DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Parts 310, 700]

AEROSOL DRUG AND COSMETIC PRODUCTS CONTAINING ZIRCONIUM

Notice of Proposed Rule Making

The Commissioner of Food and Drugs proposes to determine that any aerosol drug or cosmetic product containing zirconium is a new drug or an adulterated cosmetic. Interested persons have until September 3, 1975 to submit comments.

Pursuant to procedures promulgated in the FEDERAL REGISTER of May 11, 1972 (37 FR 9464), a review of the safety and effectiveness of over-the-counter (OTC) drugs has been undertaken by the Food and Drug Administration (FDA).

Notice inviting submission of data and information, published and unpublished, and other information pertinent to the safety and effectiveness of OTC antiperspirant products was published in the FEDERAL REGISTER of September 7, 1973 (38 FR 24391). The Panel on Review of Antiperspirant Drug Products has reviewed the submissions of data and other information regarding the use of antiperspirant products containing zirconium.

The Commissioner of Food and Drugs received, on April 29, 1975, a report of the OTC Antiperspirant Panel on aerosol antiperspirants containing zirconium.

In its report, the Panel indicates that the benefit from using drug and cosmetic aerosol products containing zirconium is insignificant when compared to the risk. The Panel notes that zirconium-containing aerosol antiperspirants are not more effective than non-aerosolized antiperspirants containing zirconium or aluminum salts. The Panel further states that there is little evidence that consumers can perceive a difference between any of the aerosolized or nonaerosolized products under conditions of actual use. The Panel concludes that there is so little benefit to be derived from the use of zirconium-containing areosol antiperspirants when there are far safer aerosolized and nonaerosolized antiperspirants, that it is unjustified to subject even a few individuals to such a risk.

On the basis of the Panel's report, the Commissioner tentatively concludes that aerosol products containing zirconium cannot be considered generally recognized as safe (GRAS) for use in drug and cosmetic products. Therefore, he proposes that any drug product containing zirconium in an aerosol form should be classified as a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(p)), implemented by § 310.3 (g) and (h)(5) (21 CFR 310.3 (g) and (h)(5)). Section 310.3(h)(5) states "The newness of a drug may arise by reason (among other reasons) of: (5) The newness of a dosage, or method or duration of administration or application, or other condition of use prescribed, recommended, or suggested in the labeling of such drug, even though such drug when used in other dosage, or other method or duration of administration or application, or different condition, is not a new drug." The Commissioner has reached this tentative conclusion because of the above noted safety issues in the Panel's report and because the aerosolized form of zirconium was not on the market in 1962 as required under section 107(c)(4) of the 1962 amendments to the Federal Food, Drug, and Cosmetic Act (Pub. L. 87-781 (21 U.S.C. 321 note)) in order to qualify for exemption from the amendments. Under this proposal, any zirconium-containing aerosol antiperspirant will, therefore, be considered a new drug for which a new drug application (NDA) pursuant to section 505 of the act and Part 314 (21 CFR Part 314) is required.

The Commissioner, based upon the same safety considerations, also proposes that aerosol products containing zirconium are deleterious substances which may render any cosmetic product injurious to users. Accordingly, any such cosmetic product would be deemed to be adulterated under section 601(a) of the act.

Although the Panel's report concerned itself only with aerosol antiperspirants containing zirconium, the Commissioner is of the opinion that, without evidence to the contrary, no aerosol drug or cosmetic product containing zirconium can be considered as generally recognized as safe. Therefore, the Commissioner tentatively concludes that the proposed regulation shall extend to any aerosol drug or cosmetic product containing zirconium including, but not limited to, antiperspirants.

The Panel recommends that action to remove aerosol products containing zirconium be implemented expeditiously and not await the full procedural review that has been established for OTC drug products in § 330.10 (21 CFR 330.10). Accordingly, on the basis of the Panel's concerns, the lack of toxicologic data adequate to the establishment of a safe level for use, the availability of other safer agents, the adverse benefit-to-risk ratio, and the recommendation for prompt action to remove these products from all drug and cosmetic products, the Commissioner has determined that the action he proposes regarding the use of these zirconium-containing aerosol products shall be taken through this notice of proposed rule making. The Commissioner tentatively has concluded that any delay in action regarding the use of these drug and cosmetic products is unjustified in view of the Panel's report and the evidence now at hand that such use cannot be generally recognized as safe and is contrary to the public interest.

However, because the major safety issue is attributable to prolonged use, the Commissioner at this time does not anticipate that a recall of previously marketed zirconium-containing aerosol drug and cosmetic products is necessary to protect the public health. It is the intention of the Commissioner that the effective date of the final regulation will be 30 days after publication in the FEDERAL REGISTER. Accordingly, under the provisions of this proposal, such products shipped in interstate commerce after the effective date of the final regulation which are not in compliance with the regulation will be regarded as not an approved new drug or, if the product is a cosmetic, as adulterated under section 601(a) of the act and subject to regulatory action.

If published as proposed, the final regulation regarding the use of these zirconium-containing aerosol products will apply to all drug and cosmetic products until such time as new evidence on their safety results in amendment of a monograph to be established for OTC antiperspirant products pursuant to the OTC drug review procedures under § 330.10.

In accordance with § 330.10(a)(2), all data and information concerning OTC zirconium-containing aerosol antiperspirant drug products submitted for consideration by the Advisory Review Panel have been handled as confidential by the Panel and the Food and Drug Administration. All such data and information shall be put on public display at the office of the Hearing Clerk, Food and Drug Administration, on or before July 7, 1975, except to the extent that the person submitting it demonstrates that it still falls within the confidentiality provisions of 18 U.S.C. 1905 or section 301(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(j)). Requests for confidentiality shall be submitted to the Food and Drug Administration, Bureau of Drugs, Division of OTC Drug Evaluation (HFD-510), 5600 Fishers Lane, Rockville, MD 20852.

The conclusions and recommendations contained in the April 29, 1975 report of the Advisory Review Panel on OTC Antiperspirant Drug Products for antiperspirant products containing zirconium are as follows:

The Commissioner appointed the following panel to review the data and information submitted, and to prepare a report on the safety and effectiveness and labeling of OTC antiperspirant drug products pursuant to § 330.10(a)(1):

E. William Rosenberg, M.D., Chairman
J. Wesley Clayton, Ph.D.
Charles A. Evans, M.D., PhD.
Zenona Wanda Mally, M.D.
Jane M. Rosenzweig, M.D.
Robert J. Scheuplein, Ph.D.
Eli Shefter, Ph.D.

The Panel was first convened on March 15, 1974 in an organizational meeting. Working meetings have been held on April 25-26, July 9-10, August 8-9, September 19-21, October 31 to November 2, December 16-17, 1974, and January 30-31, March 24-25, and April 24-25, 1975.

Two non-voting liaison representatives serve on the Panel, Ms. Marsha Gardner, nominated by an ad hoc group of consumer organizations and Robert Giovacchini, Ph.D., nominated by the Cosmetic, Toiletry and Fragrance Association.

Ms. Mary Bruch, an employee of the Food and Drug Administration, serves as Executive Secretary to the Panel. Lee Geismar, an employee of the Food and

Drug Administration, serves as Panel Administrator, Gary Trosclair, R.Ph., served as Drug Information Analyst until November 1974 followed by Joe Hussion, R.Ph.

In addition to the Panel members and liaison representatives, the Panel has utilized the advice of the following consultants:

Dov Boros, Ph.D.
George Comstock, M.D.
Helen Dickie, M.D.
Robert Drew, Ph.D.
William Epstein, M.D.
Robert Jones, M.D.
Michael Lebowitz, M.D.
Lollie Marchant
W. G. Spector, M.D.
Irwin Stolloff, M.D.

The following individuals were given an opportunity to appear before the Panel to express their views either at their own or the Panel's request:

Harold Baer, Ph.D.
Edwin V. Buehler, Ph.D.
Robert Choate
Ron Crytal, M.D.
Kenneth Ericson
Leon Golberg, M.D., D. Sc., Ph.D.
Leonard Harber, M.D.
Lester B. Hardy, Ph.D.
Clark Hoffman, Ph.D.
Herman Jass, Ph.D.
Frank Johnson, M.D.
William Jordan, M.D.
Albert M. Kligman, M.D.
Adalbert Koestner, D.V.M., Ph.D.
Edwin Larsen, Ph.D.
Bertil Magnusson, M.D.
Henry C. Maguire, Jr., M.D.
Howard I. Maibach, M.D.
Joseph Page, Esq.
Herbert Stokinger, Ph.D.
Hans Weill, M.D.
Ronald Wulf, Ph.D.

No person who so requested was denied an opportunity to appear before the Panel.

The Panel has thoroughly reviewed the literature, and the various data submissions, has listened to additional testimony from interested parties and has considered all pertinent data and information submitted through April 25, 1975 in arriving at its conclusions and recommendations.

The purpose of the OTC Antiperspirant Panel is to advise the Food and Drug Administration on the safety and effectiveness of currently marketed OTC antiperspirant drug products.

The Commissioner of Food and Drugs has stated that because self-medication is essential to the nation's health care system, it is imperative that over-the-counter drugs be safe, effective and adequately labeled. He further stated, "FDA accepts as necessary and desirable the tradition of self-medication . . . The consumer in turn has every right to expect that the OTC drugs he buys are safe and well labeled, and that they will perform as the manufacturer claims."

One of the specific charges to the Panel is: "To make recommendations to the Commissioner of Food and Drugs regarding those agents, their amounts, and combinations thereof, which based upon the available data, are not considered safe and effective . . ." The Panel acting under this charge has sent to the Commissioner its recommendation of March 25, 1975 that zirconium-containing aerosol antiperspirants be placed in OTC Category II and that appropriate steps be taken to withdraw these agents from interstate commerce until the safety testing adequate to secure the approval of an NDA has been performed.

The Panel has prepared the following in further explanation and support of these recommendations:

A. Guidelines

The Panel's recommendations were made within the framework of the following regulations pursuant to the OTC drug review procedures identified in § 330.10.

1. *Safety.* Means a low incidence of adverse reactions or significant side effects under adequate directions for use and warnings against unsafe use as well as low potential for harm which may result from abuse under indications of widespread availability. Proof of safety shall consist of adequate tests by methods reasonably applicable to show the drug is safe under the prescribed, recommended, or suggested conditions of use. This proof shall include results of significant human experience during marketing. General recognition of safety shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data (Ref. 1).

2. *Effectiveness.* Means a reasonable expectation that in a significant proportion of the target population, the pharmacological effect of the drug, when used under adequate directions for use and warnings against unsafe use, will provide clinically significant relief of the type claimed. Proof of effectiveness shall consist of controlled clinical investigations as defined in § 314.111(a)(5)(ii) (21 CFR 314.111(a)(5)(ii)), unless this requirement is waived on the basis of a showing that it is not reasonably applicable to the drug or essential to the validity of the investigation and that an alternative method of investigation is adequate to substantiate effectiveness. Investigations may be corroborated by partially controlled or uncontrolled studies, documented clinical studies by qualified experts, and reports of significant human experience during marketing. Isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered. General recognition of effectiveness shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data (Ref. 1).

3. *The benefit-to-risk ratio.* The benefit-to-risk ratio of a drug shall be considered in determining safety and effectiveness, and further, as stated in paragraph 62 of the preamble to the final order establishing the procedures for classification of OTC drugs published in the Federal Register of May 11, 1972 (37 FR 9464), "any drug which claims to be effective must have some pharmacologic action whether it is beneficial, aggravates an already existing condition, or results in an adverse reaction or side effect. In every instance the Panel must evaluate whether, balancing the benefits against the risks, the target population will experience a beneficial rather than a detrimental effect. Where little or no benefit is obtainable, of course, little or no risk is acceptable" (Ref. 1).

4. *General recognition of safety.* Only those drugs that are generally recognized as safe and effective and that are not misbranded may be lawfully marketed without an NDA. In § 330.10(a)(4)(i), the basis for general recognition is stated: "General recognition of safety shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data."

The Panel has been charged with making the determination of whether or not specific antiperspirant drug products are generally recognized as safe and effective and not misbranded. The judgment of the Panel has been based on the following criteria: (a) factual information available from the scientific literature; (b) factual information available from FDA, from manufacturers of antiperspirant drug products, from producers of raw materials which are used in antiperspirant drug products and from companies engaged in testing antiperspirant drug products; (c) the informed judgment of knowledgeable experts testifying at open sessions of the Panel; and (d) the experience and informed judgment of the Panel members themselves.

B. Other Attributes of Antiperspirant Drug Products

The Panel's charge with respect to both effectiveness and risk-benefit is to consider the "pharmacological effect of the drug"; for antiperspirant drug products, this is the antiperspirant action as measured by the degree of inhibition of axillary sweating.

The Panel has therefore concluded that the aesthetic attributes of the product per se or any other characteristics of the product per se that do not bear directly on the safety claims or efficacy are not relevant to this discussion. Such characteristics were considered only in terms of their impact on the overall safety or on the effectiveness of the antiperspirant drug product.

The specific form of the antiperspirant (aerosol, cream, lotion, or roll-on) or its method of application (by aerosol spray, by spray, by applicator or by hand) was considered when it related directly to safety or effectiveness.

C. Risk-Benefit and the Safety of T[he] Antiperspirant Drug Products

The Panel is specifically charged with balancing risk and benefit in its determination of the safety and effectiveness of antiperspirant drug products. The Panel has concluded that if a significant benefit is obtained by the users of effective antiperspirant drug products, some degree of risk is acceptable.

The degree of risk considered acceptable in the use of an antiperspirant is a

matter of judgment. Some insight into the Panel's judgment on this matter may be found in its consideration of the topical zirconium-containing antiperspirants.

The Panel recognized distinct differences in the safety of topically applied versus aerosolized zirconium-containing compounds. Many adverse reactions to topically applied antiperspirant formulations include reports of irritation, stinging, rashes, boils, lumps and other manifestations of allergic and nonallergic contact dermatitis. Nonetheless, the Panel has tentatively agreed on the safety of topically applied, nonaerosolized, zirconium-containing antiperspirants because:

1. *Adverse reaction.* These adverse reactions are ordinarily not serious and are reversible.

2. *Site of reaction.* These reactions occur locally at the site of application where they are to be expected, where they are visible and where, once detected, they can be treated and the product discontinued.

3. *Incidence.* The incidence of such adverse reactions is extremely low, of the order of 6 per million units sold.

4. *Body burden.* Because these are applied topically, the entrance of zirconium-containing particles into the body is reduced virtually to zero when the skin's barrier is intact.

5. *Effectiveness.* This topically applied antiperspirant is reasonably effective.

