ISRP Conference Findings
Opinion: The FDA could not base regulatory decision on the ISRP conference findings. CTFA's response statement regarding the 1994 workshop was extremely misleading. The industry should not use the workshop proceedings as a basis for the safety of talc.

a. Dr. Carr's workshop summary report stated that John Bailey, co-chair of the workshop, "reminded participants that the workshop was not part of a formal rule-making process and could not be a forum to reach a consensus for regulatory decisions" (IMERYS037983-IMERYS037987). 

b. CTFA released a response statement after the workshop, which Dr. Wehner considered to be misleading. (IMERYS209939) (JNJ000040596)

CTFA RESPONSE STATEMENT

TALC

A scientific workshop on "TALC: CONSUMER USES AND HEALTH PERSPECTIVES" co-sponsored by the International Society of Regulatory Toxicology and Pharmacology (ISRP) and the FDA was held at the National Institutes of Health in January, 1994.

The workshop focused on the latest toxicologic and epidemiologic studies conducted on talc and discussed how study findings relate to the use of this material in consumer products. Over 20 leading experts in epidemiology, safety assessment, toxicology, and clinical medicine participated as speakers or as panel members.

A number of epidemiology studies conducted to investigate a possible association between talc use in consumer products and ovarian tumors were reviewed. The workshop concluded that, when taken together, the results of these studies are insufficient to demonstrate any real association.

In addition, participants at the FDA workshop agreed that there is no basis to conclude that talc is capable of migrating to the ovaries in the first place, and this has recently been confirmed by studies conducted by the National Toxicology Program (NTP). No scientific study has ever demonstrated that talc causes ovarian cancer.

In summary, the weight of scientific evidence and the conclusions of the FDA workshop support the safety of talc and all types of talc-containing consumer products.
## Metadata

<table>
<thead>
<tr>
<th>AttachCount</th>
<th>0</th>
<th>ORIGINAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confidentiality</td>
<td>No</td>
<td>ORIGINAL</td>
</tr>
<tr>
<td>Custodian</td>
<td>Sharma, Shripal;</td>
<td>ORIGINAL</td>
</tr>
<tr>
<td>DateCreated</td>
<td>1/12/2009 1:36:28 PM</td>
<td>ORIGINAL</td>
</tr>
<tr>
<td>DateMod</td>
<td>10/24/2013 1:28:58 PM</td>
<td>ORIGINAL</td>
</tr>
<tr>
<td>DocumentType</td>
<td>eDoc</td>
<td>ORIGINAL</td>
</tr>
<tr>
<td>FileName</td>
<td>Carr1995.pdf</td>
<td>ORIGINAL</td>
</tr>
</tbody>
</table>
Talc: Consumer Uses and Health Perspectives

Bethesda, Maryland, January 31-February 1, 1994

Co-Sponsored by:
The International Society of Regulatory Toxicology & Pharmacology
and The United States Food and Drug Administration

Rapporteur
C. JELLEFF CARR

Professor Emeritus, Department of Pharmacology and Experimental Therapeutics, School of Medicine,
University of Maryland, Baltimore, Maryland 21201

Received October 1, 1994
EXECUTIVE SUMMARY

This issue of the journal is largely dedicated to report on a January 31–February 1, 1994 workshop on talc, organized under joint sponsorship of the U.S. Food and Drug Administration (FDA), the Cosmetics, Toiletries, and Fragrances Association (CTFA), and the International Society of Regulatory Toxicology and Pharmacology (ISRTP). Although not all papers given at the meeting were made available for publication, this offers a general overview of the substance of the presentations and discussions.

The workshop was to provide a forum for an updated discussion of the origins, manufacture, characterization, toxicity, and epidemiology of talc. Principal focus of the meeting was on the latest toxicologic and epidemiologic studies, as they reflect on the safe uses of talc in consumer products. The characteristics of cosmetic-grade talc, the history of its uses in a variety of products, and the current quality-control measures to ensure safety were followed by a review of the regulatory history of talc and by an appraisal of recent National Toxicology Program (NTP) studies of chronic pulmonary exposure of rodents to talc.

