Talc Nominations for the 12th Report on Carcinogens; Threat Assessment and Recommendations for "Cosmetic Talc" (Talcum Powder)

Introduction

The purpose of this paper is to trace the history of the 10th RoC reviews of talc not containing asbestiform fibers, the issues that were raised during those reviews and how they were disposed of, and then compare the 12th RoC nomination for "cosmetic talc" to that history along with any new scientific studies published or discovered since the 10th RoC reviews in order to assess whether the new nomination poses different issues and poses a greater or lesser threat of listing than the previous nomination. Note that the focus is only on "cosmetic talc". This review should also illuminate the key issues in the 10th RoC review and that might need more attention in a coming review. In addition, possible impacts of the new Data Quality standards, including the new peer review requirements and the recent OIRA suggestions for changes in the RoC review procedures are discussed, and some specific action recommendations are made. Since the emphasis is on the current "cosmetic talc" nomination, there is no discussion of talc containing asbestiform fibers and little discussion of occupational exposures to talc not containing asbestiform fibers.

The Talc Nominations for the 10th RoC

On April 5, 2000, NTP published notice of nominations for the 10th Report on Carcinogens (RoC). Included were two separate nominations for talc. One was for "Talc (14807-96-6) (Non-Asbestiform)"; the other for "Talc (14807-96-6) (Containing Asbestiform Fibers)". The notice provided tabular-arranged explanations of the nominations, divided into "Primary Use or Exposure" and "Basis for Nomination". For non-asbestiform talc, the following information was provided:

Primary Use or Exposure (non-asbestiform talc)
"Talc (non-asbestiform) occurs in various geological settings around the world. Occupational exposure occurs during mining, milling and processing. Exposure to general population occurs through use of products such as cosmetics."

Basis for Nomination (non-asbestiform talc)
"Nominated by RG1 based on NTP Technical Report (TR 421, 1993) which reported clear evidence of carcinogenic activity of talc (non-asbestiform) based on increased incidences of alveolar/bronchiolar adenomas and carcinomas of the lung in female rats and also recent published epidemiology studies that suggests [sic] that talc exposure among pottery workers has been associated with lung cancer, and ovarian neoplasms in women."
For asbestiform talc, the following information supporting the nomination was provided:

**Primary Use of Exposure (asbestiform talc)**

“Talc (containing asbestiform fibers) occurs in various geological settings around the world. Occupational exposure occurs during mining, milling and processing.”

**Basis for Nomination (asbestiform talc)**

“Nominated by RG1 based on IARC finding identification of sufficient evidence of carcinogenicity in human epidemiology studies and identifying talc (containing asbestiform fibers) as a Group 1 - Known Human Carcinogen (Sup 7, 1987). IARC listing based on the observed association between exposure to talc containing asbestiform fibers and mesothelioma in humans.”

The 10th RoC RG1 and RG2 Reviews

There is no information on the dates of the RG1 and RG2 reviews, although they were obviously held sometime between April 5, 2000 (after the above notice) and October 17, 2000, when the notice of the RoC Subcommittee meeting and availability of the draft background document (“DBD”) were announced (see below).

The DBD contained narrative summaries of the RG1 and RG2 reviews. The summaries were written in the form of narrative conclusions, without discussion of dissenting points of view, and also without information on the voting tallies. The summaries were each about one and one half pages and contained identical wording with regard to non-asbestiform/cosmetic talc. The identical RG1/RG2 findings pertinent to non-asbestiform were as follows:

**Carcinogenesis**

... Talc not containing asbestiform fibers is *reasonably anticipated to be a human carcinogen* based on consistent evidence from human epidemiological studies, which showed an increase in ovarian cancer in women who use cosmetic talc in the genital area, and evidence of carcinogenicity from a study in experimental animals.

... The use of talc for perineal dusting and on sanitary napkins and diaphragms has been associated with ovarian cancer. Fourteen of 16 case control studies of human ovarian cancer provided evidence for an association with the use of talc (presumably cosmetic grade, but information on fibrous content is lacking). A recent large prospective study did not demonstrate an overall increase in risk for ovarian cancer with talc use (Gertig et al. 2000). However, in this study talc use was significantly associated with one subtype of ovarian cancer, invasive serous ovarian cancer. Risk of this tumor type was also elevated in several case-control studies (Harlow et al.
1992, Chang and Risch 1997, Cook et al. 1997, Wong et al. 1999, and Cramer et al. 1999). There is conflicting evidence concerning transport of talc through the genital tract to the ovary (Hamilton et al. 1984). Several studies provided evidence that factors preventing translocation of talc to the ovary, such as tubal ligation or hysterectomy, reduce the risk associated with talc use (Harlow et al. 1992, Wittenmore et al. 1988, Cramer et al. 1999). Risk of ovarian cancer associated with talc use is unlikely to be a consequence of confounding or other biases.

... In one adequate inhalation study, rats exposed to non-asbestiform talc developed tumors of the adrenal glands and lungs (NTP 1993).

Other Information Relating to Carcinogenesis or Possible Mechanisms of Carcinogenesis

There are few published reports assessing the genotoxicity of talc, with or without asbestiform fibers. ...

The lung tumor response in female rats exposed by inhalation to non asbestiform talc has been attributed to a non specific dust overload mechanism, and its relevance for human hazard identification has been questioned (Goodman 1995, Oberdoster [sic] 1995, Zazenski et al. 1995). However, estimates of clearance rates of talc from human lung are slower than from rats (Pickrell et al. 1989) and talc particles and talc "bodies" have been isolated from human bronchiolar lavage fluid many years after exposure to talc, raising the possibility of similar pathologic responses in rats and humans to inhaled talc.”

The membership rosters of the RG1 and RG2 for the 10th RoC are provided in Appendix D to the 10th RoC. RG1: Bucher, Haseman, Huff, Jameson, Kamel, Lunn, Maronpot, Masten, Matthews, Melnick, Tennant, Thompson, and Waalkes (all NIEHS). RG2: Allaben (FDA), Bucher (NIEHS/NTP), Fung (NCI, alternate for Longfellow), Howard (FDA, alternate for Allaben), Jameson (NIEHS/NTP), Kilbourne (CDC, alternate for Sinks), Longfellow (NCI), Parker (EPA), Schuman (OSHA/DOL), Sinks (CDC), Stevens (ATSDR), Toraason (NIOSH), Wind (CPSC). Note that Bucher and Jameson served on both RG1 and RG2.

Information on the vote tallies in RG1 and RG2 for talc not containing asbestiform fibers was not provided until (1) the introductory presentation by Dr. Kamel at the Dec. 14 public meeting of the RoC Subcommittee, and (2) in the March 5, 2001 final call for public comments prior to the NTP Executive Committee meeting.

At the RoC Subcommittee meeting, Dr. Kamel described the RG1 and RG2 votes on talc not containing asbestiform fibers as follows:

There are a number of criteria that can be used to list the substance as
reasonably anticipated to be a human carcinogen. One of these criteria is the following, that there is limited evidence of carcinogenicity in studies in human, which indicates that causal interpretation is credible but that alternative explanations such as chance, bias, or confounding factors could not be excluded. On the basis of this criteria, the NIEHS Review Group [RG1] voted to list talc [not containing asbestiform fibers] as reasonably anticipated to be a human carcinogen. The vote was six for and one against. The one negative vote was based on the lack of biological plausibility. The Interagency Review Group 2 also voted to list talc not containing asbestiform fibers as reasonably anticipated to be a human carcinogen. Here the vote was seven for and one against. The negative vote was based on insufficient animal evidence and possible confounding by asbestos contamination in human studies.

