Luzenac

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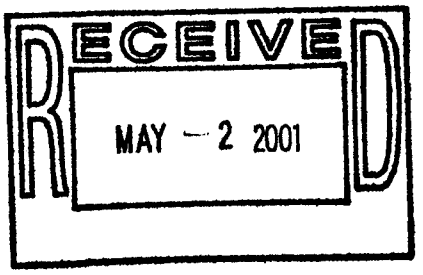

Dr. C. W. Jameson
NTP - Report on Carcinogens
Room 3118
79 Alexander Drive, Bldg. 4401
Research Triangle Park, NC 27709
(919) 541-4096

Dear Dr. Jameson:

Luzenac is hereby submitting its comments on the NTP proposal to list talc not containing asbestiform fibers in the 10th Report on Carcinogens. These comments are in response to the request for public comments that appeared in the Federal Register notice of March 5, 2001, 66 Fed. Reg. 13334 et seq.

As explained below, the recommendations of the RG1 and RG2 Report on Carcinogens review groups, as presented in the Draft Background Document (hereafter referred to as the "DBD"), are contrary to the formal listing criteria, and lacking in supporting evidence; and if they were to be submitted to the Director of NTP and the Secretary as valid recommendations, a final decision to list talc not containing asbestiform fibers in the Report would be arbitrary and capricious, an abuse of discretion, or otherwise not in accordance with law, and would be set aside by the Federal courts pursuant to the Administrative Procedure Act.

The great disparity between the 8-2 recommendation of the RoC Subcommittee not to list[1], made after lengthy and careful deliberation, and the recommendations of RG1 and RG2, are a red flag that something went wrong in the RG1 and RG2 deliberations. Fortunately, the Department decided to establish the RoC Subcommittee as an external review group so that errors made by RG1 and RG2 might be caught and corrected. Those errors, as recognized in the RoC Subcommittee deliberations, are itemized and explained below. We trust that in this case the external review process works as was intended.

The following discussion is based principally on the contents of the Draft RoC Background Document ("DBD") for both asbestiform and non-asbestiform talc. The DBD is the sole administrative record of the deliberations and conclusions of RG1 and RG2.

1. **In evaluating the ovarian cancer studies in humans, RG1 and RG2 <u>assumed</u> that current exposures to all kinds of cosmetic talc contain asbestos. Reliance on an assumption rather than evidence is contrary to the listing criteria. Furthermore, that assumption was contrary to evidence and findings contained in the DBD.**

The formal listing criteria for the Report on Carcinogens ("RoC") require that all listing decisions be based on "evidence". For listing in the reasonably anticipated category, there must be either

[1] The *Federal Register* notice states that the vote was 7-3. While it is technically accurate that the vote on the motion not to list was 7 for and 3 against, it was also clear that one of the three votes against the motion, by Dr. Smith, was a vote to defer, which is equivalent to a vote against listing in the 10th RoC. Thus, the vote on whether to list in the 10th RoC was 8 against and 2 for.

"limited evidence of carcinogencity from studies in humans" or "sufficient evidence of carcinogencity from studies in experimental animals". (DBD at i, emphasis added.) It is clear from the DBD, however, that evidence was completely lacking concerning the nature of the "talc" exposures in the ovarian cancer studies.

Although the opening Introduction in the DBD contains a statement that there is "evidence" from human and experimental animal studies of "talc" suggesting an association between exposure to non-asbestiform talc and cancer, other explicit statements in the DBD contradict that opening statement and make it clear that the composition of the talc in the ovarian cancer studies in humans is unknown, and that the statement in the Introduction regarding "evidence" is based on assumption rather than evidence:

- The Summary Statement of the conclusions reached by RG1 and RG2 (DBD at iii-vi) states only that the "evidence" from the ovarian cancer epidemiological studies relates to use of "cosmetic talc", and that the "talc" that was studied was "presumably cosmetic grade, but information on fibrous content is lacking". (Emphasis added.)