6. *Misuse.* The Panel recommends that adequate labeling be provided to warn against applying the product to open, broken or abraded skin where the skin's barrier is breached. But even if this warning is ignored by the consumer, and the product is misused, the Panel believes the consequences will not be unreasonably severe.

The Panel believes that the risks of the non-aerosolized product are inherent in the effective use of the drug and are therefore unavoidable; other topically applied, nonaerosolized antiperspirants give comparable adverse reactions. Overall, the impact of these adverse reactions on the health of the target population is not large; these reactions are ordinarily not serious, they are reversible and their incidence is extremely low.

The Panel has not addressed the question of whether or not the ability to reduce underarm perspiration is an important social or occupational problem. The desirability of using antiperspirant drug products for this purpose is regarded as a personal decision by the individual consumer.

D. Alternative Convenience Forms and Risk-Benefit

It is possible that antiperspirant drug products which are proven equally effective may not be judged equally safe. It may happen that a larger degree of risk is incurred by the use of an alternative convenience form of the product; e.g., a different method of application or a different formulation with the same active ingredient. Such alternative forms may be designed to achieve a more acceptable product, a product of greater convenience, or simply one with greater consumer appeal. The Panel concludes that adequate safety may be a reasonably broad area which defines an equally broad area of minimal risk. As long as the safety of the product is considered adequate, in terms of the benefit achieved by its use, there would seem no need to insist that only the single safest form be marketed.

However, the Panel believes it is appropriate to consider comparative safety or the safety offered by alternative forms of the product when a substantial question of safety exists in a specific "convenience form." An alteration in the form of a drug product which may substantially compromise its safety without offering a compensating improvement in effectiveness seems to the Panel to be an instance where the following comment applies: "Where little or no benefit is obtainable, of course, little or no risk is acceptable" (Ref. 1).

When such a question of safety exists, the Panel concludes that the existence of safer and equally effective products must have weight in the determination of acceptable risk or adequate safety. The prospect of the acceptance of an unnecessary risk in one form of a product when forms that are generally recognized as safe are available, is significant to a consideration of risk-benefit.

E. Historical Development

Zirconium compounds were first used as antiperspirants in the 1950's when sodium zirconium lactate was incorporated into a deodorant stick. Soon after introduction of this compound into the American market, users developed small, flesh-colored, indolent papules (small elevations of the skin) in the axillae. Papules would occur in streaks in a configuration which could be explained by a reaction to some material introduced along cuts induced by shaving. Shelley and Hurley (Ref. 2) concisely reviewed the experience of American dermatologists with this new clinical entity (Refs. 3 through 9). Histologically these papules resembled the so-called granuloma seen in sarcoidosis, a disease which can affect many organs of the body and is of unknown cause.

Several years later a different zirconium salt, zirconium oxide, was introduced for use on the skin, this time as a treatment for poison ivy dermatitis. Again, the areas of skin treated with the zirconium oxide cream developed small papules which, when biopsied, revealed epithelioid-cell granulomas (Refs. 10 through 14). It had thus been established that two zirconium products, sodium zirconium lactate and zirconium oxide, could cause sarcoid-like granulomas when introduced into human skin.

Although attempts to produce comparable skin granulomas in animals were unsuccessful, it was possible to reproduce the disease regularly in man. Shelley and Hurley (Ref. 9), and Epstein (Ref. 15) concluded on the basis of their studies that the mechanism responsible for zirconium granulomas in man depended on allergic hypersensitivity. The conclusion that zirconium-induced granulomas were a reaction of allergic hypersensitivity was based on the course of the disease, the time required for elicitation of a positive response, the individual's varied reaction and the minute, microgram dose required to elicit the response. Definitive supportive evidence in the form of sophisticated in vitro immunological techniques was not then available for the study of this process. The absence of a suitable laboratory test animal also limited the amount of investigation which was then possible.

As will be discussed later, while the allergic hypersensitivity mechanism remains a probable one, it is by no means out of the question that other mechanisms now known to account for granuloma formation might also be operative for zirconium-induced granulomas. Because sarcoid-like lung disease may result from the inhalation of many substances, the Panel has been particularly concerned about the safety aspects of zirconium-containing aerosol antiperspirants. In addition to the cases of skin granuloma due to sodium zirconium lactate and zirconium oxide reported above, the Panel considers the following reports of disease induced by these and other zirconium compounds pertinent to this discussion.

F. Published Scientific Reports

1. Epstein (Ref. 15) produced granulomas in three sensitized individuals with several zirconium compounds. These included zirconium carbonate, zirconium oxychloride, mixtures of zirconium oxychloride and glycerine, zirconium lactate and zirconium chlorhydrate. The intact zirconium-aluminum-glycerine complex did not produce skin granulomas in any of these individuals.

2. Obermayer (Ref. 17) reported a case of axillary granuloma. The cause and effect relationship with the woman's deodorant was not conclusively shown. At the time of this report only one zirconium-containing antiperspirant was marketed and it contained zirconium-aluminum-glycine complex.

3. Prior, Cronk, and Ziegler (Ref. 18) exposed rabbits to a mist containing very high concentrations of sodium zirconium lactate daily for 6 weeks. At the end of that time all test animals showed effects in the lungs such as bronchiolar abscesses, lobular type pneumonia or peribronchial granulomas. Prior's work has been criticized on the basis of the very high concentrations of sodium zirconium lactate (49,000 milligrams/cubic meter of air) used in this test. It is possible that a simple overload of the rabbits' resporatory system was responsible for many of the changes seen.

4. The same criticism cannot be levied, however, at the studies of Brown et al. (Ref. 19). Brown and his associates treated groups of 10 guinea pigs, 10 rats, and 10 hamsters for a period of 225 days by inhalation exposure to either 15 or 150 mg/cubic meter of air of zirconium lactate, to 15 mg/cubic meter of air of barium zirconate, or to room air. In the animals exposed to room air, no signifi-

cant changes were seen. In the animals exposed to zirconium lactate at a concentration of 150 mg/cubic meter of air, the lungs showed more pathological changes. These included pleural thickening, thickening of alveolar walls, and localized deposition of round cells in subpleural areas. Changes in the bronchi and bronchioles were minimal. Of even more interest were changes seen in the animals who were exposed to the lower dose of 15 mg/cubic meter of air. Marked pathological changes similar to those seen in the group receiving the higher dose were observed, but the animals receiving the lower dose had these changes to a much greater degree. In addition to the more severe changes in the animals treated with the lower dose, were findings in the lungs of these animals of a number of giant cells, although no granulomas. Animals treated with barium zirconate at a concentration of 15 mg/cubic meter of air developed comparable pathological changes. These were even more substantial than those produced by zirconium lactate. The general pathological picture in the lungs of these animals was one of a chronic interstitial pneumonitis with associated hypertrophy of the media of the arterioles, which in some cases had led to complete occlusion of the vessels. It was noted that removal of some of the animals from the dust exposure for a period of 3 months did not cause any marked regression in the lung pathology.

Studies attempting to define an immunologic mechanism for production of these pathologic changes were not conducted. The finding of more severe changes in animals exposed to a lower rather than higher dose, however, suggests that such might be a possible explanation. Whether immune mechanisms or other factors are involved, the medical experience with pneumoconiosis (a chronic fibrous reaction in the lungs eventually resulting in reduced lung function) includes instances in which people living in the neighborhood of a beryllium processing plant had more severe disease than the beryllium workers themselves (Ref. 20).

Investigators in one submission (Ref. 21) noted the fact that Brown, et al., amidst all the changes they produced in their experimental animals, did not observe formed granulomas. The Panel's interpretation of Brown et al. was different. The Panel is concerned about the possibility of zirconium-induced serious lung disease which begins with inflammation and goes on to produce fibrosis. The fully formed sarcoid-like granuloma, such as was seen in the skin, may not regularly appear in the lung even under the same sort of stimulus as produced the skin granuloma. Furthermore, the finding of giant cells suggests that comparable mechanisms may be operating because giant cells are characteristically found in granulomatous reactions.

5. An even more significant report was made available to FDA (Ref. 22). In this study, cynomolgus monkeys were exposed to an aerosol of an antiperspirant spray whose active ingredient was a complex of aluminum chlorhydrate and zirconium chlorhydrate. This product's composition was similar to one marketed zirconium-containing aerosol antiperspirant and differed from the other only in the absence of glycine. The test protocol specified the monkeys be exposed to the zirconium-containing aerosol antiperspirant for 15 seconds every 5 minutes for a period of 20 minutes in the morning and again in the afternoon. The test was continued for 90 days. The results in the monkeys' lungs showed "histopathologic pulmonary findings of granulomatous reactions in the terminal bronchioles." The analysis of the changes was of a "terminal bronchiolitis, with an inflammatory response exemplified by increased macrophagic activity."

6. Shelley (Ref. 23) studied the effect of the injections of several metal salts into the external ear of mice. Changes described as cartilaginous dysplasia (cartilage abnormality) were produced by the injections of zirconyl chloride or hafnium oxychloride, but not by a variety of other metal salts including aluminum chloride, beryllium sulfate, cadmium acetate, chromium potassium sulfate, cobalt chloride, and nickel chloride. Shelley concluded that the effects of zirconium and hafnium salts appeared to be unique and predictable. Even though some may consider this work irrelevant to the zirconium-containing aerosol antiperspirant issue, it does show a further toxicity of a zirconium compound.

7. Brackhanova and Shkupko (Ref. 24) found that zirconium hydride given in an intratracheal dose at 15 mg to rats caused pneumoconiosis. The effect was five to six times less severe than that caused by silicon dioxide. Silicon dioxide is recognized as a fibrogenic dust.

8. Mogilevskaja (Ref. 25) found that aerosols which contain metallic zirconium and zirconium dioxide produced a mild fibrogenic (formation of fibrotic tissue) reaction in rats. Inhalation of soluble zirconium salts produced further damage as well as a general toxic reaction. The changes were interpreted as being those suggestive of a tissue response arising from a low grade irritant.

G. The Relationship of Inhaled Particles, Lung Disease, Granulomas and Fibrosis

The problem of lung disease caused by inhaled aerosols is a complicated one which has recently received much attention. Parkes (Ref. 26) provided a recent comprehensive review of much of this material. A much more detailed treatment of theoretical aspects of the problem may be found in the symposium on inhaled aerosols edited by Lourenco (Ref. 27). The study of human disease caused by inhaled particles is a dynamic and rapidly moving field. The traditional tools of the epidemiologist and the morphologist are now being augmented by those of immunologists, electron microscopists, physical chemists, and others. For example, Miller et al. (Ref. 28) described a patient with no known exposure to pathogenic dust in whom electron microscopy revealed asbestos in amounts too small to be seen with a light microscope. The same group (Ref. 29) reported a patient with sarcoid-like disease in whom minute amounts of talc were established as the probable cause of disease.

Those papers and comparable ones cited in previous references point clearly to the conclusion that forms of pulmonary disease heretofore considered idiopathic (of unknown causation) must now be studied carefully for possible environmental causes. A review of this literature reveals also the substantial difficulty involved in ascribing causality of a sarcoid-like lung disease to various environmental agents.

In current medical practice, a substantial amount of recognized granulomatous disease is of unknown cause. The term sarcoidosis is applied to one group of granulomatous changes whose cause is unknown but in which the clinical course often conforms to a recognizable pattern.

Since its tendency to induce granulomas is crucial to the Panel's concern about zirconium, the Panel will summarize very briefly what is meant by the term granuloma. The granuloma (Ref. 30) is considered to be a distinctive form of inflammatory reaction which results when cells of the mononuclear phagocyte system encounter some substance they are unable to eliminate effectively.

The cells of the mononuclear phagocyte system are scavenger cells, widely dispersed throughout the body. It is now recognized that they are all derived from a common precursor (source) cell in the bone marrow. Depending on where they are located in the body, they take on different appearances and are called by different names. These locations and names include circulating blood (monocytes), connective tissue (histiocytes), liver (Kupffer cells), lungs (alveolar macrophages), lymph nodes (free and fixed macrophages), bone marrow (macrophages), and serous cavity (pleural and peritoneal macrophages). The osteoclast of bone tissue and the microglial cells of the nervous system are possibly also cells of this type. The term granuloma is used for the lesion produced by those cell aggregates when organized in a particular fashion.

As long as these cells are effectively able to remove foreign substances from their respective tissue, no cell aggregation occurs. It is thought that in at least three instances this effective elimination of foreign substances may be impaired and cells derived from mononuclear phagocytes aggregate.

One such instance occurs when the foreign substance has low biological activity for which there is no effective mechanism of elimination. Here the mononuclear phagocytic cells become stuffed with material that resists the cell's degradative enzyme system. These cells are immobile, resistant, long-lived macrophages which do not divide. These cells store the offending substance, often over a prolonged period. The granuloma thus formed is metabolically relatively inactive and has been termed a "low turnover" granuloma.

A different form of granuloma occurs in two other instances. In one of these, the foreign substance is toxic to the scavenger cell and damages it, releasing further toxic material into the tissue. In the other, the foreign substance acts as an allergen and brings cells of the body's immune system into play. In both of these cases, when the foreign substance is toxic or when it acts as an allergen, the resulting granuloma is characterized by a metabolically active derivative of the mononuclear phagocyte called the epithelioid cell and also by a form called the giant cell. Such granulomas are now termed "high turnover" granulomas.

Unlike the low turnover granulomas in whose cells the offending agent is easily found, the cells of the high turnover granulomas usually do not reveal the presence of the causative agent. The epithelioid cell granuloma has thus been more difficult to study and understand. More recently, however, it has been found that present techniques of immunology have helped to clarify the nature of high turnover granulomas caused by immune mechanisms (Ref. 30).

Of considerable interest is the recent observation that the mononuclear phagocytic cells of the granuloma produce a substance which acts as a stimulant to nearby connective tissue fibroblast cells. These fibroblasts are stimulated to produce more collagen, the basic fiber of connective tissue (Ref. 30). This effect of granuloma cells on fibroblasts would seem to explain the tendency of chronic granulomatous disease of the lung to result in a condition called pulmonary fibrosis. In this condition the required mobility of the breathing process is interfered with by excessive amounts of connective tissue in the lung .

H. The Panel Statement of November 27, 1974

The previous discussion of the nature of granulomas was taken from the Panel's statement of November 27, 1974. That statement was based on the Panel's assessment of the zirconium-containing aerosol antiperspirant problem. It was written following the review of pertinent literature and after a 2-day open session in which a number of invited distinguished experts in the fields of granuloma pathology and pathophysiology and of pneumoconiosis participated. These experts answered the Panel's questions for 2 days. A transcript of that session is available (Ref. 30). All these experts emphasized that further testing was required. At no time during the 2-day open session would any of the experts state that, in their opinion, zirconium-containing aerosol antiperspirants were generally recognized as safe.