The RG1 and RG2 votes and rationales were also summarized in the March 5, 2001 notice of the final opportunity for public comment subsequent to the RoC Subcommittee meeting and prior to the NTP Executive Committee meeting. While that summary is mainly consistent with the Kamel summary above, with one possibly significant difference. The Kamel summary stated only that one of the RG1 members voted against listing on the basis of “lack of biological plausibility”. Dr. Kamel did not explain whether “biological plausibility” referred to translocation or to the mechanism of carcinogenesis. The March 5, 2001 notice stated additionally that the negative vote was cast “because member questioned the biological plausibility of talc use causing ovarian neoplasms in women.” This could be interpreted to refer to lack of a plausible mechanism of carcinogenesis rather than the translocation issue, but it is far from clear.

The 10th RoC Draft Background Document

The next NTP Federal Register notice regarding the review of talc for the 10th RoC was issued on October 17, 2000, as part of a notice of the upcoming reviews of nominated substances by the RoC Subcommittee of the NTP Board of Scientific Counselors, scheduled for Dec. 12-15 in Washington, DC. The notice solicited public comment, and it provided the anticipated order of review (talc was listed as number 7, later revised to 6), and also the following information for “Talc / (14807-96-6) (Asbestiform and (Non-Asbestiform))”:

Primary Uses or Exposure

“Asbestiform talc (i.e., talc containing asbestiform fibers) occurs in various geological settings around the world. Occupational exposure occurs during mining, milling and processing. Non-asbestiform talc (i.e., talc not containing asbestiform fibers) occurs in various geological settings around the world. Occupational exposure occurs during mining, milling and processing. Exposure to the general population occurs through use of products such as cosmetics.”

This Federal Register notice also announced, for the first time, availability of the draft background document ("DBD") for talc, and the other substances under review, on the NTP website (or in hard
copy, if requested).

The RoC review procedures in effect at this time indicated that the same DBD would be reviewed by RG1, RG2 and the RoC Subcommittee as the basis for their recommendations.

It should be noted that the public was not given an opportunity to comment on the DBD prior to the RG1 and RG2 reviews, so that only the RoC Subcommittee had the benefit of any public comments on the DBD.

The DBD states that it was prepared by Technology Planning and Management Corporation in Durham, NC.

The DBD contains the following Summary sections pertaining to the human studies portion of the DBD for non-asbestiform (or cosmetic) talc:

### 3.2.6 Summary [of human studies for “3.2 Talcum powder use and ovarian cancer”]

The accumulated evidence from studies examining the risk of ovarian cancer in relation to genital exposure to talc suggests an increase in cancer risk, on the order of 30% to 60% for any exposure. The principal findings of these studies are quite consistent, despite variation in the details of duration, frequency, and route of exposure and the limitations of exposure assignments based on retrospective self-reports. Of the 16 studies, 14 reported a positive association between perineal talc use and cancer, which was statistically significant in eight studies. Studies that did not find a positive association may have been limited by the use of hospital controls with other types of cancers (Wong et al. 1999) and insufficient power because of the small number of exposed cases (Tzonou et al. 1993). Moreover, positive risk estimates remain after adjustment for confounders. The evidence for causality is weakened by the absence of exposure-response trends in most studies, but this absence may be a result of the difficulty of measuring exposures by retrospective recall. 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 (Heller et al 1996a, b, IARC 1987a, Wehner 1994; see Section 6 [discussing mechanistic data]).

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1 The DBD does not show a release date. Its cover indicates only that it is for the “December 13-14, 2000” “Meeting of the NTP Board of Scientific Counselors Report on Carcinogens Subcommittee”.

2 The procedures also provided that RG1 would make any revisions to the DBD it deemed necessary after an initial review and before proceeding to the review in which it would make its recommendations regarding listing.
3.3 **Talc containing asbestiform fibers and talc not containing asbestiform fibers** [Summary of human studies]

The limited information in the literature on talc mineralogy and asbestos content poses a key challenge in assessing carcinogenicity. . . .

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.

The evidence from occupational studies concerning the carcinogenicity of non-asbestiform talc is extremely limited. . . .

... In light of these findings, the evidence from studies of occupational exposure to non-asbestos-containing talc is not sufficient to support a conclusion that this form of talc is carcinogenic. In contrast, the evidence from studies of ovarian cancer suggests that talcum powder is a carcinogen.

It should be noted that the human studies chapter contained a brief discussion of possible mechanisms for ovarian cancer, and states that “asbestos and talc exposures” cause ovarian inflammation. No studies are referenced. (P. 24.) This section of the chapter also stated: “Talc was suspected of being a risk factor for ovarian cancer based on its mineralogical and chemical similarity to asbestos, possible contamination of talc by asbestos (Rohl et al. 1976), published reports of postoperative talc granulomas (Eiseman et al. 1947, cited in Harlow and Hartge 1995), and the presence of talc particulates in ovarian tumors (Henderson et al. 1971, 1979, Harlow and Hartge 1995).” (Id.)

While the above summaries of the human studies are probably the most important portions of the DBD, there are other portions that should also be considered.

The exposure chapter (ch. 2) contains a section on “Cosmetic applications” which identifies a large number of cosmetic products in addition to talcum powders which contain talc, and notes that the powders include foot, body, and baby powders.

The chapter on animal studies includes discussion of oral and inhalation studies, including
the NTP bioassay, as well as studies involving injection. The Hamilton et al. 1984 study which involved injection of non-asbestiform Italian talc into the ovarian bursa of rats without significant effects is discussed at p. 46 and set out as the last entry in Table 4-6, p. 55. The summary portion of this chapter pertaining to non-asbestiform talc states:

Inhaled non-asbestiform talc was associated with increased incidences of benign or malignant pheochromocytoma of the adrenal gland in male and female rats and with an increased incidence of alveolar or bronchiolar adenoma and carcinoma of the lung in female rats. Inhaled non-asbestiform talc did not cause tumors in female rats at the lowest exposure concentration (6 mg/m³) or in male and female B6C3F₁ mice or Syrian golden hamsters. The lungs of the male and female rats and mice showed signs of marked toxicity, characterized by inflammation, focal fibrosis, and hyperplasia, suggestive of impaired clearance. Although no definite determination was made, the lung burden data suggested that clearance was not significantly impaired.

The chapter on genotoxicity concluded that there was no evidence of genotoxicity for talc with or without asbestiform fibers, although there was abundant evidence of genotoxicity for asbestos and other mineral fibers. (P. 63.)

The potential for systemic distribution of talc particles is discussed in chapter 6 (“Other Relevant Data”) at pp. 65-66, and the DBD concluded that systemic distribution of inhaled or ingested talc particles was unlikely. (P. 71, 72.)

The issue of translocation of talc particles through the female genital system after perineal application was discussed in the same chapter at pp. 66-67. No conclusions were stated in this section or in the summary at the end of the chapter.

The summary for chapter 6 contains the following noteworthy statement regarding inhalation risk from non-asbestiform talc (pp. 71-72):

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.

Also note, however, that this conclusion was worded in terms of “risk”, while NTP has always insisted that the RoCs are “hazard” identification documents in which level of exposure is not relevant.

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3 It should be noted that the summary of the animal studies chapter refers to Italian talc as “presumably containing asbestiform fibers”. P. 56.