Of special interest was the relevance of these studies to human risk assessment, in view of reported technical problems of lung overload for these bioassays, and of the standing concerns about the physiologic, anatomic, genetic, and other differences of rodents and man. Experimental data were then evaluated against the contrasting evidence emerging from epidemiologic studies of human talc exposure. A critical panel of invited experts and speakers completed each session. Faculty and panelists included talc mineralogists, geologists, toxicologists, epidemiologists, pathologists, food/drug/cosmetic/medical device manufacturers, qualified regulatory specialists, and consumer representatives.

In brief opening remarks, Dr. John E. Bailey (FDA) reminded participants that the workshop was not part of a formal rule-making process and could not be a forum to reach a consensus for regulatory decisions. Emphasis was to be on a free interaction between participants to explore and possibly reach some conclusion on the validity and significance of the existing knowledge regarding the safety of cosmetic talc.

A first and essential presentation by Dr. Gettings (CTFA) addressed conclusively the nature of cosmetic talc, the specific form of talc under study now recognized in the 1990 U.S. Pharmacopoeia, and other official standards. Unique physical and chemical properties—inertness, hygroscopicity, self-aggregation, lubrication, tactile sensation, translucency, and color—make powdered talc desirable, useful, and virtually indispensable in cosmetic applications. Cosmetic talc is a negligible fraction of the nearly 60,000 tons mined for industrial use in the United States, and today stringent safety and quality-control measures ensure the absence of asbestos fibers formerly considered as a potential hazard, albeit not a defined one.

Dr. Gilbertson (FDA) reviewed the harmonization of international standards and regulations for cosmetic talc and its consumer applications. In their joint evaluation, talc has proven to be among the safest of all consumer products.

In addressing fundamental aspects of inhalation toxicology, Dr. Oberdorster (Rochester University) noted that any inhaled dust—and most substances for that matter—may cause inflammation and cell proliferation in the lung, possibly leading to tumor formation if the challenge is sufficiently strong and persistent to overcome the natural defenses of the animals under test. This condition implies the presence of a no-effect threshold at levels below which natural defenses remain functional to prevent tumor formation. He noted that the NTP inhalation bioassays of talc invariably created lung overloads, thus making the interpretation of results quite problematic. In his overall evaluation of the toxicologic literature on talc, there is no reason for concern for low-level uses of cosmetic talc.

As a staff scientist of the National Toxicology Program, Dr. Boorman emphasized that NTP protocols call for maximum tolerated doses (MTDs) in an attempt to identify any hazards. Negative findings may receive little or no further attention, but positive ones call for detailed mechanistic studies to determine their relevancy for human health. In a detailed description of the talc inhalation bioassays at NTP, their protocol, and pathology findings, he concurred with evidence of dose overloads in most of the animals that ended up developing tumors. He explained the lack of an ovarian effect of lifetime exposure in F344/14 rats and B6C3F1 mice. In his summary report he notes the many factors that complicate interpretation of these rodent studies.

The results of the NTP inhalation bioassays on talc were first evaluated as customary in 1992 by the Technical Reports Review Subcommittee of the NTP Board of Scientific Counselors. Dr. Goodman (Michigan State
University)—a member of that review—reported on events that transpired during that review, which concurred with NTP staff the recommendations, namely that talc was to be listed as a carcinogen even though it caused lung tumors in female rats only, pheochromocytomas in male and female rats, and no tumors in mice. Dr. Goodman recalled being the single member to vote against this motion. His dissent derived from the obvious overload conditions of the high-dose animals—no tumor elevation was observed at the low dose (NOAEL threshold)—and from more general objections to the lack of mechanistic input in the standard protocols and bioassay evaluation procedures by NTP. During his tenure on the NTP Board of Scientific Advisors, Dr. Goodman participated in an official review of the NTP bioassay methods and procedures, as the Chair of the carcinogenesis working group. This review resulted in a report (Fed. Reg. 57, 31721-31730, 1992) that emphasized the need to change the standard bioassay so as to incorporate mechanistic studies in order to provide the biological information that is required to take a rational approach to risk assessment.

Dr. Kushner (State University New York) reviewed in detail many of the issues of the relevance of the results of the rodent bioassays to human beings and Dr. Crapo (Duke University) explained present knowledge of species differences in lung physiology that influences the toxicity of inhaled substances. These reports were followed by Dr. Mossman (University of Vermont) who reviewed the cellular pathology in animals and man as influenced by inhaled particles, especially many kinds of well-known dusts, the effects of smoke inhalation, asbestos, and other kinds of mineral-induced particles' toxicity related to lung disease. It was obvious that talc particles are fundamentally different than such materials as chrysotile asbestos. It was evident from the many hypotheses describing the mechanisms of lung toxicity caused by such things as titanium dioxide and carbon black that high exposure levels are very different from the lower exposures that humans have. This strongly suggests that one should be careful in relating these to cosmetic talc exposure. At one point there seemed to be general agreement in the discussions that the rodent data on talc exposure were not relevant to human inhalation toxicity.

