Beyond the GRAS Lists

The Minimal Risk of Additional Nature Identical Flavoring Materials

By Dr. Jan Stofberg, PFW Division of Hercules Incorporated
Middletown, New York

Among all food additives used, it is generally accepted that flavoring materials form a class by themselves. This class outnumbers by far all other food additives combined. The number alone makes individual testing of all flavoring materials unrealistic.

Flavoring substances have the following characteristics that make a classical toxicological approach to their individual safety evaluation not only impossible, but clearly of a very low priority from the viewpoint of public health:

—the levels at which flavoring materials occur, or are added, are in the ppm range. Their flavor impact limits the risk of an accidental overdose, as the food would become unpalatable.
—most flavoring materials occur widely in traditional foods; they are not "new."
—the chemical structure of flavoring materials is generally of the type that may be expected to occur in foods as a result of biogenetic processes or traditional food processing.
—controlling the direct food additive use of most of these flavorings, regardless of results of toxicity testing, would have little impact on human health since similar control over the consumption of foods in which they occur naturally is not feasible.

A different approach to their safety evaluation is, therefore, clearly needed.

Over the last 25 years, significant progress has been made in the evaluation of the safety in use of flavoring materials. The GRAS lists, published by various authors on behalf of the Flavor and Extract Manufacturers' Association of the U.S. (FEMA), contain the conclusions of the Panel of Experts of this organization, consisting of non-industry related medical and toxicological scientists of the highest caliber. These lists deal with approximately 1300 chemically defined flavoring substances. Approximately 400 of these have not yet been identified in traditional foods and, therefore, are considered to be artificial flavoring materials by any definition. They have been evaluated and can be considered safe if used at the concentrations mentioned in the GRAS lists based on structure, known test and metabolic data and concentration used. The remaining 800 flavoring materials on the GRAS lists, though manufactured by chemical synthesis and therefore artificial according to the U.S. Code of Federal Regulations (21 CFR 101.22.a.1), are "nature identical" according to the definitions in the Code of Practice of IOFI (the International Organization of the Flavour Industry), and of the Codex Alimentarius, as well as the regulations of most countries other than the United States.

Consumption Ratio

A special approach to the setting of priorities for the safety evaluation of nature-identical materials has been proposed.[1-3] In this approach, the consumption of these nature-identical flavoring substances as components of traditional foods has been taken into consideration, in addition to their traditional safety evaluation as food additives. The Consumption Ratio has been designed as a quantitative measure for their nature-identical status. This ratio compares the quantity of flavoring substances consumed unavoidably as food ingredients with the quantity of the same materials consumed as added flavoring.

 0272-2666/87/0005-1901$04.00/00

The third cumulative series of data on the Consumption Ratio of 500 substances occurring on the GRAS lists has been published.[4] For 62% of these, the average increase of their consumption in the form of added flavor is less than 10%. This is hardly significant to the management of public safety against the background of the assumed safety of traditional foods. As far as total quantity by weight is concerned, the 500 flavoring substances for which Consumption Ratios have been calculated, represent over 99% of all nature-identical flavoring substances used in the U.S. An additional 400 nature-identical materials have been evaluated for safety under the FEMA GRAS and Council of Europe expert review processes.

We know, however, from the qualitative data on the flavoring materials naturally occurring in food published by CIVO,[8] that, so far, close to 5000 flavoring materials have been identified in food. Many more will no doubt be identified as the analytical research on food progresses, and the analytical techniques are further developed. In most countries other than the U.S., all such flavoring materials may be used legally as nature-identical. It is quite likely that many of these several thousand generally known materials are indeed being used, probably in relatively small quantities. Moreover, it is to be expected that flavor companies, as a result of their own research, are aware of the existence of many more nature-identical flavoring materials. Even though the individual and total quantities of such substances used can be assumed to be relatively small, a Consumption Ratio could only be calculated for them if the quantity used is known. We will try to estimate the risks involved in the use of these nature-identical materials not yet individually reviewed for safety by the experts from FEMA, JECFA (the Joint Expert Committee of the Codex Alimentarius) or the Codex Alimentarius ad hoc Working Group.

The risk of the use of "unlisted" flavoring materials in addition to the published lists will clearly depend on the following factors:

1. their chemical structure and related properties
2. the dosage of the substance in the food as consumed by the addition of the materials as flavoring ingredient
3. the percentage by which the unavoidable total intake of this substance as a food ingredient is increased by its use as a flavoring additive.

Since we are discussing materials that do not appear on a published list, a review of their individual chemical, toxicological and metabolic properties is not possible. It can be argued that, nevertheless, if their Consumption Ratio is high enough and if the total quantity consumed on average as well as the highest concentration in any food is low enough, their use presents a small risk.

