The Safety of Fragrance Materials

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When one considers the long history of the use of fragrances, their broad distribution, and the extent of exposure to them, one is impressed with the very few examples of injury to humans that can be attributed to these materials. The only problems reported have been occasional rashes on the skin, and even more specifically, light-induced rashes. And yet there is a persistent myth in the cosmetic industry that any problem encountered in the safety testing of a new cosmetic must be attributable to the fragrance component. Only systematic screening of all of the materials used in fragrances by an independent scientific body, and systematic and voluntary conscientious response by the industry to eliminate ingredients shown to cause harm can dispel this myth.

The Research Institute for Fragrance Materials, Inc., an international non-profit organization, was established in 1966 by the industry to do research on the many ingredients employed in perfumery. At present, RIFM is supported by 52 of these companies, representing most of the industry in the United States, Europe, and Japan.

In order to ensure an independent scientific status for the Institute, it is structured so that the only link between the administrative branches and the scientific arms is the President, who performs a dual role as scientist and administrator. The President has available to him the advice of a Scientific Advisory Committee composed of perfumers, research scientists and analytical chemists drawn from the fragrance industry.

Judgments in matters pertaining to the evaluation of *safety* are made independently by an international Panel of Experts, who are toxicologists, pharmacologists, or dermatologists drawn from the academic world and who have no connection whatsoever with the fragrance industry.

RIFM is conducting its program *only* on raw materials. These are carefully selected by the Scientific Committee of the Essential Oil Association or by the International Fragrance Association.

Raw materials are selected on the basis of the following criteria: 1) they must be representative of the materials in actual *use* by the industry; 2) they must conform to the specifications and standards of the Essential Oil Association of the USA (EOA), or the International Fragrance Association (IFRA); 3) they must be supplied to RIFM without any indication of the supplier, with name and identification number only; 4) they must be accompanied by gas-chromatographic, ultraviolet, or infrared curves to "thumb-print" the materials.

Levels of usage of the materials were determined by an industry-wide survey, and are constantly updated by the Scientific Advisory Committee.

Golberg states: "The complexities of fragrances are not the outcome of a conspiracy to 'soak' the consumer: they are an essential basis of a highly skilled art that seeks to create aromatic loveliness appropriate to the particular circumstances of use, while satisfying the exacting technical requirements that have to be met in a wide variety of products. As long as we seek to pander to our aesthetic susceptibilities, and not to outrage them, highly complex fragrances are inescapable and, indeed, play a most important role in a wide range of consumer goods.

Nancy McConkey, president of the British Society of Perfumers, with Fred Brown, president of the Society of Cosmetic Chemists of Great Britain. The accompanying paper was presented at the annual joint meeting of these two societies, February 3, 1976, in London.

"Facing up to the facts of real life, one *has* to establish priorities for safety evaluation in regard to the fragrance components being tested and the tests that are most necessary."[1]

Priorities have been established to determine how toxic a material might be by both oral and dermal routes, and to test its allergenicity and, where pertinent, its phototoxicity, to humans. Other areas of investigation will begin when these priorities are satisfied.

When each raw material arrives at the Institute, a retain sample is taken. The rest is sent out to various commercial laboratories for testing. A sample in petrolatum is prepared by the Institute for repeated insult patch testing, or maximization testing on human skin using, where feasible, a tenfold exaggeration of the maximum use level to which human skin could be exposed, based on the updated survey data.

In the course of testing these materials, it was found that the Kligman maximization test[2] gave more uniformly reproducible and consistent results in the hands of two testing facilities than the repeated insult patch procedure did in six. Consequently, this was chosen as the preferred test for potential allergenicity. In this procedure, four materials are tested on each subject. It was learned the hard way that each of these materials had to be *completely* unrelated, that is, one cannot test two essential oils, two acetate esters, two alcohols, two aldehydes, or two cinnamates, in the same group.

Testing at ten times the highest use level gives a considerable exaggeration of exposure by a very severe and exaggerated test procedure. When tested in this fashion, the test becomes a pass or fail test. *Any* positive result is taken as an indication that the material is a sensitizer.

The tests for potential *phototoxicity* to human skin are done by testing undiluted materials on the skin of

hairless mice, swine, and humans by the procedures used by Urbach,[3] using natural sunlight and a solar ultraviolet simulator.

All of the results obtained by RIFM are being published as a regular feature of the *Food and Cosmetics Toxicology.*[4] Thus far one special issue of that journal, containing only fragrance monographs, has appeared. Another will be issued early this year and the RIFM Board of Directors has authorized the publication of a special issue every year as long as RIFM has unpublished monographs.