4 This NTP position is, however, contrary to the evidence of legislative intent.
The 10th RoC RoC Subcommittee Review

The RoC Subcommittee talc review, held Dec. 14, 2000 in Washington, DC, was semi-split between the two nominations at the time: talc with asbestiform fibers, and talc without asbestiform fibers. The review took almost a full day. The review proceeded with (1) a summary presentation on the evidence pertaining to listing of talc containing asbestiform fibers by Dr. Huff of NIEHS, followed by questions of the presenter by the subcommittee members (and some discussion), (2) a summary presentation on the evidence pertaining to listing of talc not containing asbestiform fibers by Dr. Kamel of NIEHS, followed by questions of the presenter by the subcommittee members (and some discussion), (3) plenary discussion among the subcommittee members on both nominations, and (4) motions and votes on listing for both nominations.

The Subcommittee voted 7-3 in favor of a motion not to list talc without asbestiform fibers. One of the three votes against the motion was a vote for deferral (by Dr. Smith). So actually the vote was 8-2 against listing in the 10th RoC. NIEHS/NTP has persisted in stating that the vote was 7-3, even though, with regard to the Agency’s summary of the voting on the other nomination (talc containing asbestiform fibers), the Federal Register notice describing the vote explained that one of the votes against listing was a vote for deferral (Dr. Smith’s). The two members who voted against the motion not to list were asked for an explanation, and one (Dr. Kelsey) simply stated that he would have voted for a “reasonably anticipated” listing; the other (Dr. Moure-Eraso) stated that he thought the evidence was sufficient to list as “reasonably anticipated”, and that if they could ascertain the exact composition of the talc in the studies (presumably the epi studies), they would find that it was less than one percent, and that such a small amount of asbestos contamination could not account for the positive findings. (This was apparently a mistake on Dr. Moure-Eraso’s part, since the DBD and the presentation at the meeting indicate some brands of talc had been found to contain, prior to 1979, asbestos in quantities up to 30-50 percent of the product weight.)

Considerable time was spent at the outset of the discussion of both nominations in determining the meaning of “abestiform”. This was finally, and clearly, resolved with a revision in the description of the nomination to indicate that “talc containing asbestiform fibers” referred only to talc containing minerals in fiber-like form or “habit” (“asbestiform”) that were not asbestos. The implication of this for talc not containing asbestiform fibers was that such talc could not be considered as including asbestos, as it was in the DBD.

The Subcommittee discussion on talc not containing asbestiform fibers was divided between discussion of the NTP 1993 bioassay and the ovarian cancer epi studies, and some discussion of talc pleurodesis. The discussion of the relevance of the NTP bioassay consumed more time. From the start (immediately following Dr. Kamel’s summary of the evidence), the Subcommittee members indicated that they had an issue with considering the positive epi studies relevant because they all involved exposures prior to 1976 and therefore could likely have involved exposure to asbestos along with the talc. Some reviewers indicated they were impressed with the fact that, while most of the 16 case-control studies were positive, the one large prospective cohort study (which thereby eliminated the possibility of recall bias) was not positive (except possibly barely statistically
significant positive for a sub-type of cancer, serous invasive). (This was the Gertig et al. nurses study.) Dr. Smith, who was in favor of deferral, raised the issue of how much asbestos contamination was present, and whether this could be discovered by obtaining additional data. He felt that if it could be determined that the contamination with asbestos was very minor, or that very little of it actually reached the ovaries, the epi studies would support listing. Dr. Smith indicated he was not impressed by the case control studies due to lack of information on exposure, weak RRs with half not statistically significant. He also indicated that he was not impressed with the slightly elevated RR for serous invasive cancer in the Gertig et al. study, particularly since the lower confidence interval was 1.0.

Dr. Portier of NIEHS, who at several points injected himself into the discussion, asked why asbestos should not be considered a confounder under the listing criteria, which provide for the presence of confounders. (P. 314.) One member answered by stating that the problem was the definition in the nomination, which did not allow for the presence of asbestos. Another indicated later that even if there was a confounder or possible bias that could not be excluded as an explanation for positive findings, the criteria called for a causal interpretation being “credible”, and that was crucial.

Dr. Portier also stated that he was unaware of any studies showing a linkage between ovarian cancer and asbestos. (Pp. 314-15.) As noted below, subsequent to this, in the CTFA supplement, we provided citations to five studies showing such a linkage, in addition to one which had been cited in the DBD.

The possible, or likely, presence of asbestos contamination in the talc involved in the epi studies was not the sole reason for the members being unwilling to give weight to those studies. Some indicated that, apart from the asbestos contamination issue, they did not think the studies very persuasive given their weak results, lack of dose-response pattern, and lack of biological plausibility, including the conflicting evidence on the ability of talc to translocate to the ovaries from the perineal area.

The studies of occupational exposure to talc not containing asbestiform fibers were not discussed by the Subcommittee members. This was apparently due to the fact that the DBD had dismissed the evidence from such studies as insufficient, and this was repeated by Dr. Kamel when she made her summary presentation prior to the start of discussion. (P. 153.) However, the discussion of the NTP bioassay (involving pure talc) was clearly regarded by some Subcommittee members as relevant to occupational exposures, and Dr. Froines felt that it indicated that the current legal exposure limit of 5 mg/m³ was not sufficiently protective and that it should be reduced to 1 mg/m³.

5 In 2001, after this proceeding, ACGIH (the American Council of Government and Industrial Hygienists) issued a recommendation on occupational exposure to talc “containing no asbestos fibers” which found it to be “not classifiable as a human carcinogen” (category A4) and recommending a TLV of 2 mg/m³. (Talc containing asbestos fibers was recommended for listing as a “confirmed human carcinogen”.)
Reference to substituting a nomination of “cosmetic talc” for “talc not containing asbestiform fibers” was made twice by Dr. Froines (pp. 161, 264). He felt that if the nomination were so changed, the issue of possible contamination of cosmetic talc with asbestos would become irrelevant. He did not explain why he was of this view.

Several other issues that came up in the Subcommittee discussion are worthy of mention:

- During the discussion of the meaning of “asbestiform”, there seemed to be agreement that before the government had worked out a definition of asbestos, there was likely some confusion among study authors over whether what they had observed as “asbestos” was really “asbestos” as we now understand it, rather than simply some type of asbestiform mineral.

- It was mentioned that there really was no evidence that talc producers today were complying with the CTFA voluntary standard promulgated in 1976.

- It was noted that the mineral which had been observed in ovarian tissues was described as talc only, and that there was no evidence of asbestos in ovarian tissues.

- Dr. Kamel’s explanation of the 1976 CTFA voluntary standard appeared to imply that 10 percent of cosmetic talc could consist of asbestos. She stated: “[The CTFA 1976 guidelines] state that cosmetic talc should contain at least 90 percent talc that is free of detectable amounts of fibrous materials, including asbestos.” (P. 144.) Subcommittee member Dr. Zahm later commented that “even after 1976 it’s supposed to be 90 percent free, well, that means that 10 percent may not be free. So you know, I just don’t think that we can allow and classify this [the exposure in the ovarian epi studies] as non-asbestos.” Dr. Froines then said he was about to say the same thing. (P. 160.)

- During her presentation, Dr. Kamel referred to the studies on translocation to the ovaries as involving “direct application into the vagina”, but that the NTP bioassay, after which the ovaries of the animals were found to be free of talc, did not involve direct application into the vagina (P. 165.) Dr. Medinsky, however, subsequently pointed out that the animals in the bioassay most likely were exposed to talc in the vaginal area, “which I imagine is the way that these women apply talcum powder, in the vaginal area, not intervaginal application.” (P. 168.)

