Safety Aspects of Flavors and Fragrances

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The flavor and fragrance industry has, for a long time, been conscientious about the safety of its products. From the very beginning it has participated in the development of safety evaluations and regulations for flavors and fragrances, both in the US and Europe. In this paper the developments of both flavors and fragrances will be summarized. The difference in approach in these two areas will be discussed, as well as possible future developments.

History—Flavors, US

The first significant regulatory developments in the US took place in the flavor area. Prior to 1958 there was really very little activity, although on paper there was a black or white situation: only materials approved by the FDA were permitted, whereas other materials were "poisonous and deleterious," regardless of their application or concentration.

In the Food Additives amendment of 1958, this situation was confirmed for food additives: their specific application and use levels are being decided by the FDA. However, a new class of materials was created, exempt from the regulations for food additives—the materials "Generally Recognized As Safe under the conditions of their intended use." This class became known by its acronym GRAS. In 1958 and 1960, the FDA published relatively short lists of such GRAS materials, indicating what kinds of materials belong in this class. Only a few comments from the scientific community were received on these lists.

However, as the definition of GRAS clearly indicated that the general recognition of safety of a substance has to be "among experts qualified by scientific training and experience to evaluate its safety," FEMA took the initiative of setting up a panel of non-industry related scientists. This panel published its first GRAS list for possible comment by other experts in 1965, and many more such lists have followed. No. 10 was published this year and no. 11 is in the making. The key elements in the procedure that was followed were:

1. A non-industry Expert Panel
2. Safety evaluation based mainly on chemical structure and existing knowledge about toxicity and metabolic pathways
3. A list of safe flavoring ingredients indicating use and use levels

FDA, in a way, expressed its approval of this approach by adopting almost the entire FEMA GRAS lists 3 and 4 as FDA lists 21 CFR 101 1163 and 1164 (now 172-510 and 511), but it took no further action on the subsequent FEMA GRAS lists. The situation remained dormant until 1969, when President Nixon, probably stimulated by controversies about cyclamates and MSG, decided that it was incorrect to set narrow safety standards for new materials while leaving all existing materials alone. He ordered a review of all GRAS substances.

To execute this review, FDA contracted with special committees for various facets of the review. A Select Committee on GRAS Substances was asked to review many GRAS substances. So far SCOGS has reviewed 229 materials including a few flavorings.

As most of the knowledge on flavors is to be found in the industry, FEMA was engaged under contract to conduct a Scientific Literature Review of flavoring materials. This literature review will cost about 1.5 million dollars; it is expected to be completed by the end of 1978.

Under another contract a committee of the Federation of American Societies for Experimental Biology was retained to establish the criteria to judge the safety of flavoring materials. It is called the Select Committee on Flavor Evaluation Criteria (SCOFEC).

For the safety evaluation of flavors, the knowledge of accurate application and use levels is of primary importance. A first survey of the use and use levels of flavoring materials, carried out in 1970 by FEMA together with the National Academy of Sciences/National Research Council (NAS/NRC), led to unrealistic data on the intake of flavoring materials. This was caused by the fact that the use levels were extended to the staple foods in the food categories that were considered. For instance, if a usual use level of a flavoring material is given for "baked goods," the assumption that it is being used in bread leads to a highly exaggerated dosage level in the diet. By increasing the number of food categories, an attempt is made to avoid this kind of unrealistic conclusion in the "Phase III" survey on the use levels of flavoring materials that is under way right now. This usage survey can be estimated to have a one million dollar price tag.

In 1971 FDA announced its intention to become the sole judge of what can be considered GRAS, an interpretation which is being strongly disputed. In 1972, FDA also published GRAS procedures. It almost looks as if the criteria for

GRAS and for food additives have become the same. However, GRAS still has a very important meaning of its own. GRAS means a low priority for future testing, it means that it is not necessary to set limitations, and there is not that "unsafe under any condition" concept. The criteria for GRAS are more in line with the hazards that we know are inherent to life, and which lead us even to knowingly consume foods containing small amounts of carcinogens, such as roasted meat, smoked fish or escarole.

History—Fragrances, US

It can generally be said that the consideration of the safety of fragrance ingredients has had a lower priority than that of flavor ingredients. But the fragrance industry also took the initiative in starting a safety evaluation program, in this case without the incentive of a federal regulation. This was in 1968, about ten years after the start of the GRAS approach to flavors, and one might expect that, as many of the same industries were involved, the same pattern would have been followed. However, the situation with fragrance ingredients was different in many respects. The fact that there is no oral intake and the general feeling that the hazard of fragrance materials to public health had a lower priority led to the conclusion that a positive list of fragrance materials, of the GRAS type, would be unduly restrictive. However, it was recognized that there were very few experimental data available on the potential hazard of fragrance materials. This led to the formation of the Research Institute for Fragrance Materials (RIFM), an institute to organize and supervise the systematic testing of fragrance ingredients. RIFM formed a panel of non-industry related scientists to evaluate the experimental data.

