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November 29, 2000

Via FedX

Dr. Mary S. Wolfe
Executive Secretary
RoC Subcommittee of the NTP
Board of Scientific Counselors
NIEHS
Building 101, Room A322
111 TW Alexander Drive
Research Triangle Park, NC 27709
(919) 541-3971

Dear Dr. Wolfe:

Attached are written comments for distribution to the individual members of the RoC Subcommittee of the NTP Board of Scientific Counselors for consideration prior to their public review of substances nominated for listing in the 10th Report on Carcinogens on December 13-15 in Washington, DC. Public comment on the proposed listings was solicited in the *Federal Register* notice of October 17, 2000, 65 Fed.Reg. 61352.

Our comments focus solely on the proposed listing for non-asbestiform talc (*i.e.*, talc not containing asbestiform fibers).

I am submitting these comments on behalf of the Center for Regulatory Effectiveness ("CRE"). CRE is not affiliated with any particular industry, company, or other entity. It was established in 1996 at the urging of Members of Congress to assist in analysis of federal regulatory and quasi-regulatory issues likely to be of interest to Congress, particularly proposed rules that would require Congressional review under the Congressional Review Act. Since then, it has expanded its mission into related areas. Of particular relevance to this proceeding is its goal of reviewing federal programs that involve dissemination of information to the public to ensure that such information is of the highest quality, and utility to the public, in accordance with the goals of Congress in enacting the data quality provisions of the Paperwork Reduction Act of 1995. CRE has no members, but it receives, from time to time, financial support, services in kind, and work product from trade

associations and private firms. Consequently, at any one time, CRE benefits from the input or advice of literally hundreds of small and large firms.

I have also registered to make an oral presentation in connection with the RoC Subcommittee's review of non-asbestiform talc at the December 13-15 meeting.

Sincerely,

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Attachment

November 29, 2000

COMMENTS BY CRE ON THE LISTING PROPOSED FOR TALC NOT CONTAINING ASBESTIFORM FIBERS IN THE *REPORT ON CARCINOGENS, TENTH EDITION*

Presented to the RoC Subcommittee of the
NTP Board of Scientific Counselors
for Consideration at its Peer Review Meeting
December 13-15, 2000, in Washington, DC

Introduction

The Center for Regulatory Effectiveness ("CRE") has been closely monitoring and commenting on the RoC program since the advent of reviews for the 9th RoC. (See the CRE website at www.thecre.com.) CRE's interest in this program stems from the fact that Congress intended the Reports to be informative to members of the general public, rather than a document for the scientific community. Therefore, CRE has been particularly interested in how the RoC and its review committees have handled nominations for exposures of interest to large segments of the U.S. public, as opposed to exposures which are primarily of occupational interest.

CRE's interest is based on the realistic appreciation that the Reports are documents which can substantially impact consumer choices and behavior – in effect, operating as a kind of indirect regulation of the listed exposures in contrast to direct regulation. Such indirect regulation has the potential to conflict with safety or risk assessments made by federal agencies, such as FDA or EPA, to whom Congress has delegated responsibility for direct regulation.

More broadly, CRE has an established interest in seeing that the Congressional mandates concerning the quality of information disseminated to the public by government agencies, contained in the Paperwork Reduction Act of 1995, are fully implemented. As expressed in the stated Congressional goals of that Act, agencies should ensure that the information they disseminate is accurate, up-to-date, objective, clear, and useful to the public.

CRE also has an established interest in ensuring that federal agencies adhere faithfully to their own rules in developing and disseminating information to the public.

After making numerous recommendations for improvement in the RoC program during preparation of the 9th RoC (some of which have been adopted, and others not), CRE has continued

to monitor the program during preparation of the 10th RoC. In doing so, it has found that some of the same substantial deficiencies it commented on during the 9th RoC reviews have persisted into the current 10th RoC reviews. In reviewing the various 10th RoC Draft Background Documents and public comments, CRE has been struck particularly by glaring deficiencies in assessment of the listing proposal for non-asbestiform talc. Since exposure to non-asbestiform talc, particularly in its cosmetic form, is of wide consumer interest, CRE has chosen to review and comment directly on this proposed listing. In doing so, CRE has concluded that the listing proposals by RG1 and RG2 reflected in the Draft Background Document ("DBD") contain a number of fatal flaws which make it impossible for the RoC Subcommittee members, and subsequent reviewers, to concur with the proposed "reasonably anticipated" human carcinogen listing. These fatal flaws, discussed in more detail below, include:

1. In its assessment of the evidence from studies in humans, the DBD fails repeatedly and at critical points to differentiate between evidence concerning asbestiform and non-asbestiform talc, and effectively concedes that it is not possible to determine whether the human studies relied on involved exposures to non-asbestiform talc. In place of scientific evidence regarding whether the human exposures were to non-asbestiform talc, the DBD substitutes assumption and policy for scientific evidence, contrary to Congressional intent and the weight of the evidence.

2. The DBD recommendations for listing of non-asbestiform talc as "reasonably anticipated" to cause cancer in humans are based on a combination of (a) conclusions regarding the relevance of the epidemiologic evidence, and (b) conclusions regarding evidence from animal studies. The epidemiologic evidence is admitted to be inadequate, and there is no finding of "sufficient" animal evidence consistent with the listing criteria and established interpretations of the criteria. With regard to (b), the DBD omits discussion of the conclusion reached by FDA scientists that the evidence from the single NTP animal study relied on is not relevant to human exposures.

3. The DBD treats "reasonably anticipated" as equivalent to "possibly", "suggested", or "may", contrary to the plain meaning of "reasonably anticipated" and judicial precedent.

Detailed Discussion

1. <u>The DBD presentation of evidence from studies in humans demonstrates, on its face, that the epidemiologic evidence is inadequate to support a listing for non-asbestiform talc, because it cannot differentiate non-asbestiform talc from talc containing asbestiform fibers in its assessment.</u>

The listing nominations, as presented in the April 5, 2000, *Federal Register* notice (65 Fed. Reg. 17899), presented separate nominations for "Talc (Non-Asbestiform)" and "Talc (Containing Asbestiform Fibers)". In describing the separate exposures, only non-asbestiform talc was described as being used in cosmetic products.

The RG1 and RG2 listing recommendations contained in the DBD contain separate recommendations for asbestiform and non-asbestiform talc. While the two groups differed on the appropriate listing for asbestiform talc, they concurred on recommending to list talc not containing asbestiform fibers as "reasonably anticipated to be a human carcinogen", based on epidemiologic studies of ovarian cancer in woman who used "cosmetic talc" and a single animal study.

The summaries or the RG1 and RG2 evaluations of the evidence from studies in humans, however, immediately evidence a fatal flaw of failing to differentiate asbestiform from non-asbestiform talc. In summarizing this evidence supposedly supporting a listing of non-asbestiform talc as "reasonably anticipated" to cause human cancer, both review groups refer to the studied exposure simply as "cosmetic talc", then "talc", and then comment that the substance was "(presumably cosmetic grade, but information on fibrous content is lacking)." (At iii and v, emphasis added.) In other words, it is not known whether the exposure in those epidemiologic studies was in fact cosmetic talc not containing asbestiform fibers. This failure to differentiate the evidence is all the more surprising because, immediately following the above statements regarding the epidemiologic evidence, both groups differentiate between talc with asbestiform fibers and non-asbestiform talc in summarizing the evidence from studies in animals. This deficiency, and confusion, is carried forward in the Introduction to the DBD (p. 1) in the statement that "[a] number of human and experimental animal carcinogenicity studies of talc have been published since the IARC listing [decision in 1987 to classify non-asbestiform talc as having inadequate evidence of carcinogenicity] . . . that suggest an association between exposure to non-asbestiform talc (including cosmetic talc) and cancer risk in humans." (Emphasis added.)

The DBD then proceeds to explain that cosmetic talc may, in the 1960s and 1970s, have contained significant quantities of asbestiform fibers, but that currently such talc may be free of such contamination. In the section on "Asbestiform talc", the DBD states:

> Although talcs 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 5. In the portion of Section 2 ("Human Exposure") apparently referred to in the above quotation, the DBD, after noting that the FDA has considered talc as GRAS (Generally Recognized as Safe) for use in cosmetics, states:

> Under the voluntary guidelines initiated in 1976, the CFTA [sic[1]] stated that all cosmetic talc should contain at least 90% platy talc that is free of detectable amounts of fibrous minerals, including asbestos . . . .

