Toiletry, and Perfumery Association). Dr. Oberdorster has also published on this subject (The NTP Talc Inhalation Study: A Critical Appraisal Focused on Lung Particle Overload. Regulatory Toxicology and Pharmacology [1995] Vol. 21, p. 233-241).

The public comments submitted in response to the NTP draft report were acknowledged at the BSC meeting as providing valuable information, and were not available to the two previous committees (RG1 and RG2) reviewing talc not containing asbestiform fibers. One of the three principle reviewers of talc specifically noted that the scientific evidence in the public comments and presentations caused her to change her recommendation from "reasonably anticipated to be a human carcinogen" to "not list".[9]

In summary, talc not containing asbestiform fibers does not meet the standard as "reasonably anticipated to be a human carcinogen." The BSC agreed with this conclusion and voted 7-3 to not list talc not containing asbestiform fibers in the 10th Report on Carcinogens.

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

Sincerely,

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

[9] Condensed Transcript, National Toxicology Program (NTP), Board of Scientific Counselors Report on Carcinogens (RoC) Subcommittee Meeting, December 14, 2000, pages 280-281.