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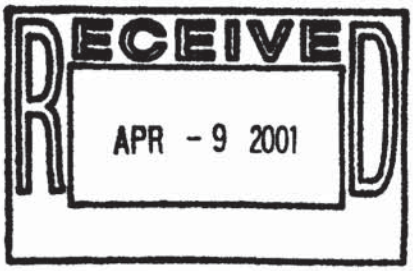

April 4, 2001

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

Dear Dr. Jameson:

Following are our comments on the proposal to list talc not containing asbestiform fibers in the 10th Report on Carcinogens, as requested in the *Federal Register* notice of March 5, 2001, 66 Fed. Reg. 13334 *et seq*.

At the outset, it should be noted that the very marked divergence between the voting by the two Federal agency review groups (RG1 and RG2) and the external peer review group (the RoC Subcommittee of the NTP Board of Scientific Counselors) on this particular listing proposal is highly unusual, and therefore it is important to examine carefully why such a divergence occurred. The two agency committees (RG1 and RG2) voted 6 to 1 and 7 to 1, respectively, to list talc not containing asbestiform fibers as "reasonably anticipated" to be a human carcinogen, while the external peer reviewers voted 8 to 2 against listing (not 7-3 as indicated in the *Federal Register* notice[1]).

We have reviewed the various review committee vote counts on all substances proposed for listing since the RoC Subcommittee came into existence in 1996. Among the 51 substances reviewed by the RoC Subcommittee, the subject talc listing proposal is the only one for which there

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[1] The *Federal Register* notice states erroneously that the vote was 7-3 against listing. A review of the transcript shows that 8 members voted against listing, including all three of the primary reviewers (Drs. Carpenter, Froines, and Medinsky), with one of the members, Dr. Smith, explicitly voting to defer. Dr. Smith's intent is clearly stated on page 354 of the transcript. The Chair polled the members after the vote, and Dr. Smith stated that in his view the ovarian cancer epidemiology studies had not been adequately addressed in several key respects, and therefore he wanted to defer the listing proposal. We informed Dr. Portier of NTP of this vote count error contained in the March 5 *Federal Register* notice in a March 1 letter.

has been a substantial degree of divergence between the agency review committees and the Subcommittee.[2] This degree of disagreement is even more remarkable when one considers that of the two Subcommittee members who agreed with the agency reviewers, one could not provide a rationale for his vote, and the other gave a rationale that conflicted with the record evidence presented in the Draft Background Document. (This is explained further below.)

The *Federal Register* notice requesting these comments contains an explanation for the RoC Subcommittee vote: "The 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 those studies might have been contaminated with asbestos." To the extent this statement might be taken as a full explanation of the Subcommittee's reasons for rejecting the listing proposal, it is incomplete and inaccurate. We have reviewed the full transcript of the Subcommittee's deliberations in reaching this conclusion. Three members of the Subcommittee stated that the felt the ovarian cancer epidemiologic studies were not relevant for this reason; however, for one of those members its was not the decisive factor[3], and other members of the Subcommittee gave other reasons for deciding that the ovarian cancer studies did not present evidence which allowed a credible interpretation of causal relationship. In addition, the Subcommittee also clearly regarded the single animal bioassay presented to support the proposed listing as inadequate (or "limited" in the listing terminology) due to serious questions concerning its relevance to humans.

Based on our review of the transcript, we are presenting below a more complete summary of the Subcommittee's reasoning for voting against the proposed listing of talc not containing asbestiform fibers as "reasonably anticipated" to be a human carcinogen. The Subcommittee concluded that (1) the ovarian cancer epidemiologic studies (as well as the occupational epidemiologic studies) did not, considering all relevant aspects of the studies, indicate that a causal interpretation was credible; and (2) that the single animal study asserted to support the proposed listing was "limited" rather than "sufficient" evidence.