The 10th RoC NTP Executive Committee Review and other Events Subsequent to December 2000

On January 31, 2001, CRE wrote to Dr. Portier, with copies to Dr. Olden and members of the NTP Executive Committee, arguing that NIEHS must apprize the NTP Executive Committee that the dramatic divergence between the RG1 and RG2 votes and RoC Subcommittee vote was based on a different understanding of the talc nominations. It was determined during the RoC Subcommittee meeting that “asbestiform” should not include asbestos, and the RoC Subcommittee
voted against listing of non-asbestiform talc on the basis that it did not contain asbestos, completely contrary to the assumption in the DBD that talcum powder contained asbestos which was apparently the basis for the RG1 and RG2 votes in favor of listing.

On February 28, 2001, Dr. Portier responded to the above letter by stating that the Agency was well aware of the complexities of the talc issues and that a decision on the matter would be made by Dr. Olden after the NTP Executive Committee meeting. The Executive Committee meeting was originally scheduled for March 15, 2001, but was not held until June 14, 2001.

On March 5, 2001, NTP issued a final Federal Register notice calling for public comments on the 10th RoC nominations which included talc. The notice contained descriptions of the RG1, RG2, and RoC Subcommittee votes. The descriptions of the RG1 and RG2 votes have been set out above. The description of the RoC Subcommittee vote was as follows:

Motion not to list talc not containing asbestiform fibers as reasonably anticipated to be a human carcinogen passed by a vote of 7 yes to 3 no. Negative votes cast either because the member felt that data meets criteria to list talc not containing asbestiform fibers as reasonably anticipated to be a human carcinogen or that the ovarian cancer studies should have been considered in the evaluation. 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 these studies might have been contaminated with asbestos.

Note that this description of the negative votes omits any mention of the Smith vote for deferral, and it is therefore inaccurate. 6

We do not know what happened in the NTP Executive Committee.

The 2001 Approach to FDA

On June 11, 2001 (just prior to the NTP Executive Committee meeting), Luzenac America wrote to Dr. Bernard Schwetz, then Acting Commissioner of FDA, with copies to other FDA personnel and Dr. Olden and the NTP Executive Committee. The letter expressed concern an assumption that present-day talcum powder was contaminated with asbestos was driving the proposal to list talc not containing asbestiform fibers in the RoC. The letter stated that such an assumption was unwarranted, and Luzenac proposed to meet with FDA and NIEHS “to discuss the specifics of those concerns and how we, Luzenac, and other companies producing and selling cosmetic talc, along with FDA, could allay those concerns through measures such as a federal standard or

6 CRE twice protested this characterization of the vote. Jim Tozzi wrote a protest letter to Dr. Portier on March 1, and Dr. Portier responded that he did not agree that the vote was different that 7-3, since three members voted against the motion and each provided a reason for voting against it. On May 3, 2001, Mr. Kelly of CRE sent Dr. Portier a more detailed protest, which was ignored.
guidelines or testing of today's cosmetic talc.

On June 29, 2001, Dr. Schwetz, as Acting Principal Deputy Commissioner, replied to Rich Zazenski of Luzenac. He stated that while he was unable to meet with him personally, staff in the FDA Office of Cosmetics and Colors would be pleased to meet, and that Dr. Adele Dennis, Acting Director of the Office, should be contacted to arrange a meeting. As far as we know, no meeting was ever held, probably because deferral of the talc review had been announced on June 14, as discussed below.

The Deferral

The NTP Executive Committee apparently met on June 14, 2001. On the same day, Dr. Olden sent a letter to some stakeholders announcing that deferral of the talc reviews. The letter stated:

It is very evident that the literature on talc, with few exceptions, provides an inadequate characterization of the actual materials under study to enable one to reach definitive conclusions concerning the specific substances responsible for the range of adverse health outcomes reported. This confusion was clearly reflected in the deliberations during the December 14, 2000, public review of the talc nomination by the NTP’s Board of Scientific Counselors RoC Subcommittee. Because of this situation, I have decided to defer consideration of the listing of talc, both with and without asbestiform fibers, in the Report on Carcinogens.

Deferring listing of the talcs in the RoC does not address the concerns raised during the review process over the excess lung cancers reported in people who were exposed to talc containing asbestiform fibers, or the apparent increase in ovarian cancers in women using cosmetic talc. Therefore, I have requested that my staff carefully review the literature on these materials to determine if a clear definition of the agent or agents to be reviewed could be developed for the RoC and if additional research would be appropriate at this time. We would welcome the participation of the talc industry in defining a suitable category for review and in identifying specific research projects that would provide clarity to these issues.

On July 9, 2001, Dr. Olden sent a very similar letter to all persons who had commented at the RoC Subcommittee meeting. The only difference from the June 14 letter was that the last paragraph did not contain the language inviting industry participation in developing a “clear definition” and “additional research”. The July 9 letter was later posted on the NTP website.

It seems significant that Dr. Olden’s letters on deferral and continuing concerns made no mention of the 1993 NTP bioassay.

Post-Deferral Commentary by Industry
On March 18, 2002, CTFA submitted to Dr. Olden and NTP a detailed supplemental review of the literature on talc (prepared by CRE). The supplemental review referenced some 50 articles which had not been considered in the DBD. The CTFA cover letter stated:

... The enclosed information is submitted in response to the offer of collaboration which you extended in your July 9 letter.

...

Our review during the 10th RoC proceedings, together with this additional literature review, indicates that the scientific literature on which the initial RoC nomination for non-asbestiform talc was based was incomplete, and that findings in the DBD are unsupported on certain key points. Re-analysis of the pertinent literature further supports our confidence in the safety of cosmetic talc. ...

The supplemental literature review attached to the cover letter ended by stating that “at present we do not see any way to define cosmetic talc in a manner that would support a RoC listing nomination.”

Among the points made in the supplemental review were the following:

• Asbestos-free talc, as provided for in the CTFA specification, is a self-enforcing marketplace requirement necessitated by public perception and potential litigation factors.

• Statements made in the DBD and the literature that talc and asbestos are mineralogically and chemically similar are erroneous.

• The clear differences between talc and asbestos are borne out by the evidence concerning the clear biological effects of asbestos.

• There is considerable epidemiologic evidence for a relationship between asbestos exposure and ovarian cancer.

• Talc shows a distinct absence of carcinogenic activity in mechanistic tests.

• Contrary to the DBD, the talc case-control epi studies show evidence of recall bias.

• The case-control studies involving talc and ovarian cancer were far less consistent than the DBD made them out to be. The DBD lacked focus on talc exposure via sanitary napkins, diaphragms and condoms, and the epi evidence concerning such exposures (which were much more likely to result in transmitting talc to the ovaries than external dusting) was extremely equivocal, in contrast to that concerning external dusting in the perineal area.
Talc particles have been reported in the ovaries of supposedly unexposed subjects, and asbestos fibers had been reported as observed in ovarian tumors and mesotheliomas of women who had no recorded asbestos exposure history.

The DBD had not considered all the studies on potential talc translocation from the vagina (not the external areas of the genitalia) to the ovaries, and those additional studies found no translocation.

The New Nominations for the 12th RoC and Their Potential Significance

The 12th RoC nominations were announced on May 19, 2004. There were two new nominations for talc, and the basis for the nominations was different from the stated basis for the 10th RoC nominations.