- The portion of the DBD discussing and evaluating the ovarian cancer epidemiological studies (pp. 23-29) addresses only exposure to "talcum powder" or "talc"; it never claims that any of the studies addressed "non-asbestiform talc" or "talc not containing asbestiform fibers".

- The DBD discussion of Human Cancer Studies (sec. 3) concludes with a statement which makes it perfectly clear that the conclusions reached by RG1 and RG2 were based on assumption rather than evidence (while it equates assumption with evidence):

> Neither occupational studies conducted outside of the talc and pottery industries nor the extensive literature concerning cancer and perineally applied talcum powder [the 17 ovarian cancer epidemiological studies] provide any characterization of talc mineralogy or morphology that could be used to determine the effects of different kinds of talc. However, because of the widespread contamination of talc and commercial talc products with asbestiform materials, it must be assumed that "talc" without further specification of mineralogy or morphology may contain asbestos fibers. The weight of the evidence thus indicates that it would be prudent to regard such undifferentiated talc materials as carcinogenic. (At p. 28, emphasis added.)
>
> The final sentence in this section of the DBD states, "the evidence from studies of ovarian cancer suggests that talcum powder is a carcinogen." (At p. 29, emphasis added.)

These statements and conclusions totally lack supporting evidence and are incongruent with a recommendation to list talc not containing asbestiform fibers.

- "Undifferentiated talc materials" and "talcum powder" were not proposed for listing. The listing proposals differentiated clearly between talc containing asbestiform fibers and talc not containing asbestiform fibers. The above statements conclude essentially that the "undifferentiated talc materials" involved in the epidemiological studies should be regarded as containing asbestos or asbestiform minerals. This conclusion therefore cannot

be regarded as relevant to a proposal to list talc not containing asbestiform fibers.

- The statement concerning "the widespread contamination of talc...with asbestiform materials [including asbestos]" does not concern current cosmetic talc products. No support is given for this statement, and it is contradicted by other portions of the DBD. Those other portions of the DBD make clear that any evidence of such contamination was obtained during the 1970s and earlier, and that since then it appears than any such contamination has been eliminated by stricter industry purity standards. The following relevant statements appear in the DBD:

  - "Although talc's can be virtually free of fibrous materials, they also have been reported to contain asbestos fibers in quantities sometimes constituting almost half the total product weight (Dement and Zumwalde 1979). Surveys published in the late 1960s and 1970s reported that talcum powders contained measurable amounts of chrysotile, tremolite, and anthophyllite fibers that may be of asbestiform nature (Rohl et al. 1976). However, the purity of cosmetic talc appears to have improved as a result of voluntary guidelines proposed by the cosmetic industry in 1976 (see Section 2)." (At p. 5, emphasis added.)

  - Section 2, as indicated above, contains the following information: "Under the voluntary guidelines initiated in 1976, the CFTA [sic– CTFA, Cosmetic, Toiletries, and Fragrance Association] stated that all cosmetic talc should contain at least 90% platy [i.e., non-fibrous] talc that is free of detectable amounts of fibrous minerals, including asbestos (Harlow and Hartge 1995, Gilbertson 1995, Zazenski et al. 1995)." (At p. 15.)

  - The DBD states at the beginning, in describing the chemical composition of talc: "Cosmetic talc ... contains at least 90% talc mineral and no detectable asbestos." (At p. 3.)

On the other hand, there is no data cited in the DBD indicating that post-1970's cosmetic talc, and particularly present-day cosmetic talc, contains asbestiform fibers or asbestos.

The unsupported conclusion in the DBD that present-day talc must be assumed to contain asbestos fibers was highly prejudicial, since asbestos has been classified as a known human carcinogen.[2]

2. RG1 and RG2 erroneously considered talc to be similar to asbestos.

Talc, and particularly cosmetic talc not containing asbestiform fibers, is very distinct from asbestos, both mineralogically and chemically.[3] The DBD, however, represented them as similar. It states:

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[2] When read exactly, the above-quoted summary of the evidence from studies in humans at page 28 of the DBD actually states that it must be "assumed" that undifferentiated talc "may" contain asbestos. Such an incredibly tenuous statement cannot support a listing recommendation or decision. In overall context, it appears that the statement concludes that cosmetic talc should be regarded as if it contains asbestos.