Evaluation of The Studies of Ovarian Cancer in Humans (Epidemiology)

The Draft Background Document ("DBD") discussed 17 epidemiologic ovarian cancer studies, of which 16 were case-control studies, and the most recent, the 17th, was a large prospective cohort study (Gertig et al. 2000).

The DBD admitted that a "key challenge" with interpreting the epidemiologic studies was that they did not "provide any characterization of talc mineralogy or morphology that could be used

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[2] On only two other proposals has the RoC Subcommittee diverged at all from both agency review committees: saccharin and dioxin. On saccharin, the Subcommittee diverged from the agency committees by one vote; on dioxin by two votes (on re-review after initially agreeing with the agency committees by one vote). In two other cases, methyl ether and TCE, RG2 diverged from RG1, and the Subcommittee voted in agreement with the RG2 position.

[3] Medinsky, at 351-352.

to determine the effects of different kinds of talc." (At. 28.) The RG1 and RG2 deliberations, as recorded in the DBD, circumvented that critical issue by assuming that, because of "widespread contamination of talc and commercial talc products with asbestiform minerals", the talc in the epidemiologic studies "may contain asbestos fibers" and therefore "it would be prudent to regard such undifferentiated talc materials as carcinogenic." (DBD at 28, emphasis added.)

Both the Subcommittee members and public commenters noted that not only was an assumption not evidence, and that "undifferentiated talc" was not proposed for listing, but also that historical changes in the talc industry which were acknowledged in the DBD itself precluded such an assumption. The DBD noted that during the 1970s and prior thereto there was evidence that some talc was substantially contaminated with asbestos or asbestiform fibers; however, it also noted that in 1976 new industry standards were promulgated which appeared to have improved the purity of cosmetic talc, and that "talcs can be virtually free of fibrous materials". (At 4, 5.) The new industry standards promulgated in 1976 "stated that all cosmetic talc should contain at least 90% platy talc that is free of detectable amounts of fibrous minerals, including asbestos." (DBD at 15.) It appeared that all of the ovarian cancer studies involved use of cosmetic talc prior to 1976.

The summary of the voting rationale against listing provided in the March 5 *Federal Register* indicates that the only reason why the 8-member majority of the Subcommittee voted against listing was because "[t]he Subcommittee did not consider the ovarian cancer studies . . . because it was unclear if the talc used in these studies might have been contaminated with asbestos." (At 13337.) This statement is not accurate. While several members of the Subcommittee did indicate they would not consider the ovarian cancer studies to be relevant due to the great uncertainty about the composition of the talc exposures in the studies, the Subcommittee certainly gave careful consideration to all qualitative and quantitative aspects of those studies and determined that they did not consider a causal interpretation to be credible (paying careful attention to the listing criteria).[4] In the end, it was clear that the Subcommittee as a whole found that the epidemiologic evidence was beset with numerous problems weighing against listing, in addition to the talc composition problem.

Before summarizing those other problems, however, it is appropriate to discuss a further aspect of the talc composition issue. During the Subcommittee discussion, Dr. Portier of NIEHS broke in with a question for Dr. Zahm or Dr. Froines after hearing them discuss the historical issue of the composition of the talc exposures in the epidemiologic studies. He asked why the ovarian cancer studies would not support a "reasonably anticipated" listing as "limited" evidence from studies in humans because, under the terms of the listing criteria, "[a] causal interpretation is credible

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[4] Only three of the Subcommittee members who voted against listing clearly indicated that they would not consider the ovarian cancer studies relevant due to lack of information concerning whether the exposures contained asbestiform fibers. (Zahm at 285, 314-15, 324; Froines at 264; Bonney at 331-33.) Dr. Kelsey, one of the two members who voted in favor of listing, but who did not give a rationale, also indicated he had problems with weighing those studies due to the historical issue of possible contamination, and he was "in a quandry" and tended to favor deferral. (At 333-34)

