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March 29, 1994

Mr.M.R.Chudkowski,Manager
Preclinical Toxicology
J&J Consumer Products,Inc.
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Skillman, NJ 08558-9418

Dear Mike:

In response of your fax of March 28 I have prepared the following points as a contribution to the planned conference call, which are to some extent a reiteration of points in my letter of March 17 to you.

- I am at a loss to understand the rationale for Dr.Boorman's (and, according to him, supposedly Dr.Lorentzen's) desire to analyze the ovaries of the Lovelace rats for talc. This would make some sense to me if there had been ovarian lesions that by any stretch of imagination could have been attributed to talc exposure. But there were none! So what does he want to prove? (See also the first two pages of my letter of 3/17/94 to you).
- What Dr.Boorman wants to investigate as an afterthought to an inhalation study has already been investigated more or less competently in a number of species, including rodents, in studies specifically designed to determine whether particles translocate from the perineum/vagina to the ovaries (for specific literature references, see Wehner et al,Fd.Chem Toxicol, 24:329-338,1986; Wehner, special report to J&J, Nov.1993).
- Neither the authors of the NTP report nor the speakers and organizers of the recent FDA workshop implied that the Lovelace findings had any relevance to human risk assessment. In fact, at the workshop it was repeatedly stated specifically that they had no relevance to human risk assessment. Yet Dr.Boorman's first sentence in his letter

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of March 24 to Dr.Gettings states, "I have talked with Dr.Ron Lorentzen (FDA) about some continuing concern about the potential hazard of talc for human risk of ovarian cancer". Then he proceeds to advocate examining unremarkable rat ovaries from a talc inhalation study in which lung cancer was found in some animals, but which was nevertheless for well-known reasons deemed irrelevant for human risk assessment! If positive lung findings in that inhalation study are considered irrelevant, what does he think to contribute to human risk assessment with negative or positive ovarian findings?

- My recommendation to J&J and CTFA would be to point all of this out to the FDA and whomever else is involved in the most diplomatic terms possible, but without objecting to the contemplated studies. However, J&J/CTFA certainly should not provide financial support for such a study for the reasons outlined above. Research funds should be allocated to projects that offer reasonable hope of contributing to the solution of the problems at hand.
- As I have pointed out before, the idea of collecting human ovaries (in a prospective study under appropriate precautions) is meritorious from a scientific point of view. Tactically/psychologically it probably will be interpreted unfavorably for the talc industry if talc particles are found in the ovaries because this probably would be automatically associated with cancer by many lay people and the media, which, of course, is an unwarranted conclusion. Nevertheless, I believe that sooner or later such studies will have to be done.
- I do not believe that additional epidemiological studies would be helpful because epidemiology is too insensitive a tool to detect risk ratios smaller than 2. If the perceived ovarian cancer risk from chronic hygienic talc use is true (and I don't believe it is), it would be well below 2, based on the reported epidemiological associations. Therefore, conducting another imperfect epidemiological study (there never will be perfect ones!) would be like continuing to fish for small fish with a wide-mesh net.

. As mentioned under (1) on the last page of my letter of March 17 to you, I believe it would be advisable for J&J/CTFA to look into the validity of the findings of Henderson et al who reported 10^3-10^5 particals in human ovaries. Even if verified, it does not mean that the talc particles caused cancer, but I believe it needs to be verified neverthless because the notion that inanimate particles translocate from the perineum to the ovaries unassisted defies the laws of physics.

I would like to suggest that you send copies of this and my letter of March 17 to the participants of the planned conference call. It may provide a useful basis for our discussion. Based on the results of our discussion you may want to consider a meeting between two or three J&J/CTFA people and the individuals mentioned in Dr.Boorman's letter, including himself, to discuss matters. I would be pleased to participate if you deem it helpful.

Sincerely

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Dr.Alfred P.Wehner

cc:D.Jones

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March 31, 1994

Mr.Michael R.Chudkowski
Manager, Preclinical Toxicology
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Dear Mr.Chudkowski:

In discussing the need for further studies to determine the risk of cosmetic talc for the human consumer, you asked me for my opinion on the following questions:

(1) Would I recommend analyzing the rat ovaries of the Lovelace inhalation study for talc particles?
(2) Would I recommend additional studies to determine translocation of talc particles from the perineum/vagina to the ovaries?
(3) Would I recommend any other studies?

Here is a summary of my thoughts on these topics:

(1) No, I would not recommend analyzing the rat ovaries of the Lovelace study for talc particles for the following reasons:

. The Lovelace inhalation study resulted in a significantly increased tumor incidence in the target organ, the lungs, of the high-dose (18 mg/m^3) female rats. As far as I recall, the Lovelace study was nevertheless considered irrelevant for human risk assessment by a panel of experts at the recent ISRTP/FDA workshop in Bethesda. There were no opposing views. This position of the expert panel was based primarily on the observation that (a) chronic exposure to 18 mg/m^3 (for 7 weeks even twice as high) resulted in lung overload, and (b) the particle size of the talc used in the Lovelace study was significantly smaller than that to which the human con-

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sumer is exposed. The verdict of the panel of experts per se precludes use of the Lovelace study, or any parts thereof, in assessing human risk. Furthermore, NTP pathologists examined the ovaries (not a target organ) of the Lovelace rats histologically and found to no one's suprise no evidence of talc-induced tissue changes. Therefore, what would be the significance for human risk assessment of finding talc particles in these rat ovaries (and I don't believe that there will be any) when there are no histopathological changes and when the study is already considered irrelevant to human risk assessment? In summary, while analyzing the rat ovaries for talc particles might be of certain academic interest, it would not, in my opinion, contribute anything to human risk assessment for the reasons stated. Limited research resources/funds could be spent more productively on other talc studies.