Following the open session with the testimony of experts and after a careful review of submissions of zirconium-containing aerosol antiperspirants and their respective ingredients, the Panel issued a statement on November 27, 1974, which expressed concern about the safety of zirconium-containing aerosol antiperspirants. It was the opinion of the Panel that some zirconium-containing particles would be inhaled from the use of these zirconium-containing aerosol antiperspirants, and that there was inadequate information about the fate of inhaled zirconium-containing particles once they reached the lung. The Panel noted a lack of information about how particles were excreted, at what rate, and whether they broke down into products releasing zirconium in forms which might be allergenic or toxic in other ways. The Panel was unconvinced, in view of the brief history of the use of zirconium-containing aerosol antiperspirants, that long term use in susceptible subjects would not result in development of pulmonary fibrosis. The Panel concluded that tests to measure the immunogenic potential of zirconium-containing aerosol antiperspirants had not been done. The Panel was not satisfied with the follow-up that had been made on users who had complained of respiratory difficulty after exposures to zirconium-containing aerosol antiperspirants. At that time, the Panel discussed the zirconium-containing aerosol antiperspirants in light of what they perceived as benefit-to-risk considerations. It was pointed out that comparable degrees of control of underarm perspiration could be achieved either with zirconium-containing cream products or, in fact, with the most effective forms of aluminum chlorhydrate-containing rollons. Although consumers would be expected to want the most active antiperspirants available, it by no means seemed clear that consumers could always perceive the kinds of difference in activity that could be determined in laboratory studies. The majority of users, for instance, preferred aerosol sprays of aluminum chlorhydrate to creams or rollons containing the same ingredients, even though the latter were somewhat more effective than the sprays.

Although the Panel had voted at its November meeting to place zirconium-containing aerosol antiperspirants in Category II (not generally recognized as safe) the Panel agreed, when requested by industry, to express its concerns and position with a statement and to defer a decision until industry could respond.

I. Assertion of Safety From Representatives of Industry

On December 16 and 17, 1974, representatives of industry presented their reasons for believing that zirconium-containing aerosol antiperspirants did not present a hazard to health. Their case was supported by supplemental submissions (Ref. 31). Because these submissions represent the basis for industry's assertion that zirconium-containing aerosol antiperspirants are safe, the Panel's analysis is set forth in the following sections.

Four main conclusions were offered by industry as follows:

1. Aerosol antiperspirants containing zirconium-aluminum-glycine complex have shown no potential for producing granulomas of the lungs.

2. Zirconium-aluminum-glycine complex is cleared from the lung by the mucociliary escalator (natural lung clearance mechanism whereby hair-like projections called cilia transport particles out of the lung) and is eliminated through the gastrointestinal tract.

3. Zirconium-aluminum-glycine complex does not contain zirconium chlorhydrate.

4. Zirconium-aluminum-glycine complex does not break down in the lung.

Particular attention will now be paid to these four points and their supporting data; later comment will be made generally on other portions of these submissions and also on the other supplemental submissions.

1. "Aerosol antiperspirants containing zirconium-aluminum-glycine complex show no potential for producing granulomas of the lungs."

It is the Panel's opinion that this statement, viewed in the most favorable light possible, can only be described as conclusory and not supported by specific data. In the Panel's considered view, published reports of disease induced by several zirconium salts, the testimony of experts about the risks of inhaling zirconium-containing aerosol antiperspirants and some aspects of the submissions themselves are sufficient to justify the contrary conclusion: a real possibility exists that zirconium-aluminum-glycine complex will induce lung disease.

2. "Zirconium-aluminum-glycine complex is cleared from the lung by the mucociliary escalator and eliminated via the gastrointestinal tract."

Three experiments in the submission are adduced to support this assertion. They are as follows:

(i) Each of 2 rabbits was intratracheally infused (Ref. 32) with solutions containing either 0.5, 5.0, or 50 mg of zirconium-aluminum-glycine complex, or 0.073, or 7.3 mg of sodium zirconium lactate (volume of solution not provided). The 2 animals dosed with 50 mg of zirconium-aluminum-glycine complex were sacrificed 5 days after dosing. All other animals were sacrificed 15 days after dosing. Lung tissue was obtained from all animals and was examined by an electron microscope x-ray analyzer for the presence and distribution of zirconium and aluminum.

Ashed samples from some (an undisclosed number) of the rabbits were examined for zirconium. Zirconium was detected only in the group dosed with 7.3 mg of sodium zirconium lactate. The experimenter concluded that, even at an exaggerated dose of 50 mg, zirconium-aluminum-glycine complex is cleared from the lung within 5 days, whereas sodium zirconium lactate is not cleared even after 15 days. From the submission it is not clear how many rabbits were used in the experiment since either 6 or 12 animals were present at the beginning and only 4 or 8 were reported on at the end. Similarly, the experiment promised data on six different solutions of zirconium-aluminum-glycine complex and sodium zirconium lactate, but presented results for only four solutions. The concentrations of the solutions were not given nor was the actual technique of intratracheal infusion used described. It is not

clear whether the final ashed samples listed represent pooled or individual samples. This experiment, as described, does not support the conclusion that zirconium-aluminum-glycine complex is cleared from the lung by the mucociliary escalator and eliminated via the intestinal tract.

(ii) In another experiment 75 mg of powdered zirconium-aluminum-glycine complex was intratracheally infused into 2 rabbits. One animal was sacrificed within a few minutes after dosing; the other after 16 hours. The trachea and lungs were removed and sectioned. The tissue was ashed and analyzed for both zirconium and aluminum by x-ray fluorescence. The results showed that the zirconium-aluminum-glycine complex had been substantially cleared from the lung in 16 hours and that the zirconium-aluminum-glycine complex remaining after 16 hours was in the upper portion of the lung, indicating that the material is being cleared by the mucociliary escalator.

The Panel agrees that properly conducted powder insufflation experiments of the type described are useful. But such experiments can show only how materials presented to the lungs by powder insufflation may be distributed and cleared. Aerosolized particles of respirable size and characteristics can be distributed within the lung in a manner completely different from those introduced by powder insufflation. This is not a minor technical point but a major reason for substantial investments in inhalation toxicology by industrial firms and test laboratories. Particles produced by a propellant system would be expected to have typical characteristics which are quite different from powdered material for insufflation; for example, different particle size and surface characteristics. This, in turn, would influence the amount of material that reaches the lower lung. Propellant generated particles would be more likely to reach the deepest portions of the lung because of their smaller particle size characteristics.

Lung retention studies of insoluble aerosol particles, including zirconium oxide, have shown effective half-lives of 1000 days in the lungs of beagle dogs (Ref. 30 and 33). The major portion of zirconium-aluminum-glycine complex particles are expected to be insoluble. In general, the class of insoluble particulate aerosols are more likely to remain in the lung than relatively soluble aerosols (Ref. 30). The Panel cannot accept conclusions about the safety of zirconium-aluminum-glycine complex aerosol products without definitive measurements of pulmonary retention times as well as the anatomic distribution of zirconium-containing aerosol antiperspirant particles in the respiratory tract.

(iii) The clearance of zirconium-aluminum-glycine complexes from the lung was investigated in another pilot study. According to the submission: "Guinea pigs were intratracheally infused with doses of either 0.8 or 7.7 mg of zirconium as zirconium-aluminum-glycine complex, which are 200,000 to 500,000 times that of human exposure. The material used was radiolabeled with zirconium[95] [radioactive zirconium]. The absorption, distribution, and elimination of zirconium-aluminum-glycine complex was followed by radioactive analysis of all tissues and excreta."

These experiments are cited to show that when aqueous solution of zirconium-aluminum-glycine complex are introduced into the lungs of guinea pigs, there is minimal systemic absorption, and that essentially all of the zirconium-aluminum-glycine complex is found in the lung, gastrointestinal tract, and feces. It is claimed further that levels in the gastrointestinal tract and feces indicate that the material is being cleared by the mucociliary escalator.

The Panel agrees that for intratracheally infused solutions of zirconium-aluminum-glycine complex, the results support the assertion that there is minimal systemic absorption. This is not proof of the complete lack of systemic absorption, nor is it proof that absorption, if it occurs, may not produce disease. Since these solutions were intratracheally infused, little can be concluded from the experiment regarding the clearance of aerosolized particles. This experiment is cited to support the general conclusion that zirconium-aluminum-glycine complex is cleared from the lungs by the mucociliary escalator and then from the gastrointestinal tract, but this conclusion is clearly unsupported for aerosolized particles. Furthermore, even for intratracheally infused particles, the experimental results ignore the real possibility of clearance by the general circulatory system via the lymphatics, blood, and bile. Statements that the mucociliary escalator can effectively clear respired particles can be made about almost any respiratory inhalant if the particle size is in a specific range. The well known ability of many inhalants to produce lung disease should be proof that the mucociliary escalator mechanism cannot be relied on for complete protection. Since reliance was placed on the ability of the mucociliary escalator to clear inhaled zirconium-containing aerosol antiperspirants from the lung, it must be emphasized further that this mechanism cannot be relied upon to totally remove inhaled particles of zirconium-containing aersol antiperspirants because of particle size differences and solubility factors.

This problem is discussed in a current reference source (Ref. 26) on inhalation-induced lung disease:

> Both inert and cytotoxic insoluble particles which are deposited in the conducting airways above the terminal bronchioles are eliminated either in a free (that is, extracellular) state or within macrophages via the mucociliary "escalator" and are expectorated in sputum or swallowed usually about 12 hours after inhalation. However, in the gas exchanging region distal to the terminal bronchioles, the behavior of inert and cytotoxic particles appears to be different.
>
> Inert particles deposited in alveoli tend to remain in the alveolar area and to be eliminated mainly by the bronchial route. They are engulfed by macrophages which migrate from the alveoli over the nonciliated zone of the respiratory bronchioles to the mucociliary "escalator" in the terminal bronchioles. It is not understood how they are able to bridge this gap but it has been suggested (Ref. 34) that a proximal movement of surfactant may be responsible. Particles lodged in the interstitium may be carried by macrophages in tissue fluids to the lymphatics whence they travel to intrapulmonary and hilar lymph nodes, but others are retained, or "stored," in the interstitial site for years.
>
> Smaller insoluble particles tend to travel to hilar lymph nodes more quickly than larger ones, but quartz particles reach the lymphatics more rapidly than non-toxic particles, such as titanium oxide, of similar size (Ref. 34). Furthermore, some small particles may pass into the blood stream; this explains the occasional presence of silicotic lesions in the liver and spleen and other organs.
>
> The efficiency with which insoluble dusts are removed from the lung varies, therefore, according to whether they are inert or cytotoxic as well as upon the load or concentration of particles imposed upon the elimination routes. Soluble particles dissolve readily and pass into the capillary blood or, possibly, are bound to lung tissue proteins; hence, if they are toxic they may cause damage either systemically or locally.
>
> The process by which inert and cytotoxic dusts pass from the alveolar lumen into the alveolar wall or its adjacent interstitium is obscure. Breaching of the wall by damage to Type I pneumocytes is thought to occur by some workers (Ref. 35) but is denied by others. There is experimental evidence to show that particles may penetrate into the alveolar wall without the mediation of phagocytic cells (Ref. 36) and that this tends to occur where alveoli are in opposition to bronchiolo-vascular bundles.

The Panel concluded that studies of the hilar and regional lymph nodes are essential because they are often involved in sarcoid-like pulmonary disorders. It therefore seems mandatory that examination of these nodes be included in studies of the clearance and distribution of zirconium-containing aerosol antiperspirants.

A much more detailed analysis of the problem of removal of aerosolized products from the lung is given by Morrow (Ref. 37). That article is comprehensive, and contains 130 references; it cannot be summarized briefly but deserves attention in this context.

The Panel has already commented about the technical problems in the experiments designed to show that the mucociliary mechanism can be expected to remove all inhaled particles of zirconium-aluminum-glycine complex. A brief review of Morrow's work and the accompanying paper by Green (Ref. 38) would indicate that such an inclusive statement as "zirconium-aluminum-glycine complex is cleared from the lung by the mucociliary escalator and eliminated via the gastrointestinal tract" cannot be supported in light of the present level of knowledge about how inhaled materials are removed from the lung. The Panel would emphasize again that certainly much of the inhaled zirconium-aluminum complex is removed from the lung by the mucociliary escalator mechanism. But, based on the substantial amount of current information, it is unlikely that all could be removed that way, nor do the studies cited prove it.

This major portion of the claimed basis for safety made to the Panel must be regarded as unsupported by the evidence.

3. The third of these four assertions states: "Zirconium-aluminum-glycine complex does not contain zirconium chlorhydrate." A similar statement appears in another submission (Ref. 22).

In the latter submission, the statement is made that the zirconium-aluminum complex product in question does not contain zirconium chlorhydrate. In each case the Panel will assume that the meaning of the statement is that the final zirconium-containing antiperspirant product is a complex of aluminum and zirconium and no longer contains zirconium chlorhydrate. The implication of this statement is that the zirconium-aluminum-chlorhydrate complex, with or without glycine, thus formed is a unique new entity which will remain intact. The thrust of the statements in OTC Volumes is that zirconium-aluminum-glycine complex is such a product. Evidence cited in another submission states that the zirconium-aluminum complex product described therein is equally as stable as zirconium-aluminum-glycine complex and no more likely to yield zirconium chlorhydrate (Ref. 22).

Submissions state that zirconium-aluminum-glycine complex or zirconium-alumium complex will not hydrolyze to zirconium chlorhydrate. This is a reasonable concern since zirconium chlorhydrate was found to produce a granuloma when injected by skin test into a patient previously sensitized to zirconium lactate (Ref. 39).

As will be shown, the Panel is uncertain about the nature of the zirconium derivative product(s) which may be derived from zirconium-aluminum-glycine complex or zirconium-aluminum complexes when they are introduced into the body. In a report (Ref. 31), it was shown that when zirconium-aluminum-glycine complex is mixed in vitro with human blood serum "the solubilization of aluminum and zirconium by blood serum appeared to be a real effect." The investigator was unable to characterize these solubilized aluminum and zirconium products further except to indicate that they were of a high molecular weight.

Whether or not zirconium-aluminum-glycine complex "contains" zirconium chlorhydrate seems less to the point than the fact that zirconium-aluminum-glycine complex will release some solubilized zirconium product upon contact with serum.