In the panel discussion following these papers a novel idea emerged. Is it possible to use some nontoxic, "inert" particulate in the airway of rodents to serve as a negative control? Or is there a positive, active "model" control that produces a true carcinogenic response in comparison with an unknown test substance?

Several cogent questions were asked without answer: What is the level of uncertainty? Are there agreed upon mechanisms? How different are adults from small 1- to 2-year-old children when exposed to cosmetic talc?

In a summary of such a comprehensive review of whether data from chronic bioassays in rodents can be used to predict human cancer risk, Dr. Gori (ISRT) suggested that presentations and discussions made it clear that this question is unlikely to have a scientific answer. This is because our mechanistic understanding of cancer pathogenesis is rudimentary and still hypothetical, while the single most significant advance during the past 10 to 15 years is an appreciation of the many complex and variable pathways that may lead from normalcy to malignancy.

This appreciation may have begun to liberate our way of thinking from the traditional naive generalizations of initiation, promotion, one hit models, and so on. We may begin to see cancer as a more complex phenomenon arising from multiple interactions of intra- and extracellular stressors—biotic and xenobiotic—with genetic and epigenetic operants in multiple cascades of events that may take from months to entire lifetimes before clinical cancer—the only truly significant cancer—develops. Dr. Gori recalled the report prepared by the NTP Board of Scientific Advisors in 1992 in which Dr. Goodman chaired the carcinogenesis working group—mentioned above—as a masterful primer about the persisting mechanistic ignorance that prevents a scientific or even a reasonable use of rodent bioassays for determining human cancer risks: "Can we trust as a human risk predictor a test that has only a 70% concordance between rats and mice? And this despite the use of test doses that regularly exceed physiologic tolerances? A process that usually labels carcinogens by partial consensus of a panel of reviewers, so controversial can the data be?"

"In the specific case of talc, the particle size of the powder used was not realistic. The MTD guidelines were exceeded with clear signs of chronic toxicity in the tumor-bearing female rats. There is no concordance of rat and mouse outcomes and there is no concordance of male and female rat outcomes." Drs. Kushner, Crapo, and Mossman spoke convincingly of the fundamental anatomic and physiologic differences and of the different responses of rat and human lungs. "Speaking scientifically—and if we forget for a moment epidemiologic data—the rodent data seem unable to tell us whether talc is or is not a human carcinogenic risk."

"Of course, knowledgeable people can express an opinion, and we do have a number of comforting experimental clues—the low acute toxicity and apparent lack of mutagenicity of talc, negative bioassay results in rodents despite exorbitant doses, and an adequate understanding of lung clearance rates in humans and of their capacity to dispose of exposures below certain threshold limits. To reasonable people—even armed with reasonable concern for prudence—these clues suggest that the probability of human risk is likely nonexistent under customary conditions of use." On the other hand, human epidemiologic studies could seem more probative, because of the lack of problems of species extrapolation, maximum tolerated doses, overloads, physiologic and anatomical differences, and so on. Is the interpretation
of epidemiologic studies more straightforward and direct.

Unfortunately—Dr. Gori suggested—epidemiology faces a new set of impediments. The epidemiology we are facing does not offer the same direct cause and effect associations typical of infectious diseases. Human cancers are multifactorial diseases arising from a combination of simultaneous exposures to many potential etiologic determinants. To extricate the significance of any one of these factors from the integrated effects of all others is a challenging task. If one adds the technical problems in the execution of these studies, we soon find that the epidemiologic fog is just as difficult to penetrate as the one generated by animal bioassays. Kenneth Rothman (1986), a leading theoretician of American epidemiology, has reviewed extensively these difficulties of interpretation of causal inferences and writes:

Despite philosophic injunctions concerning inductive inference, criteria have commonly been used to make such inferences. The justification offered has been that the exigencies of public health problems demand action and that despite imperfect knowledge causal inferences must be made.