. . . but . . . confounding factors could not be adequately excluded."[5] Dr. Zahm answered by explaining, in essence, that she felt that the language in the criteria about confounding simply did not apply in this instance because the very definition of the exposure proposed for listing did not allow for contamination with asbestiform fibers or asbestos; and, additionally, there had never been opportunity to consider the potential extent of confounding.[6] In a continuation of discussion on this point, Dr. Smith (another epidemiologist on the panel along with Dr. Zahm) explained that he simply could not "pass judgment" on the ovarian cancer studies due to lack of information about whether the exposures were contaminated with asbestos, the degree of the contamination, and the degree to which such contamination might have been translocated to the ovaries. (At 317-20, 350.)

But the problem of exposure definition and the unknown composition of the talc in the ovarian cancer studies was not the only reason expressed by the Subcommittee members for finding the ovarian cancer studies inadequate to support listing. Those other reasons, summarized below, were expressed by four members other than the three who indicated their view that the ovarian cancer studies could not be considered due to possible contamination of the talc with asbestos or asbestiform fibers.

- lack of statistical significance and small numbers of subjects: Dr. Medinsky considered it significant that 8 of the 17 studies indicating a positive association did not show statistically significant results.[7] Dr. Pelling noted that many of the case-control studies involved small numbers of patients, in comparison to the large number of subjects in the non-positive cohort

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[5] It is interesting that the possibility of confounding of cosmetic talc exposures by asbestos or asbestiform fibers in the ovarian cancer studies was not discussed at all in the DBD. (See DBD sec. 3.2.5, "Confounding and other potential biases", at 27-28.)

[6] The language of the criteria – "confounding factors could not be adequately excluded", and particularly the word "adequately" – implies that there must have been some opportunity to consider and attempt to make a judgment about the extent to which confounding factors might have influenced the findings. Drs. Zahm and Smith appeared to be pointing out that there was no information at all available on the extent of confounding, and consequently there was no opportunity to pass judgment on whether confounding had or had not been adequately excluded as an explanation for positive findings. This point is in addition to Dr. Zahm's inarguably correct point that the definition of the exposure proposed for listing, and which they were reviewing – talc not containing asbestiform fibers – did not allow for any confounding due to the presence of asbestiform fibers.

[7] RG1 and RG2 regarded only 14 studies as indicating positive associations. (DBD at 28.) Of these, the number of ovarian cancer studies lacking statistically significant findings would be 11 rather than 8 if one counted studies in which some findings appeared statistically significant while others did not, but the findings for the most-exposed subgroups were positive. (DBD Table 3-3, pp. 33-42.)

study.[8] (At 352.) Dr. Smith thought that the positive findings in the case-control studies were likely to be due to chance (at 318), and he noted that even with regard to the histologic subtype of serous invasive cancer in the nurses cohort study, the lower confidence limit was 1.0. (At 353.)

- non-positive findings in the recent large nurses cohort study: Drs. Medinsky and Pelling considered it significant that the largest and most recent study, the nurses cohort study by Gertig et al. (2000) was essentially non-positive. (At 278, 352.)

- lack of dose-response trend: Drs. Medinsky and Smith considered significant the obvious absence of a dose-response relationship in the ovarian cancer studies, including the nurses cohort study. (At 278, 354; and see DBD Table 3-3 at 33-42.)

- lack of biological plausibility: Drs. Carpenter, Medinsky, and Smith noted the conflicting or weak evidence for the biological plausibility of ovarian cancer caused by external application of cosmetic talc and translocation of the talc to the ovaries. (At 166-68, 275, 278-79, 319.)

Evaluation of the Single Experimental Animal Study

Even if the epidemiologic evidence is evaluated as not supporting a credible causal interpretation, the RoC listing criteria allow for a listing in the "reasonably anticipated" category if there is "sufficient" (rather than "limited") animal evidence. In the case of the listing proposal for talc not containing asbestiform fibers, there was a single NTP rodent bioassay that was proposed as a basis for the listing in addition to the epidemiologic studies. The Subcommittee, however, clearly thought the bioassay evidence was "limited" rather than "sufficient" because of serious questions regarding the relevance of the findings to any reasonable human exposures[9].