The two new nominations for “Talc” are “(1) Cosmetic talc”, and “(2) Occupational exposure to talc”. The nominations for the 10th RoC were “Talc (14807-96-6) (Non-Asbestiform)” and “Talc (14807-96-6) (Containing Asbestiform Fibers)”. The CAS numbers were removed from the new nominations, as was any use of the term “asbestiform”.

The statement of “Primary uses or exposure” for the new nominations is: “Talc occurs in various geological setting around the world. Exposure to general population occurs through use of products such as cosmetics. Occupational exposure occurs during mining, milling and processing.”

The statement of “Basis for nomination” is:

The NTP deferred consideration of listing talc (asbestiform and non asbestiform talc) in the 10th RoC because its 2000 review of talc found confusion in the scientific literature over the mineral nature of talc. Given the confusing over defining exposure to talc based on asbestiform fibers, the NTP [sic] has decided that the most appropriate approach would be to characterize talc exposure as cosmetic talc and occupational exposure to talc. The basis for the review of talc is as follows:

Cosmetic talc: Human epidemiological studies reporting an increased risk of ovarian cancer among women using talc for personal use.

Occupational exposure to talc: Human epidemiological studies reporting an increase [sic] risk of cancer among workers exposed to talc.

The statement of the basis for the nominations is markedly different from that provided for the 10th RoC nominations. There is no reference to the NTP 1993 bioassay, and no reference to the 1987 IARC review.

When the 10th RoC talc nominations and reviews were deferred, NTP told the public that it
would conduct a careful review of the scientific literature to determine whether a “clear definition” of the exposures in the studies of concern could be developed for further review, and would explore whether additional research should be conducted.

The new nominations for the 12th RoC are anything but clear, and there is no indication that any new research has been conducted by NTP.

Discarding of the confusing term “asbestiform” and the CAS number for talc does not clarify the nature of the exposures to be reviewed. The absence of a CAS number indicates that perhaps NTP will review talc mixtures, even though the nomination does not indicate so. That this is what was actually intended was confirmed at the June 2004 Board of Scientific Counselors meeting by Dr. Jameson. The term “talc”, however, has a scientific definition associated with it, and a CAS number, and it indicates pure talc.

With regard to the terminology “occupational exposures to talc”, it is clearly acknowledged by NTP that (a) occupational exposures to talc mixtures and products vary widely in composition, and (b) NTP has previously determined that epi studies of occupational exposures to pure talc are inadequate to support listing in the RoCs. If NTP intends to focus on pure, CAS-defined talc, it presumably would have cited its 1993 bioassay in support of the occupational exposure nomination or both nominations; but it did not. If NTP intends to focus on talc mixtures, but with non-talc minerals (presumably other than asbestos) as confounders, it will be faced with the equivocal studies of occupational exposures to relatively pure talc which point to not listing, as they did last time. If the 1993 bioassay is later thrown into the mix, however, on the reasoning that, even though the study indicates any carcinogenesis is a high-dose phenomenon, and the RoCs do not consider dose, the case for listing might be strengthened.

With regard to the terminology “cosmetic talc”, it is difficult to see how this new nomination terminology improves and clarifies the case for listing. NTP will still be faced with the issue of whether the case-control epi studies involved exposures to both talc and asbestos prior to 1976, putting aside the weaknesses in the case-control studies such as lack of a dose-response, inconsistencies in findings with respect to type of exposure (e.g., sanitary napkins vs. dusting), lack of statistical significance in half the studies, and lack of a plausible biological mechanism for carcinogenesis, and the translocation issue. The issue of potential asbestos contamination (or just variation in types of cosmetic talc) appears incapable of resolution through additional examination of the study data, since apparently all the case-control studies were based on questioning of the subjects, and therefore there are no samples of the exposure substance to examine. Moreover, the term “cosmetic talc” clearly encompasses a wide range of cosmetic products containing talc which have never been implicated in any cancer study (e.g., blush, lipstick, eye liner, deodorants, foot powder, etc.). The 10th RoC review by the RoC subcommittee for the nomination “talc not containing asbestiform fibers” would be considered the same as a nomination for pure talc, as defined by its CAS number. This leaves the likelihood that by using the term “cosmetic talc”, NTP intends to try to review both pure talc and pre-1976 talc containing asbestos by trying to treat asbestos as a confounder. Although it can be argued that this is ridiculous because asbestos is
already listed as a known human carcinogen in the RoCs and therefore any exposure involving asbestos is already by definition exposure to a listed substance, it should be noted that epi studies are routinely adjusted for potential confounding by cigarette smoke, which also is listed as a known human carcinogen in the RoCs. The difference might be that there are accepted ways for “adjusting” for cigarette smoking, but apparently no such adjustments that can be made for asbestos. At the very least, it appears that NTP must clarify this nomination by indicating its intent to confine the nomination to talc powder applied to the female genital area. Then, however, NTP will face the potential problem that it has never before specified a pathway for a nominated exposure, and has resisted doing so (e.g., in the case of nickel and dermal exposure).

In any case, it certainly is difficult to see how the new nomination of “cosmetic talc” in place of “talc (14807-96-6) not containing asbestiform fibers” is now a “clear definition” of an exposure. Is it pure talc, or talc with asbestos? Is it a dusting product applied to the female genital area or all types of cosmetic talc?

New Data Pertinent to the “Cosmetic Talc” Nomination for the 12th RoC

There is only one study of which we are aware which has been published since the 10th RoC deferral which could tend to support a listing of “cosmetic talc”. That is a California population-based case-control study conducted in two California counties in 2000-2001. The study was funded by the California Cancer Research Program.7 The study is Mills PK et al. 2004. Int’l J Cancer (published online). Perineal talc exposure and epithelial ovarian cancer risk in the Central Valley of California. The study questioned subjects concerning frequency, duration, and timing of use of talc dusting powder in the perineal area. The overall RR for “ever” use was 1.37, with confidence intervals of 1.02-1.85.

The study was conducted in the poorest area of California, where a Hispanic population predominated. However, the study did supposedly adjust for race/ethnicity.

The results of this case-control study closely resemble those of the previous 14 case-control studies (out of a total of 16) which found a positive association (but with only half statistically significant). This excludes the Gertig et al. prospective cohort study. One similarity that is significant is the distinct absence of any dose-response trend, and the study could be viewed as helped to bring this anomaly into better focus. The study evaluated cumulative exposure in terms of frequency x duration and divided the study population in quartiles. The quartile with lowest

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7 The California Cancer Research Program (CRP) is a statewide program administered by the Cancer Research Section of the California Department of Health Services with assistance from the University of California, Davis through an Interagency Agreement. The CRP was established by legislation, the California Health and Safety Code, Section 104175 et. seq. in 1998. See http://www.crponline.org/tabs/about.asp. There is no apparent connection between the CRP and any federal agency. There is no federal official on the CRP Cancer Research Council.
exposure had an RR of 1.03 (0.59-1.80); the second quartile had an RR of 1.81 (1.10-2.97), the third had an RR of 1.74 (1.11-2.73), and the fourth, the one for highest cumulative exposure, had an RR of 1.06 (0.62-1.83). The study authors also acknowledged the lack of biologic or experimental evidence to support a relationship between talcum powder use and ovarian cancer risk and the variability in recall of talc uses between cases and control which might have contributed to the findings. It should also be noted that the study is odd in that it found no indication of a latency period ovarian cancer associated with talc use. Another unexplained aspect is the contrasting findings for never parous vs. parous women.