This definition is widely accepted by mainstream epidemiologists today. On this basis however—just as we could ask whether extrapolation from animal bioassays qualifies as a scientific exercise—we are justified in asking the same question of human epidemiology.

In a general overview of ovarian cancer epidemiology, Dr. Austin (Emory University) noted the many factors that may confound the putative association of perineal talc exposure and ovarian cancer. Following a presentation by Dr. Brown (University of Wisconsin), the discussion made it clear that available histologic and physiologic studies provide no basis to conclude that talc can migrate to the ovaries from the perineal region.

Dr. Hartge (National Cancer Institute) and Dr. Harlow (Harvard University) presented a review of epidemiologic studies—including their own original studies—pertaining to perineal talc exposure and ovarian cancer risk. The studies reviewed brought to light the many interpretative difficulties of epidemiology as an observational science and are detailed in the papers by Drs. Hartge and Harlow appearing in this issue of the journal. From the unique perspective of his long and distinguished experience in the epidemiology of multifactorial diseases, Dr. Wynder (American Health Foundation) reviewed the history of the evolutionary processes that provided natural defense systems against disease. He stressed the specific problems in the epidemiology of weak associations: biases of respondents and investigators, known and unknown confounding factors, and the irresistible urge to interpret results as if only a reduced set of variables of interest was operant, without acknowledging and controlling for a more complex multifactorial reality. Following the many issues raised by all presenters, the ensuing discussion generally agreed that while some weak association between talc exposure and ovarian tumors has been reported, it was not sufficient warning for concern.

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 excess at the low doses, and because of the clear biochemical and cytological markers of excessive toxicity in female rats, the positive talc bioassay results in female F344/N rats are the likely experimental artifact and nonspecific generic response of dust overload of the lungs and not a reflection of a direct activity of talc. Given the gross differences of rodent and human lungs, the lung clearance capabilities of humans, and the possible conditions of customary human exposures, the NTP bioassay results in F344/N female rats cannot be considered as relevant predictors of human risk.

In regard to the proposed association of talc exposure and ovarian cancer, the panel found that epidemiologic data are conflicting and remain equivocal. Although it is theoretically possible that talc could reach the ovaries, the actual access to or the presence of talc in ovarian tissue is not documented. Diet, parity, contraceptive use, ovulatory frequency, familial predisposition, age to menarche and menopause, and other factors associate strongly and plausibly with ovarian cancer incidence. These possible confounders and control selection biases, publication biases, interviewer and interviewee biases, and other factors may well explain the conflicting results that have appeared in the literature.

The possibility of an association of talc exposure and ovarian cancer is an important hypothesis of potential public health importance. However, this association remains a research hypothesis whose verification or falsification needs additional study. Experimental studies may be needed to determine whether talc could access the ovaries under field conditions and, if so, whether it could be embedded in ovarian tissue and produce pathologic effects. For epidemiology, further refinements may be possible in the selection and characterization of control subjects and in the accounting of possible confounders and biases. However, epidemiologic studies have provided weak and conflicting risk signals for this association, and it is unlikely that further studies may prove adequate to raise concern at a level sufficient to warrant regulatory or public health measures.

REFERENCE

CTFA RESPONSE STATEMENT

TALC

A scientific workshop on "TALC: CONSUMER USES AND HEALTH PERSPECTIVES" co-sponsored by the International Society of Regulatory Toxicology and Pharmacology (ISRTF) and the FDA was held at the National Institutes of Health in January, 1994.

The workshop focused on the latest toxicologic and epidemiologic studies conducted on talc and discussed how study findings relate to the use of this material in consumer products. Over 20 leading experts in epidemiology, safety assessment, toxicology, and clinical medicine participated as speakers or as panel members.

A number of epidemiology studies conducted to investigate a possible association between talc use in consumer products and ovarian tumors were reviewed. The workshop concluded that, when taken together, the results of these studies are insufficient to demonstrate any real association.

In addition, participants at the FDA workshop agreed that there is no basis to conclude that talc is capable of migrating to the ovaries in the first place, and this has recently been confirmed by studies conducted by the National Toxicology Program (NTP). No scientific study has ever demonstrated that talc causes ovarian cancer.