Neither of the two Subcommittee members who voted in favor of listing indicated clearly that they thought the animal evidence was sufficient; however, it appears that Dr. Kelsey, one of the two who voted in favor of listing, might have been influenced by a plainly incorrect reading of the listing criteria espoused by Dr. Yamasaki (a non-voting member of the Subcommittee). Dr. Yamasaki argued that the criteria require acceptance of the animal data as "sufficient" unless there is "compelling" evidence that the mechanism that caused cancer in the animals does not operate in humans, and the evidence here was not compelling. He based his argument on the last sentence of the explanatory paragraph at the end of the criteria, which states: "For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals but there are

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[8] While Dr. Pelling did not give numbers, Table 3-3 (pp. 33-42) in the DBD shows, for example, that 7 of the 16 case-control studies involved less than 200 cases. The nurses cohort study involved 78,630 subjects. Of the two case-control studies that RG1and RG2 considered to be non-positive, one involved 189 cases and the other involved 499 cases.

[9] E.g., Carpenter at 275, 311; Medinsky at 279; Zahm at 286; Froines at 310, 351.

compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans." This sentence does not, however, as Dr. Yamasaki asserted, state that there must be compelling evidence that the animal mechanism does not operate in humans in order to classify a substance as reasonably anticipated; rather, it says that such a situation would be one example of a situation where the substance would not be considered reasonably anticipated to cause cancer in humans. Nevertheless, NTP staff who were present did not correct Dr. Yamasaki's assertion, and Dr. Kelsey later indicated he accepted, and was influenced by, Dr. Yamasaki's position.[10]

Lack of a Cogent Rationale for the Two Subcommittee Votes in Favor of Listing

Dr. Kelsey and Dr. Moure-Eraso were the two Subcommittee members who voted in favor of listing, and neither provided any cogent rationale for their votes. Moreover, it was apparent from his comments during the Subcommittee discussion that Dr. Kelsey was right on the line (or, as he put it, "in a quandry") about which way to vote, and was favoring deferral.

After the vote, the Chair, Dr. Frederick, asked Drs. Kelsey and Moure-Eraso (as well as Dr. Smith) to provide a rationale for their votes.[11] Dr. Kelsey did not provide a rationale, stating only "I would have supported listing it as reasonable." (At 354.) Dr. Moure-Eraso gave a rationale that clearly conflicted with the evidence presented in the DBD. He stated:

> I believe that the evidence for ovarian cancer, for me, is adequate to classify it as reasonable carcinogenic [sic]. I believe that even if we were to, if it would be possible to find what is the exact composition of the talc in this study, that it is small contaminations that I believe will be less than one percent on asbestos cannot really have cause for ovarian cancer. [Sic] I don't think there is anything in the record that will demonstrate that.

As Dr. Moure-Eraso noted, there is nothing in the record to support his opinion; but additionally, the DBD prominently presented contrary information. The DBD, which was the only record presented to the Subcommittee other than the public comments and the opening NIEHS staff presentation, stated that "talcs . . . have been reported to contain asbestos fibers in quantities sometimes constituting almost half the total product weight (Dement and Zumwalde 1979)." (DBD at 5.) The DBD also stated: "Talc may contain asbestiform fibers (tremolite, anthophyllite, and chrysoltile) in

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[10] "I don't find the animal data particularly compelling, although I agree with Dr. Yamasaki, there is no compelling reason to ignore it." (At 334, lns. 13-15.) Previously, Dr. Kelsey had indicated that he, like Dr. Smith, considered the ovarian cancer epidemiologic studies to be "problematic". (At 333-34.)