The study is different from some other case-control studies in that it did not assess type of application – e.g., direct application to the genital area vs. dusting of sanitary napkins, underwear, or diaphragms. In the case-control studies where subjects were questioned regarding the type of application, there was (as noted in the CTFA supplement) pronounced inconsistency in the RR for external perineal application vs. other types which were more likely to have resulted in internal translocation to the ovaries.

One very notable aspect of the study which might be used by NTP to support a recommendation to list is its attempt to differentiate between subjects who used talc prior to 1975 and after 1975. The RR reported for pre-1975 is 1.22 (0.84-1.77), and for post-1975 it is 1.92 (1.27-2.91). It is not clear why the authors chose the date of 1975, when they indicate that the CTFA purity standard was not promulgated until 1976 (and one might question how long it might have taken to achieve substantial compliance). Moreover, one might question the accuracy of recall for a period of 25 years.

Like many other published studies, this recent Mills et al. study mistakenly states that talc is similar to asbestos.

The Mills et al. study authors concluded that their study and others provided “suggestive though uncertain” indication of a role for talcum powder in causing ovarian cancers.

There are two “review” articles which have been published since the deferral decision. One is by Wehner AP. 2002. Cosmetic talc should not be listed as a Carcinogen: Comments on NTP’s deliberations to list talc as a carcinogen. Reg Tox Pharm 36:40-50. The author states that the article was prepared independently. The second is the Huncharek meta-analysis. Huncharek M et al. 2003. Perineal application of cosmetic talc and risk of invasive epithelial ovarian cancer: A meta-analysis of 11,933 subjects from sixteen observational studies. Anticancer Res 23:1955-60. The Huncharek analysis states that it was partially funded by the Marshfield (USA) Medical Research Foundation.

The Wehner commentary article, which was published at approximately the same time as the CTFA supplement was submitted to NTP, and which mirrors in many respects its comments and references, appears to be a compelling commentary on the inadequacy of both the epi and experimental evidence to support listing of cosmetic talc in the RoCs. On its own, the Wehner article could serve as comments on the new RoC nominations for talc, particularly since its focus is
on "cosmetic talc" (although by this he means both talc powder applied to the perineal area or pure talc which has been inhaled). Areas in which his article focuses particularly include flaws in the NTP 1993 bioassay, lack of dose-response in the epi studies\(^8\), including negative findings for talc on sanitary napkins, and the conflicting data on potential for translocation from the vagina (not the external perineum) to the ovaries.

The Huncharek et al. meta-analysis pooled subjects from 15 case-control studies and the Gertig et al. prospective cohort study. It calculated a summary RR of 1.33 (1.16-1.45). It examined the seven of these studies (out of nine which provided some information on dose-response) and found that they indicated an inverse relationship, which it termed "counter-intuitive". The study also found a selection bias as reflected in the differing results from population-based vs. hospital-based case-control studies (RR of 1.38 (1.25-1.52) vs. 1.19 (0.99-1.41), respectively). Based on lack of a dose-response relationship and selection bias, the authors concluded that the epi data "failed to show evidence of a causal relationship." One slightly negative feature of the study is its mistaken view that talc is similar to asbestos.

There are a number of new articles on the efficacy of talc in treating pleurodesis, some of which make a point of noting the lack of any evidence of talc causing cancer.

We are not aware of new experimental studies concerning a possible mechanism of carcinogenesis relevant to talc.

**Changes in RoC Staff and Reviewers**

The terms of all current members of the RoC Subcommittee of the NTP Board of Scientific Counselors either expired Dec. 30, 2004, or will expire June 30, 2005. Terms might be extended for up to six months if a replacement is not available. Terms last 3-4 years. Thus it is unlikely that we will know the composition of the RoC subcommittee until sometime in the Summer of 2005. In any case, the RoC Subcommittee which considers the 12\(^{th}\) RoC nominations will inevitably be completely different from that which considered the nominations for the 10\(^{th}\) RoC and from the roster which currently appears on the NTP website. NTP has informed us that new RoC Subcommittee rosters are published when there is a change in membership or prior to a Subcommittee review meeting.

Another potentially significant change is the scheduled departure of Dr. Olden as Director April 4, 2005. Dr. Olden has been Director of NTP and NIEHS since 1991. The new Director will be Dr. David A. Schwartz. As stated in the October 25, 2004 NIH News press release, "Dr. Schwartz is currently director of the Pulmonary, Allergy, and Critical Care Division and Vice Chair of Research in the Department of Medicine at Duke University. At Duke, Dr. Schwartz played a

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\(^8\) Interestingly, he states that there 21 case-control studies, rather than the 16 identified in the 2000 DBD, and that 15 showed barely statistically significant positive results, vs. 6 which did not. In this paper, we have not attempted to discern what epi studies Wehner included that NTP did not.
principal role in developing three interdisciplinary Centers in Environmental Health Sciences, Environmental Genomics, and Environmental Asthma.” Dr. Schwartz has a M.D. degree from the Univ. of Cal-San Diego, and an M.PH. degree from Harvard School of Public Health, and completed research fellowships at the University of Washington and Robert Wood Johnson Medical Center. He was on the faculty at the University of Iowa before joining Duke in 2000. His research focus has been on the genetic and biological determinants of environmental lung disease and host defense, including the pathophysiology and biology of asbestos-induced lung disease.

Changes to the RoC Review Process and Their Potential Significance

The one major change in the process that has been announced since the 10th RoC review is that background documents (no longer called “draft” background documents) will be released for public comment at least 30 days prior to RG1 review. During the 10th RoC review, the DBD was not released for public comment until after the RG1 and RG2 reviews and prior to the RoC Subcommittee review. It also appears that there will be greater use of substance-specific experts in the preparation of the background documents, and elimination of overlaps in membership between at least RG1 and RG2, and perhaps also the NTP Executive Committee.

The New Data Quality Requirements and Their Potential Significance

When the talc deferral decision was made in June 2001, the Data Quality legislation had been passed but neither OMB nor HHS/NIH had yet issued the required guidance. OMB issued its final guidance in September 2001 and February 2002. HHS and NIH have subsequently issued conforming guidance, specifically identifying the RoC program as an information dissemination subject to the guidance.

The legislation and guidance require that information disseminated to the public be “objective” and have “utility”. “Objective” has a long definition, but basically it boils down to requiring that information be accurate, clear, complete, unbiased, and presented in a proper context. In addition, “influential” scientific information, which the RoCs certainly are, must be “substantially reproducible”, meaning that its data sources and methods or analysis must be transparent enough so that a competent peer could attempt to substantially reproduce the information. The “utility” requirement means that the information must serve the purpose for which it was intended.

The 10th RoC posed a number of DQ problems which could arise again:

• The “assumption” that current-day cosmetic talc is still contaminated with asbestos was clearly a policy assumption and therefore was a bias.

• Statements to the effect that talc is similar to asbestos were inaccurate.

• The term “asbestiform”, and therefore the description of exposure, as used in the DBD was unclear.
• Many relevant studies and issues were omitted or neglected, making the DBD analysis incomplete.

• More broadly, the RoCs in general pose “utility” problems because, as NTP frankly admits, they do not provide information to American citizens that can be usefully applied to their daily lives, as was intended by Congress as clearly reflected in the legislative history. The utility problem resides in the persistent refusal of NTP to consider level of exposure or dose in the RoC listings. In the case of talc, this impacts, for example, consideration of the 1993 NTP bioassay, which RoC Subcommittee members viewed as demonstrating a high-dose phenomenon that was not relevant to current-day workers or the general population. Older occupational epi studies probably pose a similar problem.