Since many conclusions have been drawn with reference to zirconium's chemical reactions, further analyses of submissions relative to zirconium chemistry are as follows:

Ultracentrifugation studies on zirconium-aluminum complexes and zirconium-alumium-glycine complexes show that these complex molecules exist as polymeric species (a high molecular weight compound formed by the combination of simpler molecules). A wide range of polymeric sizes with an average molecular weight of 2000 daltons (defined as a unit of mass, 1.65×10^{-24} gm) was shown to be present in aqueous solutions of zirconium-aluminum-glycine complex under ambient, i.e., normally fluctuating, conditions by use of the analytical ultracentrifuge. As the pH of the zirconium-aluminum-glycine complex solution is increased (decreasing acidity), there is a tendency to increase the amount of higher molecular weight species until, at a pH between 5 and 6 (slightly acidic), the material gels. Though the structure of the insoluble gels has not been established, the experimental evidence reported suggests that it is an extremely high molecular weight polymer. The polymerization process appears to be reversible.

A number of studies were carried out to examine the stability of zirconium-containing aerosols under differing conditions. In the case of zirconium-aluminum-gylcine complexes, such investigations were carried out in a number of stressing systems such as phosphate buffer at pH 7 (neutral solution), simulated serum electrolyte at pH 7.4 (slightly basic), macrophage lysate (obtained by exposing rabbit lung macrophage to ultrasonic waves), viable macrophage (concentration determined to be 6 to 7×10^6 cells/ml), hamster lung homogenate and rabbit lung surfactant. The general procedure in these experiments was to incubate the zirconium-aluminum-glycine complex in the particular system and then analyze the supernatant solution of the filtered system for the presence of zirconium and aluminum. The results reported suggest that zirconium-aluminum-glycine complex is not broken down into soluble species of low molecular weight. These studies were not capable of determining any insoluble or high molecular weight zirconium complexes of organic materials in the stressing systems.

The stability of zirconium-aluminum-glycine complex and zirconium-aluminum complex gels in the physiologic pH range (7 to 8) was studied as a function of lactate ion. It was found that when the molar ration of lactate ion to zirconium was increased above 3 (that is, more than 3 lactate ions to every zirconium ion), a substantial degree of solubilization of zirconium and aluminum took place. When the ratio was below 3, the amount of aluminum and zirconium detected in the supernatant solution (solubilized material) was minute but above zero at the limit of the analytical procedure; that is, 5 parts per million (ppm) for aluminum and 1 ppm for zirconium.

In one series of stability studies on zirconium-aluminum-glycine complexes, the commercial aerosol products were tested. In these studies the aerosolized materials of two commercial products were sprayed into centrifuge tubes and a variety of buffer solutions at pH 7.4 were added. In addition, tests with pooled human blood serum were carried out. The results show that while the hydrolysis of zirconium-aluminum-glycine complexes does not take place in the buffer systems it does take place in blood serum. The approximate order of the solubilization effect in human serum was zirconium-aluminum-glycine complexes, 44 ppm of complex solubilized; a commercial zirconium-aluminum-glycine complex product, 42 ppm of complex solubilized; zirconium chlorhydrate, 37 ppm of complex solubilized; another commercial zirconium-aluminum-glycine product, 10 ppm of complex solubilized. These numbers are the average concentration in ppm of aluminum plus zirconium in these studies. "The solubilization of aluminum and zirconium by blood appeared to be a real effect," the investigator said (Ref. 38). Results of centrifugation of the serum solutions suggest that the majority of the soluble zirconium and aluminum species were of molecular weight greater than 5000 daltons; however, a significant amount of soluble species were below this size. The experimenter who carried out this study pointed out that although the concentration of solubilized aluminum generally exceeded that of zirconium, occasionally the opposite situation occurred. This would suggest nonuniformity in the breakdown by serum of gelled zirconium-aluminum-glycine complexes. This experiment points out the urgency in finding out which materials present in blood enable it to hydrolyze zirconium-aluminum-glycine complexes. Do similar species exist in other organs: for example, the lung?

The aluminum and zirconium in zirconium-aluminum-glycine complexes and zirconium-aluminum cimplexes will react with alizarin red to form distinctly colored complexes. It is likely that many other organic species will interact with these zirconium-containing antiperspirants to form coordination complexes. It is not inconceivable that some proteins in the body might coordinate with a degraded fraction of a zirconium-containing antiperspirant and become antigenic (Ref. 30).

Charged molecular species will migrate in an electrical field toward either the positive or negative electrode. Cationic species which are positively charged move toward the negatively charged electrode (cathode). Likewise, anionic species are negatively charged and will move toward the positively charged electrode (anode). Aluminum chlorhydrate, zirconium chlorhydrate, zirconium-aluminum-glycine, and zirconium-aluminum complexes are all cationic species while sodium zirconium lactate is anionic.

The electrophoretic mobility, i.e., the characteristic of a molecular species to move toward a particular electrode, is altered by the presence of lactate with the various zirconium-containing antiperspirants. This may be suggestive of some molecular interaction. Only at very high lactate concentrations was some of the zirconium-aluminum-glycine converted to an anionic form.

Another series of experiments was carried out to determine what happens when aerosolized particles of a zirconium-aluminum-glycine complex are deposited on aqueous surfaces which are representative of animal tissue. The results suggest that the buffer capacity of the

zirconium-aluminum-glycine complex is sufficient to overcome the buffer capacity of the medium in the immediate vicinity of the particle, thus facilitating its diffusion into the surrounding medium. It is possible that at this diffusional interface, in a biological medium, the zirconium-aluminum-glycine complex might be susceptible to degradation even though the pH of the medium is in the physiological range.

There is clearly a need to investigate the types of interactions that can take place between zirconium-containing antiperspirant and other compounds in tissue proteins.

The Panel was presented with evidence that there may be distinct differences in the toxicological behavior of different zirconium-containing aerosol antiperspirants (Ref. 45). There is thus a definite need to have an analytical procedure which can distinguish between these materials.

The stability of zirconium-containing aerosols was examined in the presence of lung homogenates under conditions in which the tissue was not metabolically active. It is the metabolically active lung tissue that is of major concern to the Panel. Whether or not the viable lung is capable of altering the structure of zirconium-containing aerosols is a question that has not been adequately addressed in any of the submissions to the Panel. Though zirconium-containing aerosols incubated in the lung homogenates (Ref. 31 and 42) show no solubilization of zirconium-containing aerosol, one must be aware that the metabolically active lung tissue will produce considerable amounts of lactate (Ref. 31). Lactate has been shown to break down zirconium-containing antiperspirants in nonbiological systems (Ref. 31) where the lactate to zirconium ratio is high. That small particles of zirconium-containing antiperspirants reaching the lung experience lactate/zirconium ratios which are high remains to be demonstrated.

4. The fourth assertion in the submission, "Zirconium - aluminum - glycine complex did not break down in the lung," has been touched on already in the previous discussion about zirconium chemistry in paragraph I.3. of this preamble. It was pointed out in that discussion that the critical factor was that when mixed with serum, zirconium-containing glycine complex does solubilize. In this regard, the comments of Morrow (Ref. 37) are pertinent.

In discussing mechanisms of alveolar clearance Morrow says, "However, it has been clearly demonstrated that the terms 'insoluble' or 'soluble' based on *in vitro* measurements (usually in water) are often meaningless in terms of the biological behavior of the substance including its removal from the lung."

The solubilization of zirconium from zirconium-aluminum-glycine complexes in the presence of serum provides evidence to the contrary. Detailed analysis of the evidence regarding the breakdown of zirconium-aluminum-glycine complex in the lung shows that degradation of zirconium - aluminum - glycine complex does occur in human blood serum after spraying of commercial products into centrifuge tubes containing various buffers. The solubilization of zirconium-aluminum-glycine complex in human blood serum is a real effect, as emphasized by the experimenter himself.

In the opinion of the Panel, that particular study is extremely important because it demonstrates that the zirconium-aluminum-glycine complex is capable of being degraded by body fluids, that is, human serum. This is especially true in light of the fact that any zirconium-aluminum-glycine complex particle reaching the alveoli can readily come in contact with human serum.

Another study was designed to show the effect of hamster lung homogenate on zirconium-aluminum-glycine complex stability. In this study, zirconium-aluminum-glycine complex was incubated with hamster lung homogenates, and subsequently the supernatant of the filtered system was analyzed for the presence of zirconium and aluminum by x-ray emission spectroscopy. The results indicate that zirconium-aluminum-glycine complex is not broken down into soluble species of low molecular weight. The Panel accepts the conclusion from this study. In view of solubilization of zirconium-aluminum-glycine complex by serum, however, the Panel believes that the conclusions cannot be extrapolated to indicate that zirconium-aluminum-glycine complex is stable in an intact lung. For this reason, the importance of using viable, metabolically active lung tissue cannot be overemphasized.

Zirconium-aluminum-glycine complex was incubated with rabbit lung surfactant in another experiment. The Panel agrees with the conclusion that there appears to be no interaction between lipids and zirconium-aluminum-glycine complexes or between lipids and sodium zirconium lactate. The Panel also agrees with the conclusion that the lipid distribution in lipid extracts from rabbit lung is not changed by incubation with either zirconium - aluminum - glycine complexes or sodium zirconium lactate. From this same experiment, it seems that sodium zirconium lactate does not interfere with the lung surfactant lipid either, even though sodium zirconium lactate is known to be biologically active and granulomatogenic. For this reason, the absence of a positive result with zirconium-aluminum-glycine complex is not convincing evidence of biological inactivity.

The Panel concludes that the preceding set of studies performed to show inactivity of zirconium-aluminum-glycine complex under physiologically active conditions was not conclusive. Specifically, the Panel pointed out that in the single most representative tissue fluid, serum, the zirconium-aluminum-glycine did solubilize, releasing zirconium and aluminum species of high molecular weight. Also, the failure to demonstrate biological reactivity of sodium zirconium lactate in another experiment casts doubt on the conclusion about zirconium-aluminum-glycine complex.

The Panel is impressed with the fact that a series of various buffers of salts did not degrade zirconium-aluminum-glycine complex, but that when serum, a biological fluid, is used, zirconium-aluminum-glycine complex is broken down. Examined in this light, the lengthy submission of December 16 and 17, 1974 is unconvincing because: (i) Statements about the absence of potential for granuloma production appear to be unsubstantiated.

(ii) The claim that zirconium-aluminum-glycine complex is removed by the mucociliary escalator is true to a degree, but it does not suggest the amount that is removed, the other mechanisms involved, or what the rate of removal would be from the lung.

(iii) The fact that zirconium chlorhydrate is or is not a degradation product of zirconium-aluminum-glycine complex is less important than the evidence that small, zirconium-containing products may be released from zirconium-aluminum-glycine complexes.

(iv) The statement that zirconium-aluminum-glycine does not break down in the viable lung is not supported by the evidence in the submission itself and is made unlikely by the fact that zirconium-aluminum-glycine complex is partially solubilized by serum.

J. Further Analysis of Submissions

A close reading of the submission raises further questions about the submitted data.

1. *Inhalation toxicity testing.* Another area in which the data were inadequate concerned the details of inhalation toxicity testing.

A number of subchronic inhalation tests of 90-day duration on various zirconium complexes were conducted using monkeys. Some of these were reported as producing no effects in the lungs of the exposed animals. The data from these studies are summarized in the following table:

TABLE I.—*Summary: 90-day inhalation tests*

Chamber conditions	Number of monkeys per test group	Product tested	Dose dispensed from can into chamber (grams)	Analytical conclusions in chamber, filter weight, Milligram per lambert	Histopathologic effects	Exposure conditions
Essentially static	6	ZAR [1]	33	0.034	None	2 30 s bursts per day, followed by 15 m retention time in chamber.
Do	6	Vehicle control	33.2	0	do	Do.
Do	6	ZAR [2]	31.6	0.035	Negative in this study, positive in other studies.	Do.
Do	6	ZAR [1]	Not determined	0.03	None	Do.
Do	6	Vehicle control	do	0	do	Do.
Do	6	ZAR [2]	do	0.029	Negative in this study, positive in other studies.	Do.
Do	6	ZAR [1]	35.39	0.024	None	Do.
Do	6	Vehicle control	38.29	0	do	Do.
Do	6	ZAG [3]	30.5	0.011	do	Do.
Dynamic	8	ZAR [2]	64.6	0.108	Positive effects	4 15 s bursts, twice a day (a.m., p.m.) 7 d per week.
Do	8	ZAR [2]	59.7	0.108	do	Do.
Do	8	Control	0	0		Do.
Do	8	ZAG [3]	58.6	0.043	None	Do.
Do	8	ZAR [2]	Not determined	0.071	Positive effects	Do.
Do	8	ZAR [2]	do	0.052	do	Do.
Do	8	Control		0		Do.
Do	6	ZAG [4]	73.3	0.033	None	Do.
Do	6	ZAG [3]	63.8	0.04	do	Do.
Do	6	Control	0	0		Do.
Essentially static	3	ZAG [3]	Approximately 11	Not determined.	None [5]	3 10 s bursts per day.
Do	3	Control			do [5]	
Do	3	ZAG [3]	Approximately 11	Not determined.	do [5]	Do.
Do	3	ZAG [3]	Approximately 60	do	do [5]	3 100 s bursts per day.
Do	3	Control	0	0	do [5]	

[1] Newly marketed zirconium-aluminum complex.
[2] Recalled zirconium-aluminum complex.
[3] Marketed zirconium-aluminum-glycine complex.
[4] New nonmarketed zirconium-aluminum-glycine complex.
[5] High background pulmonary disease.

One series of tests with zirconium-aluminum complex (0.10 mg/liter) produced adverse effects in monkeys exposed in a dynamic chamber. These effects have been described as mild bronchiolitis. In addition, pre-granulomatous cellular changes were reported. When zirconium-aluminum-glycine complex was tested in the same study, no effects were found. However, the analytic concentration of zirconium-aluminum-glycine complex in this study was less than one-half that of the complex producing the effect. The complex producing the effect was positive at several lower concentration levels (0.071 to 0.052 mg/liter).

In contrast, when another different complex of aluminum and zirconium from a different manufacturer and the zirconium-aluminum complex that produced the adverse effect described above were tested in a simple exposure level at 0.03 mg/liter in a chamber with essentially static conditions, no effect was found with either complex.

The results of these studies emphasized that changing the exposure concentrations and the chamber conditions changed the effects attained. Further, these data, taken together, appear to demonstrate a dose-response relationship.

The inhalation tests performed with the marketed zirconium-aluminum-glycine complex products were tested in an essentially static chamber with two exposure levels. Because only three monkeys were used per test group, in contrast to the other tests employing six or eight animals per group, the results should be considered preliminary. No adverse effects were observed in the test animals except for pigment formation from mites in the lungs and subsequent reaction to it. Pneumonitis was observed in the lungs of control and test monkeys. No other lung changes were reported. The high background of pulmonary pathology and the small number of animals make the study inadequate to support safety of the zirconium-aluminum-glycine complex products.