[11] Dr. Smith had also voted against the motion not to list, and was therefore also asked for his rationale. It was at this point that Dr. Smith explained that he voted against the motion not to list because he wanted to vote to defer. (At 354; and see also 322, 337-38, and 350.) Dr. Smith clearly did not vote in favor of listing.

total concentrations greater than the concentration of the talc mineral itself (Kleinfeld *et al.* 1973, 1974, Rohl and Langer 1974, all cited in IARC 1987a)." (DBD at 4.)

Thus, the RoC Subcommittee vote against any listing of talc not containing asbestiform fibers should be regarded as virtually unanimous. It might also be noted that the 8 RoC Subcommittee votes against listing were more than the votes in favor of listing in either the RG1 (6, with one dissent) or RG2 (7, with one dissent[12]).

Making Sense of the Extreme Divergence Between the RG1, RG2 Votes and the RoC Subcommittee Vote

There is no public transcript of the RG1 and RG2 deliberations; however, the Draft Background Document ("DBD") summarizes the evidence considered by RG1 and RG2 and their thinking. By comparing the DBD with the RoC Subcommittee transcript (including the public comments recorded in the transcript), one can discern with almost complete certainty the key areas of disagreement that resulted in the divergence:

- Asbestos contamination in the exposures involved in the ovarian cancer studies: Asbestos is classified as a "known human carcinogen". Despite acknowledgment in the DBD that the purity of talc might have improved since industry standards for asbestos-free talc were promulgated in 1976, RG1 and RG2 nevertheless assumed, without giving any support for the assumption, that there continued to be widespread contamination of "talc" with asbestos, and therefore the "undifferentiated talc materials" involved in the ovarian cancer studies should be regarded as carcinogenic. (DBD at 28, sec. 3.3). Most of the RoC Subcommittee clearly could not accept this assumption. Moreover, RG1 and RG2 asserted that talc was a risk factor for ovarian cancer "based on its mineralogical and chemical similarity to asbestos" and was "a close mineralogic relative to asbestos", in addition to possible contamination of talc with asbestos, and it discussed how exposure to asbestos had been associated with ovarian cancers. (DBD at 24, 28.) In the RoC Subcommittee meeting, experts in mineralogy and talc explained how talc in no way resembled asbestos in either mineralogic or chemical traits, and during the meeting NIEHS staff clearly changed their position partially and conceded to the Subcommittee that "asbestiform fibers" should not be considered as including asbestos. (*E.g.*, at 338.) Therefore, it followed that talc not containing asbestiform fibers could not contain asbestos, as had been assumed by RG1 and RG2, and the

[12] The dissent in the RG2 (the inter-agency review committee), as described in the March 5 *Federal Register* notice ("animal data not sufficient and human data confounded because of the uncertainty of possible contamination of talc with asbestos"), was in line with the thinking of the RoC Subcommittee. The Federal agency which cast the dissenting vote in RG2 (and the scientist who cast the dissenting vote in RG1) is not known.

Subcommittee evaluated the ovarian cancer studies for their overall strength, using traditional evaluation criteria, without being influenced by the incorrect and extremely prejudicial notion that talc not containing asbestiform fibers should be considered to be either equivalent to, or contaminated by asbestos, a known human carcinogen.