In addition to the original DQ guidelines discussed above, on December 15, 2004, OMB issued new peer review guidance which will apply to the RoC review process. It appears unavoidable that the RoC review process will have to be substantially revised to comply with this new guidance. The guidance contains the following important requirements for “influential” and “highly influential” scientific information:

Influential Scientific Information (“ISI”)

• Reviewers must not make policy determinations.

• Reviewers must be informed of data quality standards.

• Reviewers must be selected based on expertise, and must be sufficiently broad and diverse.

• Reviewers cannot have participated in development of the work product being reviewed.

• Reviewers must prepare a peer review report, and the agency must disseminate it.

• The peer review report must be discussed in the preamble to any related rulemaking. If the dissemination is a highly influential scientific assessment (below) is in support of a regulatory action, the administrative record must contain a certification of compliance with these OMB requirements.

Highly Influential Scientific Assessments (“HISA”)

(These requirements are in addition to those above.)

• HISA defined as having a potential impact of $500 million in any year or “novel, controversial, or precedent-setting or has significant interagency interest”.

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• Reviewers cannot be employed by the agency sponsoring the work product (with a very limited exception for a non-management, non-policy employee with special and necessary expertise).

• Agencies shall avoid repeated use of the same reviewer on multiple assessments unless essential.

• Whenever feasible and appropriate, agencies shall allow public comment on the draft assessment when it is submitted to the reviewers and shall sponsor a public meeting where oral presentations on the scientific issues can be made to the reviewers by members of the public.

• The agency shall prepare a response to the peer review report which explains whether the agency agrees with the peer reviewers concerns and how the actions the agency will take will satisfy the reviewers concerns.

• Every six months the agency shall post an agenda of peer review plans, and indicate whether it considers the dissemination likely to be influential scientific information or highly influential scientific assessment and opportunities for public comment.

• OIRA will consult with OSTP on implementation of this Bulletin, and there will be an interagency group chaired by OIRA and OSTP that will review progress in implementing it.

Assuming, for example, that the potential RoC listing of cosmetic talc is a "highly influential scientific assessments" (as they appear to be due to being "controversial", "precedent-setting", and having "significant interagency interest", even though it quite likely cannot meet the monetary threshold), then peer reviewers cannot be employed by the sponsoring agency. This means that the RG1 and RG2 reviews will have to be discarded. Retention of the existing RG1 and RG2 reviews would also not allow for public meetings and public presentations to the reviewers. Also of potential significance for the RoCs is the requirement, which applies to even "influential" information, that reviewers cannot have participated in the development of the work product. In the past, it appears the RoC staff who are members of RG1 have participated in preparation of the background documents, which is no longer allowed. The requirement for a peer review report and agency responses to peer reviewers comments would require a new step in the process.

The OIRA (Graham) suggestions for improving the RoC process

On November 16, 2004, OIRA Director John Graham sent a letter to the head of NIH, Dr. Zerhouni, making several suggestions for improvement in the RoC process. Some of those suggestions unavoidably intersect with the new peer review guidance issued December 15, and consideration must be given to how the suggestions and the new guidance can be best reconciled.

The Graham letter makes three "suggestions" for improvement of the RoC review process:
1. When NTP receives public comments, it should prepare a response to comments document, and it would be desirable to be able to present this document to the review committee(s) before their deliberations.

2. When the RoC review committees make technical comments aimed at improving the background document, the background document should be revised by NTP staff to incorporate those comments before a final decision on listing is made.

3. Substance profiles should undergo external peer review before being finalized.

These OIRA “suggestions” appear more forceful in that they were delivered shortly after NTP rejected similar suggestions made by the public at its January 2004 review of the RoC process.

We suggest that the new peer review requirements will necessitate substantial changes in the RoC review process. Those changes could be integrated with the OIRA suggestions by modifying the RoC review process as described below. We assume that the talc nomination is a “highly influential scientific assessment” due to its controversial nature and interagency interest. Other nominations and listings might be considered to be only “influential” information, and therefore would incur fewer new requirements. This suggests that NTP might want to have dual processes: A less stringent process for the non-controversial assessments and a more stringent one for those nominations which are clearly controversial and implicate the jurisdictional mandates of other agencies (as do talc (FDA) and atrazine (EPA and USDA), and possibly asphalt fumes (DOT)). Assuming, then, that a talc listing would be considered “highly influential” under the new guidance, the following process modifications would satisfy both the guidance and the OIRA suggestions:

1. The nomination would be announced for public comment.

2. Substance-specific experts would prepare the initial version of the background document.

3. RG1 would review the background document for sufficiency and make any needed technical revisions. If RG1 found the document sufficient after revisions, it would not vote on a listing recommendation, but would pass the document on to RG2 for review after making any changes it viewed as necessary. (In other words, RG1 and RG2 would now act as participants in the preparation of the background document, rather than as “peer reviewers” commenting on the document and making a listing recommendation through a vote.) If RG1 found the background document to be not sufficient to support the nomination, it would advise the Director, and the review process would stop if the Director concurred.

4. RG2 would review the document for any needed technical changes, but would not vote on a listing recommendation. The document would be revised to incorporate the RG2 changes.
5. (An alternative would be to simply discard RG1 and RG2 altogether.)

6. The background document would be made available for public comment prior to peer review by the RoC Subcommittee (the external peer review group).

7. NTP would prepare a response to the public comments, which would be made publicly available and given to the RoC Subcommittee.

8. The RoC Subcommittee, bolstered by substance-specific experts, would conduct the only peer review and provide a report and listing recommendation to the Director and the NTP Executive Committee. This RoC Subcommittee would, of course, still be done in a public meeting with opportunity for public comments during the meeting.

9. The Director would announce a tentative listing decision, and would issue a draft substance profile (if his decision were to list) along with a response to the RoC Subcommittee comments and recommendations. These materials would be made available for public comment.

10. The same RoC Subcommittee (and any addition substance-specific experts) would review the profile, the NTP responses to its previous recommendations, and any new public comments, and make any additional comments/recommendations it deemed advisable.

11. The Director would make a final listing decision (which would have to be approved by the Secretary).

A proposed letter to NTP and OIRA on the subject of the impact of the Graham letter and the new peer review guidance on the RoC review process is attached to this paper.

Integrative Commentary

The scientific evidence pertaining to “cosmetic talc” (what should be regarded as pure talc in talcum powder form) has not changed significantly from the 10th RoC review. The California case-control study is one more weak positive study to add to the other 14 positive studies; however, it also brings into focus even more the lack of dose-response and failed to consider pathways such as sanitary napkins and diaphragms, and it describes its final conclusions as only “suggestive”. Its analysis of pre-1975 vs. post-1975 talcum powder can be used by NTP as an additional finding supporting listing, but the analysis is rather weak and is a single study. On the other hand, the supplemental CTFA submission to NTP pointed out many additional studies and a number of important issues that did not receive sufficient attention during the 10th RoC review. NTP will still be faced with the issue of asbestos contamination prior to 1976, which was an important element in the RoC Subcommittee’s decisive negative vote last time, and we will be able to continue to stress
the weaknesses in the epi data generally, including more emphasis on the inconsistencies in findings regarding more direct application of talcum powder via sanitary napkins, diaphragms, etc.. We will also be able to raise the issue that the studies on translocation have involved introduction of particulate matter into the vagina, whereas women do not apply powder inside the vagina, but rather, externally where there are physiological barrier to entry. The new Wehner review article appears useful; the Huncharek et al. analysis does not seem to add anything.