A new, unmarketed zirconium-aluminum-glycine complex was tested for 90 days in a dynamic type chamber at 0.03 to 0.04 mg/liter with a larger group of animals and employed the previously mentioned marketed zirconium-aluminum-glycine complex as a comparative control. In this 90-day study, no adverse effects attributable to either product were observed in the lungs.

Although neither of these zirconium-containing aerosol antiperspirant products that contain zirconium-aluminum-glycine complex produced toxic effects, the Panel does not accept this as adequate proof of safety, considering the intended use of the product. Specifically, this test did not utilize positive comparative controls, did not vary dose levels to establish a dose-response relationship, and was not of sufficient duration. While these studies do not show a toxic effect, they cannot predict the long term hazard that the Panel believes can be found only if long term toxicity testing is done.

The Panel concludes that adequate animal inhalation tests should use an appropriate and adequate number of animals and extend for a longer period of time than 90 days. Also, the animals should be free of complicating background disease to facilitate detection of effects. Dynamic chamber conditions that allow adequate exchange of respiratory gases should be employed, with exposure concentrations chosen to determine a dose-response relationship.

Even though numerous animal inhalation studies have been reported, the lack of a variety of concentrations needed to produce toxic effects in animals was noted in all submissions. The sophistication already available (Ref. 37) in aerosol testing was not reflected in most inhalation studies submitted to the Panel. The Panel would stress careful selection of an animal species for the particular effect being studied. An extrapolation from studies in a single species to man is frequently misleading.

The cynomolgus monkeys have often been used as test animals, and though less prone to lung infestation than the Rhesus monkey, background effects similar to possible effects from zirconium-containing aerosol antiperspirants still make unequivocal conclusions difficult. Since toxic effects with zirconium-containing aerosol antiperspirants have been found in monkeys, this species will likely be one that is selected for study. However, more than one species should be tested.

In some studies, the amount delivered into the chamber was the only parameter known. Because the actual dose inhaled by the animal is dependent on the duration of the spray, the particle size distribution, the breathing rate, the volume of the animal, and the degree of absorption, chamber concentration per se does not sufficiently describe the dose in the animal. Sometimes animals hold their breath and will not breathe for the first few seconds of the burst, adding further complexity to estimation of the dose. The more exactly any of the variables can be controlled, the better. The

Panel would agree with most laboratories that do aerosol studies (Refs. 30 and 33) and who recommend dynamic chambers and include accurate dose determination.

In a number of the studies reported, head-only exposure was chosen and the burst was followed by a 15 minute post exposure in the chamber. The Panel would suggest the exposure of the whole body with animals retained in the chamber.

Toxicology testing should include both positive and negative controls to establish the validity of the test. Dose levels should be varied until effect levels are found; once known effect levels are determined, they can be utilized for the estimation of safety factors. Also, only by using dose levels high enough to produce toxic effects is it possible to be sure of all the sites where toxic effects may be seen. Many of these submitted studies did not include an exposure level high enough to produce an effect, and in many cases only one exposure level was utilized. The value of any chronic or subchronic, one-dose study is questionable. Conclusory statements from the test results are meaningless in such cases, especially when an insufficient number of animals, with background disease hard to distinguish from the expected effect, are used.

2. *Granuloma formation.* The Panel would not agree that low-turnover granulomas occur only after extreme overdosing with particulate material, when the mononuclear phagocytic system is presented with particulate material which is neither toxic nor degradable. If the response is a long-lived accumulation of immobilized lymphocytic cells, the reaction, called a low-turnover granuloma by Professor Spector, ensues (Ref. 30). Testimony before the Panel indicates that repeated exposures to insoluble particulate aerosols like zirconium-aluminum-glycine complex are likely to result in the accumulation of these particles in the lung. One cannot dismiss the possibility of granuloma formation based on the assertion that a dose from a single exposure is very small when 30 or 40 years' use of these products can be estimated.

In order to accept industry's proposition that zirconium-aluminum-glycine complex has no potential for producing low-turnover granuloma, the Panel would require data not yet at hand; that is, data demonstrating that, following long periods of use, there is no accumulation of particles in the deep lung.

3. *Safety versus toxicity testing.* The Panel would support the thesis throughout its guidelines that modern toxicologic research dictates that the experiment determine the dose response curve of a material, even if in animal species, so that safety factors can be estimated when normal usage and potential misuse of the product are considered. Studies performed without effect doses in the dosing regimen are not useful for determining a dose response relationship.

This concept contrasts with the older, long held concept of safety testing. In such testing, some multiple of the use level was chosen—normally the use level was used also—and if no toxic effects were observed, the material was considered safe.

4. *Skin irritation and sensitization tests.* The routine tests such as the Draize-Shelanski Test are established and have been routinely run on products to be topically applied (Refs. 50 and 58). The results from a number of these are reported in submissions. The Panel reviewed these procedures and devoted an entire meeting to an extensive discussion with a number of recognized experts (Ref. 40). The experts stated, and the Panel concurs, that for predicting identification of moderate irritants and sensitizers, some mechanism for maximizing the test must be developed. In general, the experts and the Panel concluded that the currently used tests would easily pass a moderate sensitizer. Maximization of a test to achieve predictive reliability can be done by irritation of the skin to assure penetration of the antigen, occlusion, increase in induction dose, increase in time of exposure, the addition of biologically active compounds such as Freund's adjuvant to the test material (in animals) or combinations of these. For this reason, the Panel has adopted the position that the submitted tests would not be considered as adequate support of lack of potential for irritancy or sensitization in use.

Zirconium compounds present a special problem in topical testing because of the potential for possible topical granuloma production. One published case (Ref. 12) and numerous consumer complaints describing lumps leave the Panel unconvinced that rare topical granulomas do not occur. Detailed followup of such cases is suggested elsewhere in this document.

A limited number of skin tests in individuals previously sensitized to ziroconium have been performed. The number of subjects—three—used in these tests has been understandably low because of the availability of only a small population of potential test individuals who had been previously sensitized to either sodium zirconium lactate or zirconium oxide.

5. *Acute aerosol tests.* (i) Eye irritation tests have been performed with negative results.

(ii) a mouse aerosol irritation test has shown that zirconium-aluminum-glycine complex is a mild to moderate pulmonary irritant by inhalation.

(iii) Acute aerosol tests have been performed repeatedly using a 4-hour exposure with eight 30-second bursts. Some of the tests lacked control groups, and often when controls were used, the animals appeared sick so conclusions were difficult to draw. About the only reasonable conclusion is that guinea pigs or other animals exposed to these dose levels did not die rapidly or in large numbers as a result of the dosing.

It can also be concluded that most animals survived the test conditions; where histologic tests were done and effects were seen, there was confusion caused by high background disease in the control animals.

6. *Sub-chronic aerosol inhalation testing.* The basic aerosol toxicity test has been the one described by Draize, using a 5- or 6-liter static chamber (Ref. 59). More sophisticated techniques of aerosol testing have been developed in the last three decades and better methods are now available.

It should be noted that no aerosol testing whatever was reported for one zirconium-aluminum-glycine complex containing aerosol until a year after it was initially marketed in August 1971. The first aerosol inhalation test with this product reported to the Panel was dated August 1972.

7. *Adequacy of 90-day test period.* The submission of December 16 to 17, 1974, cited a statement by the Society of Toxicology made to the Food and Drug Administration concerning the adequacy of 90-day toxicology studies as determinants of long term effects (Ref. 31). This statement points out that ". . . we believe that the most significant toxicity for drug purposes can be detected at the exaggerated dosages used in toxicological testing from other than microscopic examination of organs. While microscopic examination of tissues is certainly necessary to establish a no-effect dose or safe dose, toxicity is dictated by changes in clinical pathology, body weights, behaviour, or general appearance at the high dose levels." The statement says, "To solidly establish meaningful parameters of safety evaluation usually requires completion of phases I and II in the clinic with appropriate toxicological studies in animals . . . It seems to us that each drug must be evaluated individually, and in the course of the development of the drug that it is the common practice to initiate new animal studies in light of new information." The Panel notes that the Society of Toxicology statement is concerned primarily with the type and adequacy of animal studies run prior to, and concurrent with, phases I and II (human clinical testing) and not with final medical/toxicological clearance of a drug for national introduction. The Panel believes that in light of a specific toxicological potential, those studies required to elucidate that specific problem must be conducted. This is in keeping with experts (Refs. 33 and 42) who, when testifying before the Panel, concluded that lifetime studies might be indicated to determine the potential of these complexes to produce granulomatous or fibrogenic pulmonary disease.

The Panel would not agree that a 90-day subchronic study, even a well-designed and executed one, would necessarily predict the potential for long term granuloma or fibrosis development (Refs. 43, 19 and 33).

The Society of Toxicology statement, as made to the Hearing Clerk in response to proposed FDA guidelines on another matter before the agency, commented primarily on standardized toxicology studies and mentioned some obvious exceptions such as carcinogenicity studies. The Panel believes that an exception would have been made in the Society's statement had animal studies for either

hypersensitivity granuloma production or fibrotic lung disease been considered.

Experts testifying about occupational exposure studies involving interstitial fibrotic lung disease stated that it is often decades after exposure that the fibrotic disease surfaces, although some signs may be seen prior to the end of the first decade. As an example, these experts suggested the need to keep exposed dogs longer than 2 years.

An expert witness before the Panel (Ref. 33) indicated that if studies are performed in which animals are exposed for the purpose of determining granuloma or fibrotic response, he considered it necessary to do lifetime studies in the animals. He also recognized that this presents difficulty in clearing products for marketing in reasonable time periods.

Longer term studies were identified as particularly important when consideration is given to a large population that may be at special risk by virtue of already existing impairment of lung function; for example, asthmatics, emphysema patients or even heavy smokers. The normal animal is virtually always used in inhalation toxicity testing. However, an animal model of proliferative lung disease has been described (Ref. 42). The response of such animals when additionally exposed to zirconium-containing aerosol antiperspirants for long periods of time would provide more pertinent information regarding the possibly increased risk of lung disease to that portion of the consumer population who may be at greater risk.

8. *Particle size determination.* A wide variety of values has been reported for the size distribution of the particles released when zirconium-containing aerosol antiperspirants are sprayed. Values in the submissions range from 50 percent of particles less than 5.5 microns to 6 percent less than 5.5 microns. It is particles in this size range that are of particular concern to the Panel because they are capable of reaching the distal portions of the lung.

Holography and various impaction techniques such as the Anderson Sampler have been utilized. Experts and references in the literature emphasize the importance of an impaction technique for particle sizing when particles are inhaled and deposition is by impaction in the lung (Ref. 44).

It has become evident to the Panel that some portion of aerosol particles produced from use of these products are in the respirable range (below 5.5 microns in size). They are capable of being inhaled and deposited in the alveoli of the deep lung. The panel does not have data on the retention times, mechanism of clearance, or times of clearance for these particles. Because zirconium-containing aerosol antiperspirants produce relatively insoluble particles, evidence in the references just cited indicates that the clearance time may be long, that the amount may increase from daily dosing, and that clearance may result in deposition of particles in the lymph nodes. Time and effort will have to be expended before the details of the required information will be available.

Much research in aerosols has been possible because the conditions of aerosol generation can be well controlled by the use of mono-dispersed aerosols (aerosols generated with uniform particle size). This can be accomplished by examining the ingredient, first in a simple vehicle (mono-dispersed particles) and then in the formulated product (poly-dispersed particles). In this way, the dose, aerosol decay and characteristics of the aerosolized respirable particles can be better understood in both systems.

9. *Cytotoxicity (cell toxicity).* Experiments were reported in several submissions (Ref. 31) designed to show that zirconium - aluminum - glycine complex and zirconium-aluminum complex would be unlikely to act as cytotoxic agents. The Panel's analysis of these data are as follows:

The test of the effects of zirconium-aluminum-glycine complex on lung macrophages in vitro (Ref. 31) was undertaken as a pilot study to provide data on these effects and to compare zirconium-aluminum-glycine complex with two compounds claimed to have detrimental effects on macrophages (Ref. 45). Essentially, the tests consisted of challenging macrophages isolated from the lungs of rabbits with solutions of zirconium-aluminum-glycine complex, sodium zirconium lactate, and beryllium sulfate and then examining the viability and morphology of the treated cells.

It is claimed that the results of this study indicate that zirconium-aluminum-glycine complex does not affect lung macrophage viability or function and that zirconium-aluminum-glycine complex is phagocytized intact and is not degraded by lysosomal enzymes (Ref. 31). These studies are also used to support the more general conclusions stated at the open meeting of the OTC Antiperspirant Panel on December 16, 1974 that "Aerosol antiperspirants containing zirconium - aluminum - glycine complex show no potential for producing granulomas of the lungs" (Ref. 31).

The Panel's comments about these cytotoxicity tests are that, in the submitted data, zirconium-aluminum-glycine complex does not display any qualitative or quantitative difference from sodium zirconium lactate. Sodium zirconium lactate is a known sensitizer and has produced granuloma in human skin and in the lungs of test animals. For this reason it was included as a positive control, assuming that sodium zirconium lactate would reduce the viability of cells exposed to it. Since there was no statistical difference between the results obtained from zirconium-aluminum-glycine complex and those from sodium zirconium lactate, the test must be interpreted as inconclusive.

There was a considerably greater variation in the standard deviation in the data for zirconium-aluminum-glycine complex than in the blank controls. This was pointed out at the open session by one of the invited experts who suggested that such variation could be caused by some experiments in which increased cell death occurred when cells were exposed to the zirconium-aluminum-glycine complex. No explanation was offered for this wide variation. Several experts invited by the Panel and an industry consultant present at the open session concluded that these cell viability studies are not conclusive about the cytotoxicity of zirconium-aluminum-glycine complex. The Panel concurs in this assessment.

The Panel agrees with the stated conclusions offered with the protein synthesis experiment in which zirconium-aluminum-glycine complex and sodium zirconium lactate appeared to stimulate protein synthesis to varying degrees and where concentrations of beryllium sulfate greater than 10 mg/ml appeared to induce a toxic effect. However, the Panel does not agree that one can draw the conclusion that both zirconium-aluminum-glycine complex and sodium zirconium lactate are inert. These experiments are inadequate, and support no conclusions about the cytotoxicity of zirconium-aluminum-glycine complex or sodium zirconium lactate except, possibly, that these two compounds are less cytotoxic than beryllium sulfate.

Furthermore, study of intracellular protein synthesis within the macrophages exposed to zirconium-aluminum glycine complex and sodium zirconium lactate showed increased protein synthesis. Although in these tests sodium zirconium lactate at high concentrations showed some indications of inducing focal hyperplasia, zirconium-aluminum-glycine complex and zirconium aluminum complex did not. An increase of lysosomal enzymes in the supernatant fluid or of degranulation within the cell was not looked for. Without such studies, it cannot be logically stated that the ingested particles were not under active attack by intracellular mechanisms.