Monographs with unfavorable results are published along with the favorable ones. Prepublication copies go to the FDA, CTFA, and member companies. To date, over 348 of these monographs have been published or accepted for publication. By now, *all of the large volume items have been tested as well as those whose past reputations were questionable.* Reprint lists are huge, with copies going to health ministries worldwide and to the National Clearinghouse for Poison Control Centers. Out of 604 materials tested thus far, 22 have been found to be sensitizers, and 7 to have phototoxic properties, under the conditions of testing. All of these either are being investigated further, will be published as soon as feasible, or are already published.

Among the allergens identified are Alantroot Oil, Anisylidene Acetone, Benzylidene Acetone, p-t-Butyl Phenol, Cassia Oil, Cinnamon Bark Oil, Costus Oil, Diethyl Maleate, Dihydrocoumarin, Ethyl Acrylate, Fennel Oil Bitter, Hydrobietyl Alcohol, and Peru Balsam. It is of interest here to note that both "natural" and "synthetic" materials are found among the allergens detected thus far.

Among the phototoxic oils are Angelica Root Oil, Bergamot Expressed, Cumin Oil, Lemon Oil Expressed, Lime Oil Expressed, Orange Oil Bitter, and Rue Oil.

In the course of maximization testing in human subjects, three instances have arisen in which an individual aldehyde, occurring widely in nature has proved to be a skin sensitizer. Upon examining the essential oil in which it is naturally present, the oil did *not* induce sensitization reactions even though the aldehyde was present in concentrations as high as 85%. It appeared that some other component or components of the natural oil inhibited the induction or expression of sensitization. As a test of this hypothesis, several terpenes and alcohols, found along with the particular aldehyde in the *natural composition* were combined with each of the aldehydes in question. It appears now to be a consistent finding that each of these aldehydes, although producing sensitization reactions when tested alone, does *not* produce sensitization reactions in selective simple mixtures with other compounds.

There is no suggestion at this point that these results represent anything more than observations that require more intensive study. These phenomena are under study in a 2-year post doctoral fellowship established to explain this interesting observation. The implications are that some materials may interfere with the induction or expression of sensitization in the human; that some *individual materials* are sensitizers but when present in oils derived from natural sources, or in various fragrance mixtures, may be quite innocuous.

At the present writing, with these observations currently under investigation so they may be more completely understood, it is worth drawing attention to the fact that there appear to be safe conditions of use for these three materials. A brief paper to this effect will soon be published in *Food and Cosmetics Toxicology.*[5] As soon as the post-doctoral study has gathered enough momentum, its results will also be published.

So much for the results; now let us discuss some of these items. Marzulli and Maibach[6] have published a scholarly paper on the phototoxicity of perfumes and perfume ingredients. They attribute the phototoxic properties of Bergamot oil to a single material—bergapten, or 5-methoxypsoralen. Photoxicity is related to primary irritation, and consequently, should produce the same response with every individual exposed. In fact, this is the case if all of the conditions are met for eliciting the photoxic reaction: the stratum corneum must be adequately exposed to the material in order to allow opportunity for saturation, the material must contain an adequate concentration of photoxic agent, the skin must then be exposed to ultraviolet light of adequate intensity and frequency for an adequate length of time. Usually, this means exposure to solar radiation or its equivalent for an hour, at least one-half hour after the application of the material, *but not longer than three hours after.* If all of these conditions are met, 100% of the subjects should respond with the characteristic erythema, swelling, and subsequent hyperpigmentation.

Phototoxicity, like primary irritation, is *concentration dependent* and consequently, levels *could* be found for each of these materials for safe application to human skin. But it is *not known* if their individual properties in a given mixture are additive. Marzulli and Maibach conclude that levels of Bergamot oil below 0.3% might be considered harmless. This would provide levels less than 0.001% of bergapten.

If phototoxic materials are to be used by the perfumer at levels in which they do not individually evoke phototoxic skin responses, it would seem the only way to be assured of safety in the finished compound or mixture would be to test *the final product* for phototoxicity. Probably the answer lies with the perfumer, whether to employ the unrefined oils and test the end product, or to formulate with furocoumarin free oils or versions which have been shown to be free of the phototoxic agent.

Allergenicity is quite another matter. It is extremely difficult to predict. Methods for predictive testing in the human are not entirely satisfactory; those in animals have been completely unsatisfactory in *our* experience to date. Barbara James of Unilever and Dr. Klecak of Roche Basle have had uniformly good results which, in general, agree with RIFM's data. To be a little more specific, it *appears* to be easier to sensitize guinea pigs than humans.