At 15.

As is apparent from the two separate nominations and the discussion in the DBD, the distinction between talc containing and not containing asbestiform fibers is critical. "Talc" without contamination with asbestiform fibers, particularly that used for cosmetic purposes, has unique physical and chemical characteristics that distinguish it from asbestiform fibers. Basically, talc is a platy material, a hydrous magnesium silicate, with unique softness and lubricating qualities due to the ability of the platy structures to slide easily over each other. Asbestiform fibers, on the other hand, lack these qualities and are fibrous, rather than platy, materials with different chemical/mineralogical compositions. As stated in the DBD: "'Asbestiform habit' refers to the unusual crystallization habit of a mineral in which the crystals are thin, hairlike fibers. . . . Asbestiform describes a special type of fibrosity. . . . In particular, the term 'asbestiform' has been used in a variety of ways in the past, sometimes applying only to asbestos or to fibers that look like asbestos." At 4-5.

The DBD discussion of possible mechanisms of carcinogenicity for asbestiform and non-asbestiform talc (pp. 65-72) illustrates the lack of relevant evidence on mechanism for non-asbestiform talc, while emphasizing that the probable mechanism for asbestiform talc carcinogenicity is dependent on the fibrous structure of the asbestiform content.

In contrast to the ambiguous and conflicting summarization of evidence concerning non-asbestiform talc, the DBD is very clear about the asbestiform nature of the evidence supporting the recommendations for listing asbestiform talc. The RG1 and RG2 summaries state that "[s]tudies of facilities where the talc was <u>known</u> to have contained" asbestiform fibers give the strongest evidence of risk. (At iii and v, emphasis added). The RG1 summary adds the statement that "[t]hese studies are supported by the prior listing of asbestos as a known human carcinogen in the Report on Carcinogens (1980)." (At iii.)

The above discussion is but a prelude to a key portion of the DBD demonstrating the lack of evidence for listing non-asbestiform talc. In section 3.3, pp. 28-29, which concludes the section on evidence from studies in humans, titled "Talc containing asbestiform fibers and talc not containing asbestiform fibers", the DBD admits this lack of human evidence, but nevertheless proceeds to surmount this insurmountable obstacle to listing by employing both an assumption about the current composition of (apparently all) talc and recommending a listing for an exposure that has not even been nominated – namely "undifferentiated talc" – when the formal listing nominations require differentiation. In effect, the DBD concludes that all forms of talc should be regarded as asbestiform,

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[1] Presumably this should be CTFA, the Cosmetic, Toiletry & Fragrance Association.

unless they really are non-asbestiform! After concluding that evidence from studies of asbestiform talc exposures in the talc mining and milling industries indicates that talc containing asbestiform fibers is carcinogenic, the DBD goes on to state:

> Neither occupational studies conducted outside of the talc and pottery industries nor the extensive literature concerning cancer and perineally applied talcum powder 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 minerals, 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 28, emphasis added.

As discussed above, the DBD recognizes that there are commercial talcs, particularly ones used in cosmetic products, that may be virtually free of asbestiform fibers, and that whatever information there was on "widespread contamination" with asbestiform fibers comes from the 1960s and 1970s and prior to the time the industry took steps to ensure that consumer talc would not contain asbestiform fibers. No scientific support is cited for such an "assumption" of current widespread contamination; and assumptions are not "evidence". Perhaps the most noteworthy aspect of this quoted DBD statement is the frank admission that the epidemiologic studies on cosmetic talc are inadequate to serve as evidence pertinent to assessing the effects of non-asbestiform talc.

The use of assumptions and policy (i.e, "prudence") is also in conflict with recorded Congressional intent concerning preparation of the Reports on Carcinogens. The statements of legislative intent make it clear that the listings in the Reports are to be based on "data" and "reasonable grounds", and there is no reference to employment of assumptions or policy.[2]

This human evidence section of the DBD then proceeds to discuss the occupational studies in humans in which there was exposure to non-asbestiform talc (also confusingly referred to as "talc that did not contain asbestos"). The DBD concludes that those studies are not adequate to support any conclusions about the carcinogenicity of non-asbestiform talc. However, the DBD then surprisingly in effect restates its unsupported position that "undifferentiated talc" should be regarded as carcinogenic: "In contrast [to the occupational studies involving non-asbestiform talc], the evidence from studies of ovarian cancer suggests that talcum powder is a carcinogen." (At 29, emphasis added.) There is no nomination pending for "talcum powder", only distinct nominations for asbestiform talc and talc not containing asbestiform fibers.