The Panel agrees that both zirconium-aluminum-glycine complex and sodium zirconium lactate-treated cells appeared normal at the ultrastructural level in comparison with the macrophages exposed to beryllium sulfate. However, the Panel concludes that this is all that the test indicates. This assessment was also offered at the open meeting on December 16, 1974, by experts. Since sodium zirconium lactate is known to produce granulomas in human skin and in the lungs of experimental animals, the Panel concludes that this test is inappropriate and inconclusive with respect to assessing zirconium - aluminum - glycine complex proclivity toward granuloma formation.

The Panel agrees that the x-ray microprobe analyses of zirconium-aluminum-glycine complex exposed macrophages showed that the elemental zirconium and aluminum ratio of zirconium-aluminum-glycine complex was maintained after the particles had been phagocytized by the macrophage. The zirconium and aluminium ratio determined from these analyses is consistent with that in the zirconium-aluminum-glycine complex, but can also be consist-

ent with any number of smaller molecular weight decomposition products of zirconium-aluminum-glycine complex. Therefore, the Panel does not agree that this experiment proves that some zirconium-aluminum-glycine complex had not been chemically altered within the cell. This demonstrates a point made several times in open sessions, namely, that a definitive analytical technique for fingerprinting zirconium-aluminum-glycine complex is essential.

10. *Intratracheal infusion of zirconium-aluminum-glycine solution in hamster lungs.* Histopathological examination of the lungs of hamsters intratracheally infused with three concentrations of zirconium-aluminum-glycine complex was performed. The submitter explained that the results were preliminary but that the only effects noted were characteristic of nonspecific irritation (Ref. 31).

The investigator reports that 24 hours after the first dose (0.2 ml of 0.4-percent zirconium-aluminum-glycine solution) hemorrhaging and edema were evident. One to 2 days after the second innoculation, congestion, hemorrhaging, edema, and macrophage proliferation were histologically observable. The Panel believes that these data do not support conclusions that zirconium-aluminum-glycine complex is inert. Appropriate controls for evaluating possible histological changes indicative of pregranulomatous lesions were not included. The Panel would be interested in learning how this inflammation would compare with that produced by sodium zirconium lactate on the one hand and aluminum chlorhydrate on the other. Without such comparative controls the Panel believes that the information from this experiment does not provide adequate evidence about the question of whether zirconium-aluminum-glycine complex is incapable of producing granulomatous lesions.

11. *Antigenicity/hypersensitivity.* Preliminary attempts were made (Ref. 31) to produce delayed skin hypersensitivity in albino guinea pigs by single injections of complete Freund's adjuvant and either beryllium sulfate, sodium zirconium lactate or zirconium-aluminum-glycine complex. The results were that neither zirconium-aluminum-glycine complex nor sodium zirconium lactate produced a positive skin reaction but that beryllium sulfate did produce delayed skin hypersensitization in six of nine animals. These data are cited as evidence that zirconium-aluminum-glycine complex has no granulomatogenic potential.

The Panel disagrees. Since in this system sodium zirconium lactate, a known skin sensitizer, did not produce sensitization, the Panel must conclude that the test system was inadequate to reveal the sensitizing potential of suspect zirconium-containing compounds.

Expert testimony at an open meeting (Ref. 33) pointed out that "singleshot" attempts at induction of hypersensitivity are often inadequate. Repeated exposures were recommended instead. It was also suspected by these experts that the 10- to 17-day induction periods allowed in these experiments were possibly too few or too short to induce sensitization. The Panel concurs with these comments. Even with a potent sensitizer like beryllium sulfate, sensitization required a series of 12 biweekly injections (Refs. 46 and 43).

In vitro macrophage inhibition factor tests were performed using sensitized, isolated guinea pig peritoneal macrophages (Ref. 31). The presented data are described as preliminarly, and it is stated that no conclusions can be drawn. Nonetheless, this data is cited as evidence for the general conclusion that zirconium-aluminum-glycine complex is not antigenic.

The percent of inhibition in the controls is significant, raising serious doubt as to the validity of these observations. The goal of such a study should be to test for potential sensitization in humans. Blood lymphocytes from zirconium sensitized patients could serve in a test of this kind. It also would be important to find out how zirconium-aluminum-glycine complex previously incubated in human blood and other biologic fluids performed in these tests.

The Panel agrees that these data are preliminary and believes that it is inappropriate to draw any conclusions at this time. Further, the Panel concludes that these data cannot be used to support any conclusion asserting the nonantigenicity of zirconium-aluminum-glycine complex.

The necessity of showing that zirconium-containing aerosol antiperspirants are not antigenic is crucial in any attempt to establish their safety. This is especially important in the light of recent studies which suggest that mucosal surfaces provide a uniquely active site for the development of immunologic hypersensitivity (Ref. 60). The Panel can only conclude that not enough attention has been concentrated on problems of antigenicity and hypersensitivity. In fact, the studies submitted do not seem to be designed to discover the potential antigenicity of the test materials. Rather, the studies seem representative of the safety testing discussed earlier in this document and, therefore, are not consistent with toxicologic evaluation. The Panel cannot agree with the stated or implied conclusions that zirconium-aluminum-glycine complex or zirconium-aluminum complex have been proven to have no potential antigenicity.

12. *Acute inhalation studies in guinea pigs.* In one submission (Ref. 31), the results of acute inhalation studies are cited as evidence to support an assertion that zirconium-aluminum-glycine complex has no potential for the production of low-turnover granuloma.

The dose administered in these acute inhalation studies in guinea pigs was achieved by 8- to 30-second bursts over a 4-hour period followed by a 14-day observation period.

The Panel seriously questions an attempt to test for histologic evidence of granuloma formation 14 days after a single high dose. The Panel believes that this is clearly too short a period to find evidence of fibrotic response. Reeves and Krivanek (Ref. 43) took 16 months to produce evidence of fibrosis in inhalation studies in guinea pigs.

Acute inhalation studies are not the kind of studies to use as a model for animal studies to detect formation of low- or high-turnover granulomas. Many of the experts consulted stated that in developing or studying granuloma models they would not rely on this type of study to predict the potential of a compound to produce low-turnover granuloma because this disease is chronic in nature and develops slowly. Thus, the conclusion that the results of these studies provide evidence to show that zirconium-aluminum-glycine complex has no potential to produce low-turnover granulomas is unwarranted.

13. *Complaint file examinations.* A further source of concern to the Panel came from examination of complaint files voluntarily submitted to FDA (Ref. 47).

On October 1, 1973, one manufacturer voluntarily recalled a zirconium-containing aerosol antiperspirant containing zirconium chlorhydrate and aluminum chlorhydrate after the product produced a mild bronchiolitis in monkeys in an aerosol inhalation test. In a meeting called with another manufacturer to discuss their zirconium-containing aerosol antiperspirant formulation containing zirconium-aluminum-glycine complex, FDA asked them to submit their complete complaint file to FDA. This file showed 249 complaints received by the manufacturer of that aerosol antiperspirant from the introduction of the product in June 1973 until October 1973.

When this file was reviewed by the FDA physicians, they recommended follow-up on specific cases. The follow-up was to include interviews of patient and physician by FDA inspectors. The inspectors visited these persons and verified the details of the complaints. The decision was made at that time in FDA that it would be impossible to evaluate these complaints unless more complete baseline data on comparable complaint data with aerosolized aluminum sprays were available. Such information was requested, but not enough was received by FDA to draw a conclusion. At that time, FDA personnel turned their files over to the Panel for evaluation.

At the same time, FDA also requested complaint information from manufacturers of aluminum-containing aerosol, cream, roll-on and various other formulations. Although the number of complaints was not as high as is optimal for a baseline, some conclusions as to the type and relative frequency of complaints can be made for nonzirconium-containing aerosol antiperspirants and for nonaerosolized antiperspirants.

FDA again requested the complaint files from the producer of zirconium-aluminum-glycine complex for their zirconium-aluminum - gylcine - complex-containing formulation covering the period from October 1, 1973 to November 13, 1974. At this time, FDA also requested all of the complaint files on second zirco-

nium-aluminum-glycine complex formulation marketed by the same zirconium-aluminum-glycine complex manufacturer from its introduction nationally in August 1971 to the present. All of these were submitted to FDA and to the Panel; 406 complaints were received on the first product and 213 complaints on the latter.

These complaint files have been read by Panel members. They asked for additional follow-up material on specific cases. This was provided in a further voluntary submission to FDA. One submitter of complaint files has suggested to the Panel that every product category has a baseline rate of adverse reactions as well as specific types of reactions. It was further suggested that zirconium-containing aerosol antiperspirant complaint data be examined in the light of up-to-date information on adverse reaction complaints for the complete antiperspirant category. Attempts have been made by FDA to collect these data but only a small amount of such data were submitted.

Panel members have analyzed the complaint data. The number of complaints involving coughing, choking or respiratory distress recorded for two marketed zirconium-containing aerosol antiperspirants constituted 13 and 18 percent of all complaints received. The baseline data compiled for aluminum-containing aerosol antiperspirants showed 0.4 percent (1/245) in the period 1972 to 1973. In this same period, another product recorded 5 percent (3/55) choking symptoms.

Based on these admittedly limited data, the Panel concluded that there were significantly more complaints of respiratory distress with zirconium-containing aerosol antiperspirants than with other aerosol antiperspirants.

One of the claims stressed most to support the safety of presently marketed zirconium-containing aerosol antiperspirants is that they have a proven record of safety after widespread use. The Panel would conclude that this claim can be supported only with stringent follow-up of consumer complaints.

Most of the complaint reports were terminated with a physician's recommendation that no follow-up was indicated. From the Panel's reading of these reports, it is not clear if the physicians who reviewed these cases and recommended no further follow-up were the consumer's own physicians or physicians in the employ of the supplier of the zirconium-containing aerosol antiperspirant product. It is assumed they were the latter.

If there is a positive correlation between the use of zirconium-containing aerosol antiperspirants and initiation or exacerbation of specific lung pathology, it can be found only with precise, thorough and complete retrospective examinations of adverse reaction complaints of respiratory distress. Based on this limited follow-up, the Panel cannot accept as proof of safety, claims about the innocuousness of marketed zirconium-containing aerosol antiperspirants.

The Panel recognizes that the protocol for follow-up found in the complaints submitted to them was based on a standard for consumer complaints used for cosmetic products. However, the Panel does not consider this type of follow-up adequate to support assessment of hazard in the consideration of general recognition of safety for over-the-counter drug use.

K. Differences Among Zirconium-Containing Aerosol Antiperspirants

A further complication that faced the Panel as it tried to weigh the relative risks associated with the use of zirconium-containing aerosol antiperspirants had to do with the question of how different one zirconium-containing aerosol antiperspirant was from another. The data submitted about zirconium-aluminum-glycine complex repeatedly stressed the uniqueness of zirconium-aluminum-glycine complex as if to separate it from all other zirconium-containing aerosol antiperspirants. On the other hand, the zirconium-aluminum complex submission suggested that in no way could the zirconium-aluminum complex product be shown to be less safe. The possibility that all zirconium-containing aerosol antiperspirants might be safe was contradicted by the experience with a product that had caused disease in monkeys (Ref. 23). The Panel was then faced with the fact that at least one zirconium-containing aerosol antiperspirant was not safe; it had to decide if all other zirconium-containing aerosol antiperspirants or just one other zirconium-containing aerosol antiperspirant was safe.

Because of the difficulty in characterizing the various zirconium antiperspirant products and because the nature of the OTC review process is to write a monograph about ingredients that can be formulated into products, the Panel concluded that the OTC monograph route was not the proper way to insure safety of zirconium-containing aerosol antiperspirants. A better procedure appeared to be the investigational new drug/new drug application (IND/NDA) route in which the manufacturer of a product is able to test his own product in its finished formulation and, based on the results of those tests, apply to FDA for permission to market. In that way, even if some zirconium-containing aerosol antiperspirants were not safe, if a manufacturer could, in fact, provide data to convince FDA that his particular product was safe, he could receive permission to market.

L. Meeting of January 31, 1975

Following this analysis of the industry submission, the Panel voted, on January 31, 1975, to categorize zirconium-containing aerosol antiperspirants in Category II on the basis that they could not be generally recognized as safe (Ref. 48). At the same time, the Panel stated that it believed that the major risks associated with zirconium-containing aerosol antiperspirants would be primarily those of long term use. The Panel did not suggest a product recall but did state, "The continued marketing of these products should be contingent upon the vigorous pursuit of safety testing by industry. The Panel plans to provide guidelines for those tests it considered essential."

M. Attempt To Define Guidelines

At its meeting on March 24 to 25, 1975, the Panel set out to define those guidelines which it thought, if followed by industry, might allow continued marketing of zirconium-containing aerosol antiperspirants without subjecting the large numbers of users of these products to an unwarranted risk. At that time, the Panel realized that it was the assessment of industry that the preliminary categorization of zirconium-containing aerosol antiperspirants into Category II by an FDA advisory panel would not only allow companies already marketing zirconium-containing aerosol antiperspirants to continue to do so for some months or years until the administrative process was complete, but would also not deter other manufacturers from bringing zirconium-containing aerosol antiperspirants to market. The implications of this situation were that an even larger number of users would be subjected to whatever were the potential risks of exposure to zirconium-containing aerosol antiperspirants. Nevertheless, the Panel proceeded to try to work out what it thought would be the kind of testing that would be reassuring.

The Panel developed guidelines for zirconium-containing aerosol antiperspirants. The tests are outlined in five parts, consisting of single contact exposure, sensitization, chronic health effects, special studies and human studies:

1. *Single contact exposure studies.* These studies should be designed to determine the acute toxicity of the formulation by various routes of administration and define dose response relationships. The dosage should be administered by the oral, skin, and intraperitoneal routes. In terms of the inhalation route, the concentration necessary to produce toxic symptoms in the animal within a day should be established. If necessary, the option to increase the number or duration of exposure in the acute inhalation study should be considered. Irritation studies of the eye, mucous membranes and skin should be carried out with the formulation. In these acute toxicity studies, as in all other studies in animals, it is difficult to select a single animal model which would be most appropriate. The Panel stresses that no matter which animals are selected for the proposed studies, comparative controls must be run simultaneously. These would include both positive and negative control materials.

2. *Sensitization tests.* Tests should be run in animals to predict the capacity of a formulation to produce delayed hypersensitivity in man. Among the approaches pursued for these purposes are:

(i) *Animal tests.* Guinea pig maximization test (Ref. 49).

(ii) *Human tests.* When moving from allergenicity testing in animals to humans, the reliability of the Draize test

is improved if the concentration of the allergen is increased (Refs. 50 and 51). The 21-day repeated patch test or an adaptation of the Kligman maximization test (Ref. 52), in which the concentration of sodium lauryl sulfate is reduced, were suggested by a group of experts with whom the Panel met in September 1974 (Ref. 40). These experts expressed the opinion that the formulation be tested in addition to the ingredients comprising it.