It does appear at this time that NTP will drop its emphasis on the 1993 bioassay, which will provide more focus on the body of epi data, which NTP will argue has strong positive consistency (albeit weak findings). NTP will probably try to argue that asbestos in cosmetic talc should be considered as a confounder. There are obstacles to such an argument, not the least of which is that there is no way to adjust for such a confounder. In the end, it appears that, like last time, much will hinge on the term “credible” in the criteria – that is, whether the reviewers find the body of epi studies as presenting a “credible” case for a causal relationship – and whether they view the terminology “reasonably anticipated” as too strong for a body of evidence (both epi and experimental) that has many weaknesses.

Viewed as a whole, the evidence for carcinogenicity of talc powder applied to the genital area remains very problematic. Much may hinge on how the individual reviewers interpret the term “credible” [causal interpretation] in the criteria for “reasonably anticipated”. Our argument will have to be, as before, that such problematic data cannot be considered as establishing a “credible” causal interpretation, or justify telling the public that talc powder is “reasonably anticipated” to cause ovarian cancer.

The change is RoC Subcommittee (and perhaps also RG1 and RG2) membership, as well as the new Director, could influence the outcome, but there is no way to evaluate those factors at this time.

The new Data Quality guidelines on “objectivity”, “utility”, and particularly peer review, as well as the recent Graham letter, pose the strong possibility of changes to the RoC review process that could work to our advantage, as well as providing additional opportunities for challenges to flawed analysis or data.

It is our belief that there is a strong possibility that NTP will decide it has to make some revision in the wording of the cosmetic talc nomination. This could result in significant delay, unless NTP decides to do it in a way that does not provide a new opportunity for public comment.

**Recommendations**

**The Scientific Data**

- A threshold issue is still whether talcum powder which is applied externally can reach the ovaries, at all or in significant quantities. We need to see what we can do to try to resolve
this issue, or at least improve our position. An issue we have not researched, and which needs to be researched, is whether there is scientific data on the extent to which the labia, and vaginal mucosal secretions, form an effective barrier to the intrusion of contaminants. Studies in which particulate matter has been placed directly in the vagina do not address this issue. (It appears that the only study which has addressed it that we know of so far is the examination of the ovaries of the animals in the NTP bioassay.) We should also consider consulting with a prominent female gynecologist who might be able to comment to NTP on this issue.

- Related issues are the possibility of systemic distribution of inhaled or ingested talc particles, particularly the smallest particles. In connection with this, we should also try to see if the studies which found talc in ovarian tissue indicated the size of the particles. A further related issue is the one of possible environmental contamination of tissue samples, which has been raised by both Dr. Wehner and Dr. McConnell. In the 10th RoC DBD, NTP argued that the presence of observed talc could not be accounted for by environmental contamination of the tissues because the particles were observed to be deeply embedded in the ovaria tumors. However, it is unlikely that the tumors were intact; they were probably sectioned, which would have exposed them to contamination. The articles need to be reviewed to see if this was the case.

- The dose-response analysis present to the 10th RoC Subcommittee by Pastides, Rothman, and Samet was criticized by the Subcommittee members as providing inadequate information on confidence intervals and the data points. Dr. Pastides stated that this additional information could be supplied (but apparently it never was). Reporedly, these commenters were contacted previously about providing the information, and they wanted to have it published and cited a rather exorbitant cost. We should explore why they would not be willing to buttress their dose-response presentation with the additional data through a comment rather than a publication. (This is appropriate since they would be analyzing and commenting on existing data, rather than trying to provide new data. This should not have to be peer-reviewed and published. They might have received the impression from some of the Subcommittee comments that their data should be published.)

- The Wehner commentary article should be submitted with any further comments we make.

- If we reach the stage of another RoC Subcommittee review, it will be important to explain to the new members why the previous group voted the way it did. Portier et al. will probably try to give them impression that they were simply confused, when in reality they were not (with regard to talc not containing asbestiform fibers or asbestos) and the situation has not changed.

- We should research the issue of whether epidemiologists consider a “confounder” to include an exposure for which there is no way to make an adjustment for the purpose of calculating a quantitative relative risk. Also, we need to know if any studies have attempted to adjust for
the presence of asbestos as a confounder. (In other words, if there is no way to mathematically adjust for a particular confounder, how can one know whether a weak positive RR reported in an epi study is really positive or negative?)

Changes to the RoC Review Process

• We should write to NIEHS/NTP and OIRA to inform them of our view on how the new peer review guidance requires certain changes in the RoC review process, and how those changes can incorporate the suggestions in the Graham letter.

• We should oppose presentations to the RoC Subcommittee by NIEHS staff. The evidence is already in the background document, and any summary can be presented by the RoC Subcommittee principal reviewers.

Data Quality Challenges

• We should remain alert to opportunities to mount DQ challenges. In doing so, we must keep in mind that the OMB guidance, and agency responses to other DQ challenges to date, reflects the position that an agency will not consider correct of an information dissemination product which is still open for public comment and is not final. With regard to the RoCs, this will raise some interesting questions: At what point does RoC information become “final”? For example, it appears that the wording of a nomination for listing purpose becomes final very early in the review process, whereas the background document and the listing decision might not be considered final until much later. Do we want to focus mainly on DQ flaws that pose a clear potential for judicial review? If so, we need to be aware of legal “standing” requirements (the petitioners must be able to show actual harm to them resulting from, or likely to result from, the information dissemination), as well as the requirement that agency action is only judicially reviewable if it is “final”. Agency action on a DQ petition might be “final”, but would the court consider the challenged information to be final agency action? Likewise, a refusal to change the RoC review process to bring it into compliance with the new peer review guidance could be considered a “final” decision, but it might not be considered final in the sense of causing harm until there is final agency action on a particular listing decision.

GAO Review or Congressional Oversight

• The issues of whether the RoCs are being prepared in a manner contrary to the original legislative intent and whether they are still useful in view of the risk assessments which are provided by other agencies appears to provide valid grounds for Congress requesting a GAO review and for a Congressional committee either calling for a hearing or posing questions to NIEHS in writing. Attached to this paper is a suggested letter requesting a GAO review (which would replace the one we previously sent you for review).
Such action might not affect the talc review itself, but it could conceivably result in cancellation of the RoC program as a whole, or at least result in substantial delays in the 12th RoC reviews while NIEHS tries to figure out how it could alter the program to comply with the original legislative intent and address the issue of overlap/duplication with other agencies. (The new Director might want to conduct a thorough review and arrive at this own conclusions, which could result in additional delay.)

Request for HHS budget/PART review of the RoC program

A PART (Program Assessment Rating Tool, for budget analysis) assessment would complement a GAO review, since it would address the issues of how much is being spent on the program and its utility, including the issue of whether it overlaps with the activities of other agencies. We have previously sent a recommendation to OMB that it ask HHS to have the RoC program subjected to a PART review. We should send a similar letter to HHS budget officials. We have previously sent you a draft letter that CRE would submit to HHS, and another copy of that draft is attached to this paper. An epidemiologist should be able to provide appropriate references to treatise or other materials. If not, the issue appears to have obvious validity as stated.

ATTACHMENTS