The key elements in the procedure for the safety evaluation of fragrance ingredients were therefore:

1. A non-industry Expert Panel
2. An experimental testing program of hundreds of ingredients
3. No limitative list of fragrance ingredients

Dr. D. L. Opdyke, the president of RIFM, has reported on several occasions in detail about this institute's program.[1] It was designed in such a way that it would provide as much information as possible about the safety hazards of hundreds of ingredients. To limit the number of variables, it was decided to test only single chemical substances or natural raw materials, in one base, petrolatum, usually at ten times the maximum known dosage level. The choice of the base, and

the choice of the testing techniques for oral and dermal acute toxicity, for irritation and for sensitization by the maximization test are arbitrary. The choice was based on a preliminary study to find the most reproducible test results. This technique has been maintained over the past eight years, and 980 individual fragrance ingredients have been tested this way, in order of suspected hazard and quantity used. As a result two dozen materials have definitely been shown to cause sensitization under the conditions of these maximization tests, and eight materials, with some citrus oils in the lead, have been shown to be phototoxic. The results of this testing program are continuously being published in the form of monographs in "Food and Cosmetics Toxicology."

A noticeable difference between the GRAS lists of the flavoring materials and the monographs on fragrance materials is that the latter do not constitute a clearly formulated guideline of safe practice for the industry. This is not surprising in view of the fact that several unexpected observations have been made on the interaction between fragrance materials.

The so-called "quenching effect" has become one of the best known.[2] The tests that led to its discovery were initiated by the surprising effect that several known sensitizers, such as citral and cinnamic aldehyde, are major components of essential oils that do not show the sensitization effect. The potential for sensitization of the individual aromatic chemical is obviously quenched by other ingredients of the oil. And it was indeed confirmed that citral, after addition of 20% limonene, had lost its sensitization potential. Similarly, by trial and error, desensitized complexes of cinnamic aldehyde and phenyl acetaldehyde were discovered. A scientific investigation of this phenomenon was undertaken by Majeti and Suskind.[3,4] Two years of investigation failed to shed any light on the cause of the quenching effect. At present, the investigations are being continued at three European universities.

Inexplicable as it is so far, the quenching effect has made clear that combinations of fragrance ingredients do not necessarily have the dermatological effects of the ingredients themselves. This may explain why a traditional fragrance ingredient, such as the worst sensitizer of all, costus oil, has been used in fine perfumery for so many years without apparent ill effects to its users, even though in the experimental situation no quencher for the sensitization effect has been found. The industry, therefore, is faced with the situation that several materials have been identified definitely as sensitizers by the experts of RIFM, yet several perfume compounds containing these same materials have a history of safe use.

To briefly summarize the situation for flavors and fragrances in the US at the moment:

Flavoring materials are regulated by strict guidelines based on safety evaluation by experts. This evaluation is in the process of being reviewed by the FDA.

Many fragrance materials have been tested, and the test results have been published. The cosmetic industry, as the main user of fragrances, usually requests conservative compliance with the published test results. However, the resulting practical guidelines for the fragrance industry vary from company to company.

Situation—Flavors and Fragrances, Outside US

While the safety evaluation of flavors and fragrances was going on in the USA over the last 20 years, what happened in the rest of the world, particularly in Western Europe? Relatively little. No millions of dollars have been spent on literature surveys or use level surveys of flavoring ingredients. No millions of dollars have been spent on fragrance ingredient testing programs. However, regulatory systems have been designed in several countries that may well be as effective in protecting the public health as those in the US.

In Europe, in 1949, the Council of Europe was established as the first international parliamentary forum in European history. Its activities relate to economic and social progress. Today there are 17 member states. A limited number of members acceded to a Partial Agreement on Public Health. An ad hoc Working Party conducted a study on the safety of flavoring ingredients, which was approved by the Public Health Committee for urgent consideration by all interested parties. It is generally known as the "Council of Europe List."[5] It has been written in the form of a draft regulation, but it has no legal force in any country. Maybe it got more attention than it actually deserved. The amount of consideration and judgment that went into it is probably not comparable to the effort put into the GRAS lists by the FEMA Expert Panel.

A similar positive listing of flavoring materials was published in the UK by the Food Additives and Contaminants Committee, but this report has been tabled for the time being.

The future of flavor regulation and safety evaluation in Europe will probably be determined in the upcoming EEC (European Economic Community or Common Market) regulation. The chances are still open between:

A complete positive list, with three categories, natural, nature identical and artificial. In this case, the nature identical list will probably be easily extended with new materials, in a GRAS-like procedure. This solution may sound attractive to consumer organizations, but it is virtually unenforcible and uncontrollable in international

trade.