- Relevance to humans of the 1993 NTP rodent bioassay: In the absence of even "limited" epidemiologic evidence to support listing as "reasonably anticipated", the listing proposal hinged on whether the single positive animal bioassay was regarded by the Subcommittee as "sufficient" rather than "limited" evidence under the listing criteria ("sufficient" animal evidence being required for listing as "reasonably anticipated" under such circumstances). Based on the *Federal Register* characterization of the RG2 dissenting vote as based in part on the opinion that the animal data were "not sufficient", it appears that RG2, and probably also RG1, regarded the animal data as sufficient. The RoC Subcommittee on the other hand clearly did not accept this alternative basis for listing. The basis for this disagreement appears to have arisen from the fact that the Subcommittee had the benefit of discussion and information that was not made available to RG1 and RG2. The Subcommittee discussed in great detail the issue of whether the tumors found in the animal bioassay were the result of non-specific dust overload, and therefore the findings were not specific to talc and were not relevant to reasonable human exposures. The Draft Background Document, however, indicates that there was absolutely no discussion of these issues by RG1 and RG2. The section of the DBD which addresses the animal data is devoid of any such discussion, and contains only the curt and cryptic acknowledgment that "the relevance of these results to humans has been questioned (Goodman 1995, Oberdörster 1995, Zazenski et al. 1995)." (DBD at 67.) In fact, the DBD, and therefore also the RG1 and RG2 deliberations, clearly failed to acknowledge the extensive consideration of the issue of human relevance of this particular animal evidence, and the conclusions reached, in a large workshop held in early 1994 by FDA and the Society for Regulatory Toxicology and Pharmacology. Eighteen FDA scientists and one from NCI participated in the workshop. The published "unanimous assessment" from the concluding discussion in the workshop was that the 1993 animal bioassay results could not be considered relevant to human exposures and risk:

> 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.[13]

Conclusions

The talc deliberations demonstrate the wisdom of creating the RoC Subcommittee as an external FACA review group in 1996. The Subcommittee obtained the benefit of expert outside commentary on the mineralogy of talc vs. asbestiform fibers and asbestos, and it was informed of the deliberations of the 1994 joint FDA/ISRTP workshop on consumer exposures to talc and had the opportunity to thoroughly discuss the issues of human relevance raised in the workshop. It is also quite likely that the Subcommittee engaged in lengthier and more critical deliberation than RG1 and RG2. RG1 and RG2, on the other hand, erroneously thought that talc was similar to asbestos, unjustifiably assumed that talc continues to be contaminated with asbestos and asbestiform fibers, and failed to review the findings of the 1994 FDA/ISRTP workshop or discuss the issue of human relevance of the animal study.

The factors weighing significantly in the RoC Subcommittee 8-2 vote against listing can be summarized as follows:

- An assumption that modern-day cosmetic talc is contaminated with asbestos and asbestiform fibers is not supportable, and the ovarian cancer epidemiologic studies could not support the proposed listing because it is not known whether the subjects were exposed to talc containing asbestos or asbestiform fibers or to talc not containing asbestiform fibers.

- Talc is not mineralogically or chemically similar to asbestos. Even the NTP staff accepted this position, which was contrary to the position taken in RG1 and RG2 and undoubtedly had a strong impact on the conclusions of those two earlier review groups.

- The ovarian cancer case-control studies were statistically weak and unconvincing, while the recent large prospective cohort study was regarded as non-positive.

- The ovarian cancer studies failed to show a dose-response relationship.

- The ovarian cancer studies lacked biological plausibility.

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[13] "Talc: Consumer Uses and Health Perspectives", *Reg. Tox. Pharm.* vol. 21, no. 2, pp. 211-260, 215 (April 1995). This publication and its conclusions apparently were not unknown to NIEHS staff who prepared the DBD, since one of the articles published as part of the workshop proceedings, Zazenski *et al.* (at 218-29), was referenced in the DBD. (At 67, 86.)

- The single positive animal bioassay was extremely weak, and could only be regarded as "limited" (rather than "sufficient") evidence for listing, due to apparent lack of relevance to exposures experienced by any portion of the human population.

Because of the unprecedented extreme divergence between the votes of RG1/RG2 and the RoC Subcommittee, the proposed listing for talc not containing asbestiform fibers will be the first opportunity for NTP and the Secretary of HHS to demonstrate that the RoC Subcommittee external peer review and public comments are a meaningful part of the RoC review process and fulfill the function envisioned when the Subcommittee was created. If the RoC Subcommittee findings are not accepted in this instance, the Subcommittee might as well be dissolved.

Sincerely,

[redacted]

Jim J. Tozzi
Member, CRE Board of Advisors