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[2] See H.R.Rep. No 1192, 95th Cong., 2d Sess. at 28 (May 15, 1978); statement of Mr. Rogers in Cong. Rec.- House, Oct. 10, 1978, at 34938; and the Joint House-Senate Comparative Summary and Explanation in Cong. Rec. - House, Oct. 14, 1978, at 38657.

Consequently, based on the analysis presented in the DBD, the conclusion is inescapable that there is not adequate scientific evidence from studies in humans to support listing talc which does not contain asbestiform fibers, whether used in cosmetics or otherwise, as "reasonably anticipated" to cause cancer in humans.

2. Since the evidence from studies in humans is admitted to be inadequate, the only support for a listing of non-asbestiform talc is a single controversial animal study, and the discussion and conclusions in the DBD are not adequate to show compliance with the listing criteria. In addition, the DBD omits discussion of the conclusions reach by FDA that the single animal study is not relevant for determining risk from realistic human exposures.

The criteria for listing in the "reasonably anticipated" category are set out at page i of the DBD. Since, as established above, the DBD concedes that the evidence from studies in humans cannot be assessed for relevance to listing non-asbestiform talc, under the criteria the proposed listing must be supported by "sufficient" evidence from studies in experimental animals which shows, as relevant here, tumors in "multiple species, or at multiple tissue sites".

The DBD relies on only a single animal study, and neither the RG1 nor RG2 summary in the DBD contains a finding that there was "sufficient" evidence from that study in experimental animals, as required by the criteria; instead, both summaries simply state that there is "evidence" of carcinogenicity from a "study" in experimental animals. (At iii and v.)[3] The Introduction to the DBD (p. v) contains the same ambiguous statement. Likewise, the extended discussion of the study in Section 4 of the DBD does not contain a summary evaluation of the study as providing "sufficient" evidence to support a "reasonably anticipated" listing; instead, as in the RG1 and RG2 summaries and the Introduction, it simply states that the study provides "evidence" for carcinogenicity. (At 46.) A similarly ambiguous statement is made in Section 6, in the portion concerning possible mechanisms of action. The DBD states:

> The NTP (1993) concluded that there was some evidence of carcinogenic activity of non-asbestiform, cosmetic-grade talc in male F344/N rats, based on an increased incidence of pheochromocytoma of the adrenal gland. There was clear evidence of carcinogenic activity in female F344/N rats, based on increased incidences of alveolar or bronchiolar adenoma and carcinoma of the lung and pheochromocytoma of the adrenal gland. However, the relevance of these results to humans has been questioned (Goodman 1995, Oberdörster 1995, Zazenski *et al.* 1995). . . .
>
> Lung tumors were not induced in male rats or in male or female mice in the NTP (1993) study. . . .

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[3] While the single "study" referred to in these statements is not specified, it is obviously the 1993 NTP inhalation study in rats and mice, referred to in the DBD as "NTP 1993".

(At 67, emphasis added.) In brief, there is only one study showing increased tumorigenicity in a single species of animal (rat), with "some evidence" for adrenal tumors, and "clear evidence" for lung/bronchial tumors, although it is acknowledged that some experts regard the evidence as not relevant to humans. Since the listing criteria for the "reasonably anticipated" category require "sufficient" evidence in either multiple species or at multiple tissue sites, the DBD does not contain a finding that the criteria are satisfied.