[3] See Zazenski, R. et al., "Talc: Occurrence, Characterization, and Consumer Application", *Regul. Toxicol. Pharmacol.* 21:218-29 (April 1995); Zazenski, R., "The Commercial Significance of Talc", *Comments Toxicol.* 6(5): 313-26 (1998); See J. Addison comments in NTP- BSCS Dec. 15 transcript, pp. 221–224.

"Talc was suspected of being a risk factor for ovarian cancer based on its mineralogical and chemical similarity to asbestos...." (At p. 24, emphasis added).

"An association of ovarian cancer with genital exposure to talc is biologically plausible, given the evidence that both talc and asbestos, a close mineralogical relative, can be found in ovarian tissues." (At p. 28, emphasis added).

The DBD contains no support for these statements, and they are erroneous in associating talc not containing asbestiform fibers with asbestos. As with the unwarranted assumption that cosmetic talc not containing asbestiform fibers does contain asbestos fibers, these erroneous statements in the DBD were highly prejudicial for the RG1 and RG2 reviews, since asbestos is recognized as a human carcinogen.

3. RG1 and RG2 failed to address adequately the key issue of the human relevance of the NTP bioassay.

In the absence of adequate relevant evidence from studies in humans, the RoC listing criteria for the "reasonably anticipated" category require "sufficient" evidence from studies in experimental animals showing either tumors in multiple species or at multiple tissue sites. Findings are not considered "sufficient" if there are unresolved questions regarding the adequacy of the design, conduct, or interpretation of the study. Put another way, as indicated by the final sentence in the final explanatory paragraph of the criteria, the animal evidence will not be considered sufficient if there are reasons why the animal findings would not be reasonably anticipated to be relevant to human exposures.

In the case of talc not containing asbestiform fibers, RG1 and RG2 relied on a single animal experiment that found tumors at two sites in a single species. The DBD discussion of this animal evidence (in section 4), however, does not acknowledge that substantial questions had been raised, and not resolved, concerning the relevance of the findings for any reasonably anticipated human exposures to talc not containing asbestiform fibers. The DBD section on "Other Relevant Data" (section 6) contains some very abbreviated discussion of possible overload and impairment of clearance mechanisms, but it does not relate the discussion to human relevance and does not discuss other substantial questions that had been raised in the 1994 FDA/ISRTP workshop and related publications regarding the relevance of the animal tumor findings at both tissue sites. This section of the DBD concludes with the statement that "[t]he current data indicate that inhaled non-asbestiform talc is unlikely to pose a cancer risk to humans under exposure conditions that do not impair clearance mechanisms or cause chronic lung toxicity." (At pp. 71-72.) The DBD does not address whether any significant numbers of U.S. citizens currently do or do not experience such exposure conditions.[4]

There is no mention at all in the DBD of the carefully considered and very specific published consensus conclusions reached at the end of the 1994 workshop co-sponsored by FDA and the International Society for Regulatory Toxicology and Pharmacology. Some 20 scientists from Federal agencies, including NIEHS[5], participated, along with some 80 other experts. An express

[4] The RoC enabling statute authorizes listing of only substances to which a significant number of persons residing in the United States are exposed.

[5] RG1 is comprised of scientists from NIEHS. RG2, an inter-agency review group, also includes NIEHS scientists.

purpose of the workshop was to consider the human relevance of the 1993 NTP experimental animal study findings. The workshop concluded:

> In regard to the NTP talc bioassay in rodents, it 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 positive talc bioassay results in female F344/N rats are the likely experimental artifact and nonspecific 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.[6]

4. Neither RG1 nor RG2 made findings that the evidence from either studies in humans or in experimental animals was sufficient to satisfy the criteria for listing as "reasonably anticipated" to be a human carcinogen.