Allergenicity is *not as much a function of concentration* as are primary irritation or phototoxicity. Certainly, many familiar with the methods of skin testing have observed that reducing the concentration of an offender may enable a negative test response to be obtained. However, if one repeats the exposure at the lower concentration *for enough times,* the same allergenic response may be encountered. It appears that *the number of exposures to an allergen* is of greater significance than the actual concentration used. This was observed originally by Kligman with penicillin and we have confirmed this observation with fragrance materials.

Expert dermatological opinion differs on the use of allergens in cosmetics and toiletries. One group believes that a sensitizer may be used at a level below that required to elicit a response in a sensitized individual. However, if several companies use a material that way, any individual's total exposure and/or frequency of exposure to the material would be quite unpredictable. The more conservative objective would seem to be to work towards the eventual elimination of sensitizers.

The fact that the fragrance industry has been so relatively trouble-free may in part be attributable to the

fact that many fragrance materials are also found in flavors. In sensitizing guinea pigs to Dinitrochlorobenzene (DNCB), it has been observed that the development of the cutaneous reaction may be effectively reduced by the prior administration of the DNCB as a component of the animal's diet.

This has also been observed in the human. This phenomenon has been extensively reviewed by Lowney.[7,8] Perhaps there would be more fragrance allergies if these same materials had not been used in flavors over the years. It is an interesting point for conjecture.

There is no way of screening out *by any presently known test methodology* those materials to which the rare unfortunate individual, who has idiosyncrasies and cannot eat strawberries or have a cat, may become sensitized.

We hope to eliminate the general sensitizers. We know we cannot *eliminate* all reactions to cosmetics attributable to the fragrance moiety; we hope to reduce them to a minimum.

How do we disseminate our information?

1. Upon the receipt of a bad test result on any material, a meeting of the Scientific Advisory Committee (the industry group) is convened. They contribute by suggesting other materials, sources, or grades of purity for retesting.

2. I go to Geneva four times a year to make a similar report to the Technical Advisory Committee of IFRA. This is a similar industry group. They make additional requests.

3. Only when all of the requests of these two groups have been satisfied, is a monograph written and sent together with all of the test reports to the Panel of Experts.

4. This is discussed by the Panel of Experts at their next meeting. Decisions of the Panel are always unanimous. They are a very conservative group, reluctant to make decisions at one sitting; however, they recommend that I notify the 52 companies that a problem exists.

5. A notification is sent to the CEO of all the member companies informing them that the Expert Panel has come to a *preliminary conclusion* that the item has allergenic or phototoxic properties. The industry is thereby urged to send in any additional data, plant experience, test results, and so on.

6. The Panel meets again to consider the new information, results gleaned from their own files and experience, retesting if that is advisable, and come to a *final* conclusion.

7. A letter is then sent to the CEO of all 52 companies informing him of the Experts' *final* conclusion.

Conclusion

The Research Institute for Fragrance Materials, Inc. is the largest repository of safety data on fragrance raw materials anywhere in the world. In its ongoing program, it has tested 604 materials and has published, or submitted for publication, monographs on 348 of them. The remainder are in preparation.

We do not have all the answers. Our methods are contantly being improved. Reactions in complex mixtures are not understood. We are learning. But to the best of my knowledge no other consumer industry knows as much about as many of the *ingredients* used in their products as we do about the fragrance materials.

The ubiquity of fragrances, as such, in cosmetics, household goods, insect repellents, and so on, makes the responsibility of RIFM a significant one, and it is hoped that in time, this ingredient approach, responded to zealously by the industry, will eliminate known offenders from fragrances worldwide, and reduce to a minimum the cosmetic reactions attributable to them.

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Literature

"Multifaceted Nature of the Flavorist." Papers presented at the Society of Flavor Chemists Symposium, Rutgers University, New Brunswick, N.J., March 21, 1974.

Included in this booklet are 13 papers on the multifaceted nature of a flavorist. A person becomes a flavorist through training. The becoming is a never-ending process, however, there are initial steps to follow and basic information to know for a person to be able to develop a flavor. "The Training of a Flavorist—One on One" by Harris Shore; "The Training of a Flavor Chemist—An Organized Program" by Frank Fischetti, Jr.

Flavor development is an art that depends on technical knowledge and the use of technical processes. "The Flavorist as an Artist" by J. DiGenova; "The Flavorist as a Technical Man" by Paul Perry; "The Flavorist as Biochemist" by Charles Wiener, PhD; "Gas Chromatography—A Flavorist's Tool" by Richard H. Potter; "The Flavorist Using the Achievement of the Organic Chemist" by Manfred H. Vock, PhD.

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