In summary, the weight of scientific evidence and the conclusions of the FDA workshop support the safety of talc and all types of talc-containing consumer products.
<table>
<thead>
<tr>
<th>Custodian</th>
<th>Legacy 2</th>
<th>ORIGINAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>DateMod</td>
<td>9/17/1997 12:00 AM</td>
<td>ORIGINAL</td>
</tr>
<tr>
<td>FileName</td>
<td>J&amp;J0115053.TIF - J&amp;J0115054.TIF</td>
<td>ORIGINAL</td>
</tr>
</tbody>
</table>
Mr. Michael R. Chudkowski
Manager, Preclinical Toxicology
JNJ Consumer Products, Inc.
Skillman, NJ 08558-9418

Dear Mike:

There is a German saying which translates as follows:

"A true friend is not he who beguiles you with flattery but he who discloses to you your mistakes before your enemies discover them."

In this spirit I would like to volunteer a critique of the three CTFA response statements which you faxed me on September 11. Some of the wording leaves CTFA wide open to counterattack. The most harmless response statement of the three is the one dated July 1, 1992. It does not give the names of the authors and the title of the paper to which the response is being made. More important, I believe that different and/or additional more powerful statements along the lines of my critique faxed to Jerry McEwen, as far as applicable to the situation in 1992, would have put CTFA in a more advantageous tactical position. Several investigators have independently reported talc particles in ovarian tissue. Simply citing the Battelle study and stating that it "demonstrated that talc does not translate (sic) through the cervix to the uterine cavity and beyond" does not address the problem, does not refute these findings, and therefore does not serve CTFA's best interest. All in all, in my opinion an inept response.

The problem with the response statement dated July 8, 1992, is more serious. The last sentence in the second paragraph states: "Finally, human studies on talc and cancer in industrial settings have shown that industrial exposure to talc, both by skin contact and inhalation, even at levels thousands of times higher than lifetime consumer exposure, presents no significant risk."

This statement is outright false. All an Epstein, a Kennedy, or one of their aides knowledgeable in matters talc, would have to do at a hearing (or any occasion, at that) to demolish the credibility of the talc industry is to refer to the studies by Kleinfield et al, Thomas, and Thomas and Stewart.

Referring in a 1992 statement to a 1977 editorial in defense of one's position is not a very persuasive argument. Much can happen in 15 years.

509/375-0873    Fax 509/375-5693
Here, too, I believe that more powerful and better defendable arguments could and should have been made on behalf of the industry.

The response statement dated November 17, 1994, is just as bad. The second sentence in the third paragraph reads: "The workshop concluded that, although some of these studies suggested a weak association might exist, when taken together the results of the studies are insufficient to demonstrate any real association." This statement is also inaccurate, to phrase it euphemistically. At that time there had been about 9 studies (more by now) published in the open literature that did show a statistically significant association between hygienic talc use and ovarian cancer. Anybody who denies this risks that the talc industry will be perceived by the public like it perceives the cigarette industry: denying the obvious in the face of all evidence to the contrary. This would be a particularly tragic misperception in view of the fact that the industry does have powerful, valid arguments to support its position.

The workshop did not conclude that "the results of the studies are insufficient to demonstrate any real association." As pointed out above, a "real" statistically significant association has been undeniably established independently by several investigators, which without doubt will be readily attested to by a number of reputable scientists/clinicians, including Bernard Harlow, Debra Novotny, Candace Sue Kasper, Debra Heller, and others. What the workshop panel did conclude was that (1) the results of the studies were ambiguous, inconsistent, contradictory and therefore inconclusive, (2) therefore hygienic use of cosmetic talc does not present a risk to the consumer. So why not use these powerful and irrefutable arguments (plus some of those along the lines of my fax to Rich) instead of questionable mush that leaves one vulnerable to counterattack?

The following sentence states: "In addition there is no basis to conclude that talc is capable of migrating to the ovaries...". I submit that several reports, independently describing talc particles in/on ovarian tissue, along with other suggestive evidence (questionable as some of it might be) does provide a basis for just such a conclusion. My point is that such a complex and vexing issue cannot be credibly dismissed with one sweeping statement without any documenting references.

Mike, I realize that CTFA is not J&J. However, I believe that a defeat or embarrassment of CTFA also negatively affects J&J to some extent. As a consultant on a retainer I feel obligated to proactively act in the best interest of my client at all times, not only when I am approached with a specific assignment. This consideration alone motivated me to spend the time to bring my thoughts on this matter to your attention. I trust that in the process I did not step on anybody's toes.

Best regards,

Al