The DBD does not show that RG1 and RG2 considered the specific requirements of the listing criteria and made findings that those criteria were satisfied. This is in stark contrast to the deliberations of the RoC Subcommittee, which voted 8-2 against listing.

- The short summaries of the RG1 and RG2 findings (DBD pp. iii-vi) state that epidemiological studies showed "consistent evidence" of an increase in ovarian cancer in women who used "cosmetic talc". There is no finding for talc not containing asbestiform fibers, and there is no finding that the evidence in humans is "limited" (vs. inadequate).[7]

- The same short summaries state that RG1 and RG2 found the single experimental animal study provided "evidence" of carcinogencity. There is no finding that the evidence was "sufficient", and no indication that the two review groups attempted to apply the listing criteria to the evidence.

- The Introduction of the DBD (p. 1) states only that the proposal to list both forms of talc was based on evidence from human and animal studies of "talc" which "suggest an association" between non-asbestiform talc and cancer. This is a far cry from findings that a "causal interpretation" of the epidemiological evidence concerning non-asbestiform talc is "credible", or that the experimental animal evidence is "sufficient". The terms "suggest an association" are not to be found in the criteria, and indicate a significantly lower threshold of evidence than that required by the criteria.

- As discussed above, the section of the DBD evaluating the studies in humans (sec. 3) does not contain any findings whatever specific to talc not containing asbestiform fibers. The final conclusion in the evaluation is only that "the evidence from studies of ovarian cancer

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[6] "Talc: Consumer Uses and Health Perspectives", *Reg. Toxicol. Pharmicol.* 21/2:211-260, 215 (April 1995).

[7] "Limited" evidence requires a finding that a "causal interpretation is credible", not simply a finding that there was some degree of elevated relative risk in many of the studies. Evaluation of epidemiological studies for credibility of a causal relationship is far more complicated.

suggests that talcum powder is a carcinogen." (P. 29, emphasis supplied.) This conclusion also ignores the criterion of credible causal interpretation and any reference to a relevant category descriptor (e.g., "reasonably anticipated").

- The only relevant finding in the DBD section evaluating studies in experimental animals (sec. 4) is that the 1993 NTP rodent inhalation bioassay "provided evidence for carcinogencity of non-asbestiform talc". (P. 46.) Again there is no indication of an attempt to quantify the evidence as "sufficient" and explain the basis for that quantification in accordance with the listing criteria.

Based on the above, it is clear that RG1 and RG2 did not make reasonable evaluations and findings regarding the evidence supporting their recommendations to list talc not containing asbestiform fibers as "reasonably anticipated" to be human carcinogens. Therefore, those recommendations cannot be considered valid and cannot be given any weight in further reviews, recommendations, and conclusions regarding listing. If the RG1 and RG2 recommendations to list are considered valid and given weight despite not being in accordance with the listing criteria, a decision to list talc not containing asbestiform fibers in the 10th Report on Carcinogens would have to be considered tainted by reliance on those recommendations and would be arbitrary, capricious, an abuse of discretion, and otherwise not in accordance with law under the judicial review standards of the Administrative Procedure Act.

Fortunately, the RoC Subcommittee had the benefit of outside expert commentary and dialogue with outside experts that RG1 and RG2 did not have. Instead, RG1 and RG2 relied on information reflected in the DBD that was deeply flawed in key respects and which led them to insupportable conclusions. The RG1 and RG2 recommendations to list talc not containing asbestiform fibers as reasonably anticipated to be human carcinogens must therefore be disregarded, and the carefully-considered and well-informed recommendation of the RoC Subcommittee not to list should be followed. It is for just this sort of a situation that the RoC Subcommittee was established.

Thank you for your attention to these comments. We assume that they will be distributed to the NTP Executive Committee and other reviewers in connection with their further consideration of the proposal to list talc not containing asbestiform fibers in the 10th Report on Carcinogens.

Sincerely,

[redacted]

Daniel D. Harris
President
Luzenac America