A general permission for nature identical flavoring materials known to occur in human food, in comparable use levels. This would be combined with a negative list of known natural occurring toxic flavoring materials. This type of regulation, a combination of a general permission of nature identical flavoring materials, and positive lists for artificial flavoring materials, is usually referred to as the "mixed system."

Other foreign countries outside Europe, including Brazil, Canada and Australia, that are developing or revising flavor regulations, seem to look favorably towards the "mixed system."

No doubt, the recognition by the Codex Committee on Food Additives of the Codex Alimentarius (FAO/WHO) of the nature identical category of flavoring ingredients as a special group has been a factor in its receiving preferential treatment.[6]

The system, based on the general permission for nature identical (or really: food identical) flavoring ingredients in combination with short negative lists of known harmful materials, has made it possible to design responsible flavor regulations at a minimum cost. It is not surprising that this type of regulation is also promoted by the International Organization of the Flavor Industry,[7] in particular for those countries where no regulation now exists.

On the fragrance scene, the International Fragrance Association (IFRA) has developed a Code of Practice.[8] The results of the RIFM tests are being taken into consideration as well as the proven practical safety of fragrance compositions. The result is a practical guideline, with a constantly updated restrictive list for a limited number of fragrance materials, stating the maximum dosage recommended as harmless. The international cosmetic industry seems to welcome these guidelines, and the request for IFRA compliance has become standard in several countries, particularly in Europe and in Japan.

Future—Flavors, US

For flavors in the U.S., I foresee an ever tightening system of positive lists, made up according to very strict criteria. FEMA and its experts have made a valuable contribution to these criteria by the publication of the criteria of the Expert Panel.[9] Moreover, a "decision tree" for the classification of synthetic flavoring materials in various hazard categories, according to their chemical structure, will soon be published.[10] The SCOFEC report, published in 1976, disagrees in many points with the FEMA Experts and will influence the criteria to be set.[11]

FDA has another indirect hold on the interpretation of what ingredients can be used by the flavor industry—through the labeling regulations. Any ingredient not on a list specifically approved by FDA has to be mentioned on the label of the flavor. Because of a controversy over one ingredient, GRAS 10 was not recognized by FDA until October 18 of this year. Until that date, ingredients listed on GRAS 10 had to be mentioned on the label of flavors.

Whatever is finally decided by FDA, I still hope and expect that FDA will never quite catch up with the developments in flavor research. That would be a black day for the flavor industry and its creative flavorists. I hope the GRAS concept will remain alive, to facilitate the introduction of newly discovered flavoring materials.

It will be extremely important for the safety evaluation of flavoring materials to have available accurate data on use and use levels in food. This is where the flavor industry needs feedback from the food industry. It will be necessary to obtain accurate data on the use level of flavor ingredients in the human diet. The flavor manufacturer, with the assistance of a well-programmed computer, is able to calculate which flavor ingredients are contained in which finished flavors and in which quantities. However, where these flavors are being used by the food industry, and in what dosages, is information that has to be fed back to the flavor industry.

Reliable use levels will lead to reasonable judgments on the safety of the flavoring materials. This in turn will lead to continued permitted use of such flavoring ingredients, to the benefit of the flavor industry, the food industry and the consumer.

Future—Fragrances, US

In the fragrance field, the testing of materials in the RIFM program will continue, and we may expect that a few more materials will be identified as weak sensitizers under those testing conditions. But what will be the interpretation of those data? Is every weak sensitizer, showing up on one or two out of 25 persons tested, automatically to be banned from use? In my opinion, this calls for judgment. There are still too many conflicting opinions on whether there is a dose-relationship for weak or strong sensitizers. Various authors differentiate between a possible dose-relationship in the induction, and the elicitation stage of the sensitization.

Combined with the mysterious quenching effect discussed earlier, there is sufficient doubt whether the RIFM test should be made into a pass-fail test even for the weak sensitizers. Even though the benefit/risk ratio for fragrance ingredients is lower than for certain other cosmetic ingredients, I am of the opinion that reasonable evaluation of safety is needed for fragrance materials. This evaluation should include available test data on fragrance compositions containing the materials in question. Again, I would

recommend feedback from the using industry, in this case the cosmetic industry, to the fragrance industry; feedback of the many test results which must have been obtained by the cosmetic industry in the course of its safety assurance programs. Favorable testing results can be translated by the fragrance industry, which has the complete formula of the perfume at its disposal, into conclusions on safe use of fragrance ingredients at certain use levels. These data should be submitted, possibly through IFRA, to the RIFM Expert Panel for consideration together with the RIFM testing data. In this way, a more reasonable and scientifically more acceptable conclusion on the potential hazard of a material might be drawn as a guideline for the fragrance industry. I am sure that cooperation such as proposed here would be in the common interest of fragrance industry, cosmetic industry and consumer.

Acknowledgment

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