(2) No, I would not recommend additional studies to determine translocation of talc particles from the perineum/vagina to the ovaries because a number of such studies, specifically desinged to answer that question, have already been done at various levels of sophistication in humans and several species of animals. While the results at a first glance seem ambiguous and contradictory, closer examination suggests that (a) flawed design of a couple of studies renders their results questionable, (b) if assisted intentionally or unintentionally, inanimate "insoluble" particles such as talc, following the laws of physics, can and do translocate, and (c) unassisted particles, also following the laws of physics, do not translocate. Adding another study would, in my opinion, not contribute significantly to the knowledge base of that particular issue. Here, too, limited research funds could be spent more productively on other talc studies.

(3) Yes, namely:

(a) Validation of the findings (especially the analytical techniques) by Henderson et al who reported 10^3 - 10^5 talc particles in human ovarian tissue. This can be done relatively quickly and inexpensively.

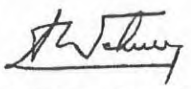
(b) A prospective study in which human ovaries would be collected under appropriate precautions and histologically examined and analyzed for talc. The donors would come from two groups, women with long-term hygienic use of talc and women without such talc use. Depending on the number of hospitals involved

in such a study, results probably could be available within one to two years.

(c) A well-controlled prospective epidemiological study of hygienic talc use in sufficiently large populations. Results would not be available for at least 20 to 30 years, but they would have the highest predictive value. Whether a substance of as low a toxicity as talc would warrant the effort is a question that others will have to decide.

I trust that this information will be helpfull to you. I will be happy to discuss details with you if you so desire. Please contact me if you have any question.

Sincerely



Dr.Alfred P.Wehner

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April 26, 1994

Mr.Michael R.Chudkowski
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Dear Mike:

Following are my thoughts on the Biggs memo to Steve Gettings.

Giving input to the FDA on analyzing the Lovelace rat ovaries is like advising them whether to shoot themselves in the right foot or the left foot. If they insist on conducting a nonsensical study, the ball is in their court. However, --while presenting logical arguments against such a study (see my letters of 17, 29, and 31) but without objecting to the study -- CTFA should pose questions (1) and (3) in the Biggs memo to the FDA and ask them how they propose to answer them to the satisfaction of the scientific community since it is they who insist on conducting it.
I strongly disagree with Dan Biggs on his point (2) for the following reasons. (a) Arguing against more histology if the FDA wishes to do so would project an image of obstructionism and lack of collaboration on part of the talc industry, an image that politically/psychologically/tactically the industry should try to avoid at all costs. (b) The industry has nothing to hide or to fear from the re-examination of any Lovelace rat tissues because the potentially most damaging finding, lung cancer in rats having inhaled talc, has already been published. (c) The Lovelace study has been unanimously judged irrelevant for human risk assessment by a panel of experts because of flaws in the design and conduct of the study. (d) Given this expert judgment it logically follows (at least to me) that any "after-thought" or follow-up effort is at least as irrelevant to human risk assessment as the original study. So why waste time and resources (money) doing it???

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For other points that should be raised in discussions with the FDA, I refer to my letters to you, dated March 17, 29, and 31 (2x).

Let me add a few thoughts on air pollution and apparently ubiquitous air pollutants to show how difficult it would be to rule out contamination in re-examining Lovelace rat tissues, assuming for a moment that such a study would make any sense. So-called "clean" country air contains an average of about 6000 particles/cm . I have read years ago (unfortunately I do not remember the source, but it impressed me enough to remember the fact) that asbestos fibers were found in the Antarctic! Our own findings suggest that carbon black particles are ubiquitous (Wehner et al, 1985). I believe it was someone at the FDA workshop who stated that talc particles also are ubiquitous. Given this situation, appropriate precautions would have to be incorporated into the original design of any translocation study to lead to scientifically valid results by ruling out contamination. This was not the case for the original Lovelace study because it was designed for a different purpose, namely as an inhalation bioassay rather than a talc translocation study. A number of specifically designed translocation studies have already been done with ambiguous results (see Wehner et al, 1986). Adding a half-baked "after-thought" study would not contribute any useful information to the resolution of that question.

To demonstrate the talc industry's spirit of cooperation/collaboration (on sensible studies), I would suggest to the FDA a prospective study on human ovaries and a well-controlled prospective epidemiological study of hygienic talc use (see my formal letter to you, dated March 31, points 3b and 3c). The former can be done relatively quickly and inexpensively; results of the latter would not be available for at least a couple of decades.

If the FDA insists on analyzing the Lovelace rat ovaries, I would like to submit for consideration to independently conduct, with or without FDA support, a quick and inexpensive air sampling study, collecting air samples in (a) operating rooms of hospitals with and without use of powdered gloves, (b) surgical suites for animals in research laboratories with and without use of powdered gloves, and (c) selected other locations. The results of such a study may well show that reanalyzing the Lovelace rat ovaries would not yield meaningful results even if reanalysis of the ovaries were to make any sense to begin with.

Please let me know if I can be of further assistance.

Sincerely

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