(iii) *In vitro tests.*

a. Lymphocyte transformation (Ref. 45).

b. Macrophage migration inhibition (Ref. 53).

c. Serum antibody measurements.

3. *Chronic health effects.* Studies of the products should be of sufficient duration to obtain dose response information so that safety factors for any aerosol product can be calculated. These tests should be designed to determine potential toxicological effects both at the site of intended application (skin) and in the respiratory system. The Panel suggests that the repeated skin contact studies should be a minimum of 90 days' duration. The dosages should be applied to both the abraded and unabraded skin of the test animals. The range of dosages should cover the normal use level and include two higher concentrations, and if possible, one which produces a toxicological effect.

The measurements which the Panel feels are important so that safety of the test material can be assessed are as follows:

(i) Percutaneous absorption.

(ii) Distribution, metabolism, and excretion.

(iii) Appropriate function studies conducted serially, to measure physiological changes.

(iv) Hematology and urine analysis to check biochemical functions.

(v) Complete histopathological examination, including organ weights, gross observation, and histology.

A reasonable animal for such a study would be the rabbit. However, other animals such as the guinea pig could be used. Comparative controls should also be employed.

Aerosolized particles produced by propellant systems will usually contain a significant fraction of respirable particles. It is thus exceedingly important to assess the safety factors regarding inhalation of these products over long periods of time.

The major factors that must be considered in developing an inhalation protocol are the mechanics of the inhalation test system, the pulmonary anatomy and physiology of the test animal, and the expected toxicity of the material. There are a number of test systems presently being utilized (Ref. 54 and 55). There are two basic aerosol chamber designs: the dynamic and static chamber systems. The animals in a static chamber system are exposed to the test aerosol in a closed environment; animals breathe only air present in the chamber. The dynamic chamber system permits the aerosol particles to be continuously swept through the chamber at a constant rate. The dynamic chamber makes experimental control of aerosol concentration more reliable. In testimony before the Panel (Ref. 33), Dr. Robert Jones, an expert in aerosol testing, stated that a dynamic chamber is preferable in toxicological studies. A description of the type of inhalation testing chambers is the subject of an FDA report (Ref. 56).

The question arises whether the whole body or just the head of the animal should be exposed to the aerosol particles in tests. Whole body exposure of the animal would more closely approximate the types of contact usually associated with aerosol products. It is thus the more logical way to carry out the repeated inhalation studies.

The choice of an animal species to be used for the chronic inhalation studies depends on the types of information desired. For example, 90-day inhalation studies with a zirconum-containing antiperspirant formulation using rabbits and rats showed no evidence of granuloma formation in the lung, but cynomolgus monkeys give positive results (Ref. 23). Beagle dogs appear to be good models to measure retention times (Ref. 33). Mongrel dogs have been suggested as good models for comparative studies of respiratory and systemic immunologic reaction (Ref. 57).

Prior to initiation of the long term inhalation testing, a dose-ranging study of approximately 30 days should be carried out to estimate the effect concentration to be used in the chronic study.

The length of study should reflect the duration of exposure of the aerosol product when used by the public. It is the Panel's opinion that these studies should expose the animals for a minimum of 6 months. Some animals in the test series should be held for 3 months following their exposure period. Longer test periods may be necessary in instances where the material is suspected of being granulomatogenic or fibrogenic. A study of the effect of beryllium sulfate on animal lungs took 16 months to produce such effects (Ref. 43).

The exposure levels of the test material should range from a high concentration dose level to the normal use level of the product. Three concentration levels are recommended with at least the highest level producing a toxicological effect. Along with the test product, two comparative controls should be used: a negative control and a positive control.

The Panel suggests the following comparative controls for possible use in these studies.

(i) Aluminum chlorhydrate.

(ii) Sodium zirconium lactate.

(iii) Beryllium sulfate.

(iv) Zirconium oxide.

(v) Commercially available products.

(vi) A zirconium-aluminum-glycine complex or zirconium-aluminum complex.

A number of measurements to gauge any alteration in the normal biochemistry and physiology of the test animals is important. Therefore, hematological tests, urine analysis, appropriate pulmonary function tests, pathology and slit lamp examination of the eyes should be carried out serially on the animals.

The metabolism, distribution and excretion of the test materials should be an integral part of these studies. It may be appropriate to use radiological test materials for such studies.

Information about the pathology produced by the test materials should be obtained from serial sacrifice of the animals and examination of their organs (gross and microscopic examination). The amount of test material present in the lung should be determined to detect any increasing burden to the lung during prolonged inhalation of the product.

4. *Special studies.* A series of special studies is felt to be warranted in the case of aerosol materials that will be used for prolonged periods. These are:

(i) Animal tests for granuloma formation (in vivo).

(ii) Pilot inhalation study to evaluate alveolar macrophage responses.

(iii) A study with rats to evaluate effects on reproduction pathology of exposed rats. Study should be carried out for 2 to 3 generations of the animals.

(iv) Microbiological tests to examine whether microorganisms on the skin surface or in the respiratory tract can alter the chemical nature of the antiperspirant materials.

(v) Experiments in exposed animals to detect any potential of the antiperspirant ingredients to produce teratogenesis, mutagenesis, and carcinogenesis.

(vi) In vitro studies with lung tissue to learn if the antiperspirant materials can be chemically altered or if the zirconium-containing aerosol antiperspirants alter the biochemical or physiologic activities of the lung.

5. *Studies in human subjects.* A series of studies in human subjects should take place only after the previous animal tests have shown that the test product has a large margin of safety. These human studies should consist of skin irritation/sensitization tests and metabolism studies which measure the distribution of active ingredients in blood, urine, and feces. If previous experiments lead to a suspicion that there may be pulmonary effects, pulmonary function tests should be carried out, and bronchial lavage should be performed to remove macrophages which might be tested for the presence of zirconium compounds.

When test marketing of the product is initiated, close surveillance is required to collect any adverse reactions that may occur. Questionnaires should be circulated to the public to learn the incidence of adverse effects. There should be complete medical follow-ups on all complaints resulting from product use. This would be especially important when complaints are suggestive of pulmonary involvement.

The Panel believes that an adequate evaluation of such subjects should include, although not be limited to, a chest X-ray and pulmonary function tests that

would reveal impaired gas exchange or early fibrosis. An appropriate battery of tests would include, but not be limited to:

(i) Tests of volumes and capacity.
a. Forced vital capacity (FVC).
b. Forced expiratory volume, 1 second (FEV).
c. Mid-maximal expiratory flow (MMEF).
(ii) Peak flow.
(iii) Diffusion of carbon monoxide.
(iv) Blood gases.

Where feasible, tests should also include these more sensitive techniques:

(v) Flow volume loops.
(vi) Closing volumes.

Where there is a question of the early changes of fibrosis, it would be desirable to utilize plethysmographic techniques for:

(vii) Frequency dependent compliance or resistance.

Also, the patient's white blood cells should be challenged in vitro with suitable zirconium-containing antigens to reveal the possibility of zirconium hypersensitivity. Skin testing with appropriate zirconium compounds should be performed on patients presenting respiratory or skin complaints.

Should any one of these tests or an especially clear history of association of signs or symptoms with exposure to zirconium-containing aerosol antiperspirants be positive, the Panel would then recommend that the patient be examined by a specialist in chest diseases and that fibre-optic bronchoscopy should be performed to examine the smaller bronchioles for suggestive signs of early granulomatous changes. Pulmonary macrophages should be obtained for further testing against possible zirconium antigens.

Because of the importance of finding out if zirconium-containing aerosol antiperspirants actually could cause human lung disease and because of the hope of finding such cases while still early and reversible, the tests, while difficult, did not seem unreasonable.

After outlining this test protocol, there was a lengthy discussion questioning whether, if tests of this magnitude and duration are required, the Panel had the right to subject a large segment of the American public to these agents that had already been determined by the Panel as not generally recognized as safe.

At this point, the Panel paused to review what had been outlined as a basis for those tests which might serve to provide reasonable evidence about the safety of zirconium-containing aerosol antiperspirants.

N. Implication of the Proposed Guidelines

First, it had become apparent that the Panel would not be satisfied with negative animal test results on zirconium-containing aerosol antiperspirant products unless many of those tests had been run also with sodium zirconium lactate, zirconium chlorhydrate, aluminum chlorhydrate, zirconium oxide, and aluminum-containing aerosol antiperspirants as comparative controls and, furthermore, unless various time dose factors had been used to produce measurable drug effects for at least some of the agents tested. Unless this were done, as has been pointed out in the preceding discussion of previous submissions (Ref. 31 and 22), it would be impossible to know if the test system employed were capable of showing toxic potential of the compound.

Unfortunately, most of these tests have not yet been done in the described manner. In practical terms, it may well take a period of some months before the precise methodology for these tests is worked out. Also, many of the animal tests would take a long time. Brown et al. (Ref. 19) took 225 days to produce disease in animals; Reeves and Krivanek (Ref. 43) took 16 months with a beryllium salt to produce fibrosis, and beryllium compounds are well known to be highly dangerous in human beings. When one adds a substantial amount of development time, some of the other 1- and 2-year tests the Panel outlined, and then adds to that the time required to analyze test results, it becomes apparent that a substantial part of the evidence required could not, even under the best circumstances, be available until after a prolonged period.

Were the marketing of zirconium-containing aerosol antiperspirants to be allowed while testing progressed, as suggested by the Panel on January 30 and 31, 1975, it is apparent that many millions of consumers would experience a prolonged exposure to products already characterized as not generally recognized as safe. Should some of the proposed tests reveal a tendency of zirconium-containing aerosol antiperspirants to produce disease, a great many consumers would have unnecessarily been exposed to the risk of developing lung disease.

The second major implication of the proposed testing guidelines concerned the kinds of human studies the Panel had agreed it would need to provide evidence about the safety of zirconium-containing aerosol antiperspirants. The kind of damage zirconium-containing aerosol antiperspirants might produce in human beings is likely to be insidious and hard to detect. The Panel was agreed that there would be no question about advising the Commissioner to order the immediate cessation of sale of these agents if it could be demonstrated that they had, in fact, produced a case of disease. The question was, however, what would constitute a case. Not fibrosis; fibrosis takes years to develop and could not be expected to be seen so soon after the introduction of zirconium-containing aerosol antiperspirants. The early changes induced by zirconium-containing aerosol antiperspirants, were there any, would be hard to find. Certainly they could not be found unless they were sought. The Panel perceived that they would have to be looked for in three ways:

(i) In users who had complained about symptoms.

(ii) In human volunteers with appropriate informed consent who agree to expose themselves to exaggerated doses of zirconium-containing aerosol antiperspirants so that tests of macrophage function, pulmonary function and hypersensitivity could be conducted.

(iii) By means of an epidemiological investigation of the antiperspirant use patterns of various patients appearing in clinics with complaints akin to sarcoidosis and/or pulmonary fibrosis.

This kind of testing would require a major effort, not only by industry but also by large groups of physicians and scientists.

The Panel recognized that the kind of work-up outlined was far more than is ordinarily followed upon receipt of a consumer complaint by industry. It would not, however, seem excessive for a complaint by a patient in a Phase II trial of an investigational new drug.

At the same time, the Panel recognized that investigational new drugs in Phase II or III trials are not dispensed freely, even among patients under careful medical supervision. Such drugs are not used unless the patient's rights are fully protected and monitored by a patient's rights committee, and there is a provision in most cases for written, informed consent.

It was this realization that continued marketing of zirconium-containing aerosol antiperspirants would constitute, in effect, a very prolonged clinical trial without the informed consent of the test subjects that then brought the Panel to consider asking the Commissioner to take steps to have zirconium-containing aerosol antiperspirants withdrawn from interstate commerce until they had been granted approval of an NDA.

Q. Review of the Problem

In the discussion of that question, the elements of benefit/risk were once again raised. The Panel has deemed several factors essential in its analysis of this judgment.

Certain zirconium compounds have caused human skin granulomas and toxic effects in the lungs and other organs of experimental animals.

Zirconium-containing complexes are the active agents in some aerosol antiperspirants now being sold and in others being readied for marketing.

When used in aerosol form, some zirconium will reach the deep portions of the lungs of users of these products.

The lung is an organ, like skin, subject to the development of granulomas.

Unlike the skin, the lung will not reveal the presence of granulomatous changes until they have become advanced and, in some cases, perhaps permanent.

The Panel was unable to find adequate evidence to support assurances that zirconium-containing aerosol antiperspirants would not produce hidden lung disease in some subjects.

Such evidence will be difficult to obtain and, in any case, cannot be available quickly.

Earlier in this report the Panel has given its analysis of the risk-benefit considerations involved in nonaerosolized zirconium-containing antiperspirants.

The conclusion there was that these nonaerosolized antiperspirants are reasonably safe.

A similar analysis of zirconium-containing aerosol antiperspirants leads to a different conclusion. The two kinds of zirconium-containing products are compared point by point, as follows:

1. *Adverse reactions.* The possible adverse reactions (lung granuloma and ensuing pulmonary fibrosis) would be severe and probably not reversible. A lump or rash in the underarm is minor compared with a progressive, worsening lung disease.

2. *Site of injury.* Unlike that of the topically applied zirconium-aluminum-glycine complex antiperspirant, the adverse effect of zirconium-containing aerosol antiperspirant can be expected to occur both in the underarm area and in the lung. The Panel contends that the consumer cannot be expected to anticipate this latter adverse effect. He cannot be warned to discontinue the use of the product or see his physician when lung granuloma develops. He is unaware of any ill effect until it is possibly too late to repair the the damage. Lung granuloma disease is an unnecessary risk to assume in the use of zirconium-containing antiperspirants; it is not inherent in their effective use; on the contrary, it is an unnecessary risk associated with the aerosol method of application.

3. *Incidence.* The incidence of adverse reactions using zirconium-containing aerosol antiperspirants are classified as follows:

(i) *Underarm.* The incidence of allergic or non-allergic contact dermatitis and irritation reactions are extremely low, similar to reaction to the nonaerosolized zirconium-containing aerosol antiperspirant.

(ii) *Bronchial.* The incidence of bronchial distress is low. However, from complaint files it appears that bronchial distress is greater for zirconium-containing aerosol antiperspirants than for nonzirconium-containing aerosolized antiperspirant sprays. There are no complaints of bronchial distress from the use of cream or roll-on antiperspirant drug products, including those containing zirconium-aluminum-glycine complex.