To examine this issue of whether the criteria could be considered satisfied by these sorts of conclusions regarding evidence of tumorigenicity in a single study of a single species at two tissue sites, one must determine whether the evidence is "sufficient" for both sites, as that term is used in the listing criteria. Although the listing criteria do not define the term "sufficient", the term has acquired recognized meaning through established practice. The term "sufficient" is used to describe the necessary degree of evidence in both the IARC criteria and the RoC criteria. The 7th RoC (1994), in discussing the relationship between the RoC criteria and the IARC criteria, commented that "[a]lthough the IARC and the Annual Report's[4] schemes do not exactly correspond to one another, the Annual Report's scheme and associated degrees of evidence are based on IARC's classification scheme and degrees of evidence." At 6. The revisions to the RoC criteria in 1996 retained the term "sufficient" without any indication of change in meaning. The Preambles to the IARC Monographs contain a discussion of how animal studies should be evaluated, which indicates that "sufficiency" requires that a study be "adequate", and that determinations of adequacy must take into consideration, among other issues, "how clearly the agent was defined", "whether the dose was adequately monitored, particularly in inhalation experiments", and "whether the doses and duration of treatment were appropriate". (Section 9(a).) The term "sufficient" is also defined by IARC in a manner which casts light on the "multiple tissue sites" portion of the revised RoC criteria. The IARC definition states: "Exceptionally, a single study in one species might be considered to provide sufficient evidence of carcinogenicity when malignant neoplasms occur to an unusual degree with regard to . . . site . . . ." Apparently more relevant, however, is the IARC definition of the term "limited evidence" in connection with animal experiments, since "limited" is considered to be not "sufficient". IARC considers animal evidence to be "limited" rather than "sufficient" if "there are unresolved questions regarding the adequacy of the design, conduct, or interpretation of the study."

As indicated by the DBD in the quotation above from page 67, there are clearly significant "unresolved questions regarding the adequacy of the design, conduct, or interpretation" of the 1993 NTP animal study for determining its relevancy to humans. In fact, the DBD eventually concludes that the evidence should not be considered relevant to humans under any exposure conditions that could be reasonably anticipated:

> The 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 71-72.

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[4] A 1993 legislative amendment converted the RoC from an "Annual Report" to a biennial report.

An RoC conclusion that the NTP animal study should be considered relevant to human risk under reasonably anticipated exposure conditions would also apparently conflict with conclusions reached by FDA personnel who have legislative responsibility for direct regulation of unsafe ingredients in cosmetics under the Food, Drug and Cosmetic Act. Although it is not referred to or discussed in the the DBD, in 1994, as a result of concerns regarding the 1993 NTP animal study, the FDA and the International Society for Regulatory Toxicology and Pharmacology co-sponsored a workshop to discuss the study and see whether they could arrive at any consensus views on how it should be interpreted. Twenty FDA scientists participated, along with numerous scientists from academia, industry, cancer research institutions, NIEHS, NCI, and other organizations.[5] At the beginning of the workshop, Dr. John Bailey, Director of FDA's Office of Cosmetics and Colors, presented the "Introduction: Overview – Scope of the Workshop", in which he stated:

> . . . I think it is reasonable to expect by the end of the workshop to have a discussion or even to reach a consensus of the many scientific and medical experts that are participating in and attending this meeting about the relevance of the recent reports to the safety of talc to human health risks.

Id. at 216. Indeed, the Executive Summary prepared by the Rapporteur, Dr. Jelleff Carr, explains the consensus that was reached:

> A final panel included most speakers and other experts and was able to reach an unanimous assessment of the workshop. 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 excesses at the low doses, and because of the clear biological 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 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.

Id. at 215. These published conclusions and related papers should have been referenced and discussed in the DBD, and should certainly be considered by the RoC Subcommittee in evaluating whether the NTP bioassay constitutes "sufficient evidence" for purpose of supporting a listing of non-asbestiform talc as "reasonably anticipated" to cause cancer in humans.

3. <u>The DBD treats "reasonably anticipated" as equivalent to "suggested", or "may", contrary to the plain meaning of that phrase, Congressional intent, and judicial precedent.</u>

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[5] The workshop proceedings and papers were published as "Talc: Consumer Uses and Health Perspectives" in *Reg. Tox. Pharm.* 21(2):211-60 (1995).

"Anticipated" is a synonym for "expected" or "predicted"; it indicates a reasonable degree of certainty, and is not equivalent to "may[be]". Nevertheless, key statements in the DBD assessments for non-asbestiform talc use terms such as "suggested" and "may". The Introduction of the DBD states that human and animal studies of "talc" "suggest an association" between non-asbestiform talc and cancer. (At 1, emphasis added.) The section on epidemiologic studies concludes that "[t]aken together, current case-control studies suggest an association of ovarian cancer with genital exposure to talc." (At 25, emphasis added.)[6] The same section concludes with the statement that "the evidence from studies of ovarian cancer suggests that talcum powder is a carcinogen." (At 29, emphasis added.)[7] "Talc may contain asbestiform fibers." (At 4, emphasis added.) "[I]t must be assumed that 'talc' without further specification of mineralogy or morphology may contain asbestos fibers." (At 28, emphasis added.)