(iii) *Deep lung.* The incidence of lung granuloma in users of zirconium-containing aerosol antiperspirants is unknown, but it may well be low. If zirconium-containing aerosol antiperspirants are permitted to be marketed, an annual sale of well over 100 million units can be expected. Even a very low incidence of disease could result in a substantial number of cases of granulatomous lung disease annually in the population at risk.

4. *Body burden.* Because zirconium-containing aerosol antiperspirants contain particles in the respirable range, zirconium-aluminum-glycine complex-containing particles can enter the body. Over the course of years this quantity of zirconium-aluminum-glycine or zirconium-aluminum complex may accumulate and produce undesirable effects other than lung granuloma. The Panel cannot predict exactly what the effects will be, if any, from long term, low-dose inhalation of zirconium-aluminum-glycine complex or zirconium-aluminum complex particles. There is no risk to the lungs or to the internal organs when antiperspirant drug products including zirconium-aluminum-glycine complex are applied as creams or roll-ons, since the intact skin prevents the entry into the body of virtually all zirconium-aluminum-glycine complex particles.

5. *Effectiveness.* Zirconium-containing aerosol antiperspirants appear to be possibly more effective in laboratory hot room tests than those aerosolized antiperspirants formulated with aluminum chlorhydrate alone. Zirconium-containing aerosol antiperspirants are not more effective than nonaerosolized zirconium-aluminum-glycine complex antiperspirants. Several nonaerosolized antiperspirant drug products formulated with aluminum salts appear to be equally effective as zirconium-aluminum-glycine complex-containing antiperspirants in laboratory tests. There is little evidence that consumers can perceive any difference between any of these products under conditions of actual use.

The Panel concluded that the risks involved in the use of zirconium-containing aerosol antiperspirants are unsupportable in view of the benefits likely to be derived from their use. Safer antiperspirant drug products are available which achieve comparable perspiration control with no risk of pulmonary disease.

P. Recommendation

The Panel recommends to the Commissioner in light of the preceding discussion, that:

1. All zirconium-containing aerosol antiperspirants be placed in Category II (not generally regarded as safe) and,

2. Because conclusive testing to establish the safety of zirconium-containing aerosol antiperspirants might take years to accomplish, and because in that time millions of consumers would be unnecessarily subjected to risk, the Commissioner should take immediate steps outside of the normal OTC drug review process to stop movement of these agents in interstate commerce until the safety testing has been done adequately to secure the approval of an NDA.

References

(1) 21 CFR 330.10. Final order promulgating § 130.301, Federal Register, May 11, 1972 (37 FR 9464).

(2) Shelley, W. B. and H. J. Hurley, Jr., "The Immune Granuloma: Late Delayed Hypersensitivity to Zirconium and Beryllium," *Immunological Diseases*, Edited by M. Samter, Little Brown and Co., Boston, pp. 722–734, 1971.

(3) Kozikowski, E. S., "Granuloma of the Axillae (Zirconium) ?," *Archives of Dermatology*, 75:892, 1957.

(4) Lewe, I. A., "Granulomas of the Axillae Caused by Deodorant," *Archives of Dermatology*, 75: 765–767, 1957.

(5) Pinkus, H., Monroe, and I. Botvenick, "Deodorant Stick Eruption (Zirconium Granuloma) of Axillae," *Archives of Dermatology*, 75: 756–757, 1957.

(6) Prior, J. T., H. Rustad and G. A. Cronk, "Pathological Changes Associated with Deodorant Preparations Containing Sodium Zirconium Lactate: An Experimental Study," *The Journal of Investigative Dermatology*, 29: 449–463, 1957.

(7) Rubin L., et al., "Granulomas of Axillas Caused by Deodorants," *Journal of the American Medical Association*, 162: 953–955, 1956.

(8) Sheard, C. Jr., et al., "Granulomatous Reactions to Deodorant Sticks," *Journal of the American Medical Association*, 164:1085–1087, 1957.

(9) Shelley, W. B. and H. J. Hurley, "The Allergic Origin of Zirconium Deodorant Granulomas," *The British Journal of Dermatology*, 70:75–101, 1958.

(10) Baler, G. R., "Granulomas from Topical Zirconium in Poison Ivy Dermatitis," *Archieves of Dermatology*, 91:145–148, 1965.

(11) Epstein, W. L. and J. R. Allen, "Granulomatous Hypersensitivity after Use of Zirconium-Containing Poison Oak Lotions," *Journal of the American Medical Association*, 190:940–942, 1964.

(12) LoPresti, P. J. and G. W. Hambrick, "Zirconium Granuloma Following Treatment of Rhus Dermatitis," *Archives of Dermatology*, 92:188–191, 1965.

(13) Williams, R. M., and G. B. Skipworth, "Zirconium Granulomas of Glabrous Skin Following Treatment of Rhus Dermatitis," *Archives of Dermatology*, 80:273–276, 1959.

(14) Wormser, H. C., "OTC Poison Ivy and Poison Oak Remedies," *Handbook of Non-Prescription Drugs*, Edited by G. B. Griffenhagen and L. L. Hawkins, American Pharmaceutical Association, Washington, DC, pp. 172–175, 1973.

(15) Epstein, W.L., "Metal Induced Granulomatous Hypersensitivity in Man," *Advances in Biology of Skin*, 11: 313–335, 1971.

(16) OTC Vol. 140038.[1]

(17) Obermayer, M.E., "Chronic Granulomatous Inflammation in Axillae: Reaction to Zirconium?" *Archives of Dermatology*, 100:505, 1969.

(18) Prior, J.T., G.A. Cronk and D.D. Ziegler, "Pathological Changes Associated with the Inhalation of Sodium Zirconium Lactate," *Archieves of Environmental Health*, 1:297–300, 1960.

(19) Brown, J.R., E. Mastromatteo, and J. Horwood, "Zirconium Lactate and Barium Zirconate: Acute Toxicity and Inhalation Effects in Experimental Animals," *Industrial Hygiene Journal*, 24: 131–136, 1963.

(20) Sterner, J.H. and M. Eisenbud, "Epidemiology of Beryllium Intoxication," *Archives Industrial Hygiene*, 4: 123–151, 1951.

(21) OTC Vol. 140049.

(22) OTC Vol. 140050.

[1] Cited OTC Volumes refer to the submissions made by interested persons pursuant to the request for data by notice published in the Federal Register of September 7, 1973 (38 FR 24391). The volumes are on file in the office of the Hearing Clerk, Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20852.

(23) Shelley, W. B., "Chondral Dysplasia Induced by Zirconium and Hafnium," *Cancer Research*, 33:287–292, 1973.

(24) Brackhanova, I. T. and G. A. Shkupko, "Hygienic Assessment of the Effect Produced on the Body by Transition Metal Hydrides with Regard to their Electronic and Crystal Structure," *Gigiena i Sanitariia*, 37:36–39, 1972 (Russian).

(25) Mogilevskaja, I. J., "The Toxicity of Zirconium and Its Compound of Industrial Importance," *Gigiena Truda i Professional'nye Zabolevaniia*, 4:27, 1960, *Abstracts of World Medicine*, 29:58, 1961.

(26) Parkes, W. R., *Occupational Lung Disorders*, Butterworth and Co., London, 1974.

(27) Lourenco, R. V., "Inhaled Aerosols," *Archives of Internal Medicine*, 131:21–22, 1973.

(28) Miller, A., et al., " 'Nonspecific' Interstitial Pulmonary Fibrosis: Association with Asbestos Fibers Detected by Electron Microscopy," *New England Journal of Medicine*, 292:91–93, 1975.

(29) Miller, A., et al., "Talc Pneumoconiosis: Significance of Sublight Microscopic Mineral Particles," *American Journal of Medicine*, 50:395–402, 1971.

(30) Transcript from Antiperspirant Panel Meeting of October 31 and November 1, 1974. Available from Bowers Reporting Co., 7309 Arlington Blvd., Falls Church, VA 22042.

(31) OTC Vol. 140042, 140043.

(32) OTC Vol. 140042, 140043–Appendix J.

(33) Transcript from Antiperspirant Panel Meeting of December 16–17, 1974.

(34) Kilburn, K. H., "Hypothesis for Pulmonary Clearance and its Implication," *American Review Respiratory Diseases*, 98:449–463, 1968.

(35) Nagelschmidt, G., et al., "Recovery of Quartz and Other Minerals from the Lungs of Rats: A Study in Experimental Silicosis," *Archives of Environmental Health*, formerly *Archives Industrial Health*, 16:188–202, 1957.

(36) Klosterkotter, W. and G. Bunemann, "Animal Experiments on the Elimination of Inhaled Dust," *Inhaled Particles and Vapors*, Edited by Davies, C. N., Pergamon, Oxford, pp. 327–341, 1961.

(37) Morrow, P. E., "Alveolar Clearance of Aerosols," *Archives of Internal Medicine*, 131:101–108, 1973.

(38) Green, G. M., "Alveolo-Bronchiolar Transport Mechanisms," *Archives of Internal Medicine*, 131:109–114, 1973.

(39) OTC Vol. 140037 and 140038.

(40) Minutes of OTC Antiperspirant Panel, September 19–21, 1974.

(41) Transcript of November 1, 1974 meeting.

(42) Strauss, B., P. R. Caldwell and H. W. Fritts, Jr., "Observations on a Model of Proliferative Lung Disease," *Journal Clinical Investigation*, 49:1305–1310, 1970.

(43) Reeves, A. L. and N. D. Krivanek, "The Influence of Cutaneous Hypersensitivity to Beryllium on the Development of Experimental Pulmonary Berylliosis," *Transactions of the New York Academy of Sciences*, 36:78–93, 1974.

(44) Lourenco, R. V., "Inhaled Aerosols," *Archives of Internal Medicine*, 131:21–22, 1973.

(45) Eisen, H. V., *Immunology, An Introduction to Molecular and Cellular Principles of the Immune Responses*, Harper and Row, Hagerstown, MD, 1974.

(46) Marx, J. J. and R. Burrell, "Delayed Hypersensitivity to Beryllium Compounds," *Journal of Immunology*, 111:590–598, 1973.

(47) OTC Vol. 140048.

(48) Minutes of Antiperspirant Panel Meeting for January 30–31, 1975.

(49) Magnusson, B. and A. M. Kligman, "Allergic Contact Dermatitis in the Guinea Pig," *Identification of Contact Allergen*, Edited by Charles C. Thomas, Springfield, Ill., 1970.

(50) Draize, J. H., "Dermal Toxicity. An Appraisal of the Safety of Chemicals in Food, Drugs and Cosmetics," Association of Food and Drug Officials of the U.S., Austin, TX, 1959.

(51) Marzulli, F. N. and H. Maibach, "The Use of Graded Concentrations in Studying Skin Sensitizers: Experimental Contact Sensitization in Man," *Food and Cosmetics Toxicology*, 12:219–227, 1974.

(52) Kligman, A. M., "The Identification of Contact Allergens by Human Assay. III. The Maximization Test: A Procedure for Screening and Rating Contact Sensitizers," *Journal of Investigative Dermatology*, 47:393–409, 1966.

(53) David, J. R., et al., "Delayed Hypersensitivity In Vitro," *Journal of Immunology*, 93–264–273, 1964.

(54) Troy, W. R., "Testing for Inhalation Toxicity," *Journal of Society of Cosmetic Chemists*, 25:283–296, 1974.

(55) Giovacchini, R. P., "Old and New Issues in the Safety Evaluation of Cosmetics and Toiletries," *CRC Critical Reviews in Toxicology*, October, pp. 361–378, 1972.

(56) FDA Report, Reports on Pressurized Consumer Spray Products, "Aerosols," February 1975.

(57) Kaltreider, H. B., F. N. Tuner and S. E. Salmon, "A Canine Model for Comparative Study of Respiratory and Systemic Immunologic Reactions," *American Review Respiratory Diseases*, 3:257–265, 1975.

(58) Shelanski, H. A. and M. V. Shelanski, "A New Technique of Human Patch Tests," *Scientific Section Proceedings*, Toilet Goods Association, 20:46–49, 1953.

(59) Draize, J. H., et al., "Inhalation Toxicity Studies of Six Types of Aerosol Hair Spray," *Scientific Section Proceedings*, Toilet Goods Association, 31:28–32, 1959.

(60) Waldman, R. H., and R. Gangley, "Techniques for Eliciting Mucosal Immune Response," *Acta Endocrinologica*, 78:262–280, 1975.

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 505, 601(a), 701(a); 52 Stat. 1052–1055, as amended (21 U.S.C. 355, 361(a), 371(a))) and under authority delegated him (21 CFR 2.120), the Commissioner proposes that Parts 310 and 700 be amended as follows:

1. In Part § 310, by adding a new § 310.510 to Subpart E to read as follows:

§ 310.510 Use of aerosol drug products containing zirconium.

(a) Aerosol products containing zirconium have been used in over-the-counter (OTC) drug products as antiperspirants. Based upon the lack of toxicological data adequate to establish a safe level for use and the adverse benefit-to-risk ratio, such aerosol products containing zirconium cannot be considered generally recognized as safe for use in drug products. The benefit from using aerosol drug products containing zirconium is insignificant when compared to the risk. Safer alternative antiperspirant products are available.

(b) Any aerosol product containing zirconium is a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act for which an approved new drug application pursuant to section 505 of the act and Part 314 of this chapter is required for marketing.

(c) A completed and signed "Notice of Claimed Investigational Exemption for a New Drug" (Form FD-1571), as set forth in § 312.1 of this chapter, is required to cover clinical investigations designed to obtain evidence that such preparations are safe for the purpose intended.

(d) Any such drug product shipped in interstate commerce after the effective date of the final regulation that is not in compliance with this section is subject to regulatory action.

2. In Part 700, by adding a new § 700.16 to Subpart B to read as follows:

§ 700.16 Use of aerosol cosmetic products containing zirconium.

(a) Based upon the lack of toxicological data adequate to establish a safe level for use, aerosol products containing zirconium are considered deleterious substances which may render any such cosmetic product injurious to users.

(b) Any aerosol cosmetic product containing zirconium is deemed to be adulterated under section 601(a) of the Federal Food, Drug, and Cosmetic Act.

(c) Any such cosmetic product shipped in interstate commerce after the effective date of the final regulation is subject to regulatory action.

Because § 330.10(a)(2) of the OTC drug review regulations provides 30 days before all data can be made public, and since such data will be needed to adequately comment upon this proposed regulation, the Commissioner has determined that it is in the public interest to provide 90 days for public comment.

Interested persons may, on or before September 3, 1975, file with the Hearing Clerk, Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20852, written comments (preferably in quintuplicate) regarding this proposal. Received comments may be seen in the above office during working hours, Monday through Friday.

Dated: May 29, 1975.

A. M. SCHMIDT,
Commissioner of Food and Drugs.

[FR Doc.75–14549 Filed 6–4–75;8:45 am]