During Congressional consideration of the RoC legislation, the original bill called for listing as either a "known" or "suspected" human carcinogen. However, in the final legislation, Congress decided to change "suspected" to "reasonably anticipated".[8]

Judicial precedent clearly distinguishes the term "anticipated" from "possible", indicating that "anticipated" requires "convincing" evidence of adverse effects. In *Natural Resources Defense Council v. EPA* (1987), NRDC assailed as arbitrary EPA's failure to take into account numerous health risks that might ("may") be connected with fluoride when the agency set drinking water standards for fluoride. The U.S. Court of Appeals for the District of Columbia Circuit stated:

> NRDC cites studies purporting to find a link between fluoride and a host of health problems. Under the SDWA, however, the RMCL is to be set with reference to known or anticipated adverse health effects, not merely possible effects. 42 U.S.C. 300g-1(b)(1)(B). EPA reviewed and responded to the studies in fair detail and gave reasoned explanations for finding that they did not convincingly establish a cognizable connection between fluoride in drinking water and the various health risks posited.

812 F.2d 721, 725 (D.C. Cir. 1987) (emphasis added).

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[6] Note that the DBD does not even claim that these studies establish that "causal interpretation is credible", as required by the RoC criteria, or that they even establish an "association"; they only "suggest" one; and an "association" can be far short of a credible causal relationship, as required by the "reasonably anticipated" criteria. Apparently an association is only "suggested" because only one-half of the 16 studies contained statistically significant positive results. At 28. In addition, the DBD states that "positive risk estimates remain after adjustment for confounders; however, ovarian cancer is far from being well-understood, and one cannot adjust for a confounder that is not known and the effect of which is uncertain.

[7] Note again that "talcum powder" is not a substance that has been nominated for listing; only talc containing asbestiform fibers and talc not containing asbestiform fibers have been separately nominated.

[8] Joint House-Senate Comparative Summary and Explanation in Cong. Rec. - House, Oct. 14, 1978, at 38657.

Summary

1. On its face, the DBD concludes that the evidence from studies in humans is inadequate to support any listing of talc not containing asbestiform fibers in the RoC because it cannot be determined whether the exposures in those studies were to asbestiform or non-asbestiform talc (or possibly other substances also).

2. The DBD does not contain a finding that the animal evidence is sufficient within the meaning of the listing criteria to support a listing of talc not containing asbestiform fibers, and a number of DBD statements indicate that RG1and RG2 concluded that the animal evidence was not "sufficient" and not relevant to any reasonably anticipated human exposures.

3. FDA scientists reviewed the relevant animal evidence and concluded that it was not relevant to any expected human exposures.

4. Key conclusions in the DBD are based on a "possible" connection between exposure to non-asbestiform talc and human cancer and therefore cannot support a listing as "reasonably anticipated" to cause cancer in humans.

5. In view of the above, the DBD cannot support a listing of non-asbestiform talc as "reasonably anticipated" to cause cancer in humans.

Recommended RoC Subcommittee Actions

The lack of scientific support for listing talc not containing asbestiform fibers is clear. The deficiencies in the DBD are fundamental and cannot be cured by clarifications or qualifications. Consequently –

1. The Subcommittee should vote unanimously against any listing of talc not containing asbestiform fibers, possibly with a recommendation for deferral of consideration of listing until it appears that sufficient relevant scientific evidence has accumulated.[9]

2. In view of the fatal deficiencies in the DBD, if a majority of the Subcommittee were to vote in favor of listing, it should provide a reasoned explanation for how its action comports with the RoC listing criteria. Even if a minority supports listing of talc not containing asbestiform fibers, those individual members voting in support of listing should explain how their position comports with the listing criteria.

Thank you for your thoughtful consideration of these comments.

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[9] Deferral would be consistent with the recommendations made by the RoC Subcommittee (as well as RG1 and RG2) regarding boot and shoe manufacture and repair during consideration of listings for the 9th RoC. The Subcommittee recommended deferral based on doubts as to whether there was adequate evidence relevant to current exposures in the United States.