De Minimis Risks

It is generally accepted that some risks are so small that it would be inefficient and unjustified to subject them to regulation and law enforcement. This is expressed in the classical phrase "de minimis non curat lex," i.e., the law does not deal with trifles. Risks of this order of magnitude are usually referred to as "de minimis risks." Recently it has been stated that this "de minimis" concept can be used to allow a substance into the market when it presents no real public health risk.[6] This procedure would not involve the safety evaluation of a single ingredient, but refers only to the application of that ingredient in a product under certain conditions. This reasoning was used to allow the presence of methylene chloride in decaffeinated coffee, up to a lifetime per capita intake of 140 micrograms per day, which was considered a minimal risk by the Food and Drug Administration (an increase in the cancer risk level of 1 in 100 million).

The main concern in allowing unidentified flavoring materials in the food supply is that they might be carcinogens. Of course, the flavoring substances under discussion here are occurring naturally in food or are generated during food preparation. They do not have xenobiotic structures. However, carcinogenicity cannot even be ruled out for the individual flavoring materials (or other ingredients) naturally present in prepared traditional foods.

To qualify for such an unregulated "de minimis" status the use of a nature-identical flavoring material would have to meet all of three requirements.

The first requirement would be that its use as an additive would be a minimal addition to its unavoidable consumption as a food ingredient. A Consumption Ratio of more than 10 would adequately establish this.

The second requirement would be that its total usage be small, so that even the chance of high exposure of a small part of the population to an unusual new flavored food item would be excluded. A total annual usage not exceeding 10 kg in a population of several hundred million people, such as that of the U.S., Europe or Japan would adequately assure this, especially in combination with the third requirement.

The third requirement would be that the

maximum added concentration in any given food be limited to a low value, e.g., not more than 5 parts per million. I propose that substances used under the above de minimis conditions be called Generally Recognized as Minimal, or GRAM.

A flavoring substance just meeting the above criteria would have an average per capita consumption of 0.5 mg per year as a food ingredient, and of 0.05 mg per year as an added flavoring. It is true that an individual with a preference for certain foods can easily consume many times more than the national average. However, a Consumption Ratio of more than 10 makes sure that a non-average consumption of foods with the added flavoring substance can be 10 times as much as the non-average consumption of foods containing the same flavoring substance naturally, and still lead only to the same order of magnitude of intake of the flavoring substance by that individual.

Proposed GRAM Requirements

Consumption Ratio	> 10
Added usage U.S.A.	< 10 kg/year
Added concentration in food	< 5 ppm

It can therefore be demonstrated that for those flavoring materials which meet the above three criteria, the increased risk of cancer posed by these materials is so trivial as to be nearly meaningless. It has to be perfectly clear that a de minimis risk, or GRAM status, is not a property of a flavoring substance, but only a description of its condition of use. For materials used as GRAM, a periodical review of the three conditions of use is needed. If the Consumption Ratio, the quantity used annually, or the highest dosage in food have changed and now exceed the above limits, the material will have to be dealt with under the food and flavor regulations of the country in which it is used.

Is there really a need for these thousands of GRAM (minimal risk) substances? It is unrealistic to assume that the effect of all naturally occurring flavoring substances can be adequately simulated by 800 nature-identical and 400 artificial flavoring materials. Consumers do not only require safety of their foods, they demand quality. Over the last ten years, there has been increased pressure on the food industry to provide the consumers with foods that are fresh, natural, and of the highest flavoring quality ever provided by nature and sophisticated home cooking procedures. Today's consumers demand the convenience and low price of mass-produced foods with the natural and traditional flavor qualities of

expensive and carefully prepared dinners.

We know that the natural and prepared foods which the consumer considers to be the standard for flavor quality contain at least 5000 different flavoring materials. This is probably only the tip of the iceberg. Only very few of the flavor components of many widely consumed foods, such as lamb, pork, shrimp and lobster, have been identified. The flavor components of sophisticated prepared dishes, containing many ingredients and their reaction products formed during food preparation, have not been investigated at all. Many flavoring materials will be identified, and will have to be used, either as individual substances or in the form of suitable complexes such as process flavors. This development will continue until the point is reached where the flavor effect of ever smaller quantities of added flavoring substances will prove not to be cost or quality effective anymore.

In conclusion, I suggest that the interests of the consumers (in regard to both safety and quality of their foods) and the obligations of those who regulate safety and public health, are best served by the following approach to the safety evaluation of flavoring materials:

- individual safety evaluation of all artificial (i.e. non-nature-identical) substances
- evaluation of all major nature-identical substances according to a priority setting procedure based on their intake, chemical, toxicological and metabolic properties, and taking into consideration their Consumption Ratio
- restricted use of many nature-identical materials with high Consumption Ratios, in very small quantities limited by GRAM conditions of use as proposed in this paper.

References

Address correspondence to Dr. Jan Stofberg, Vice-President, Hercules Incorporated, PFW Division, 33 Sprague Avenue, Middletown, NY 01940.

1. J. Stofberg, Setting priorities for safety evaluation of flavoring materials, Perf. Flav. **6**(4), 69, August/September 1981
2. J. Stofberg, Safety evaluation and regulation of flavoring substances, Perf. Flav. **8**(4), 53, August/September 1983
3. J. Stofberg and J. C. Kirschman, The Consumption Ratio of flavoring materials: a mechanism for setting priorities for safety evaluation, Food and Chemicals Toxicol. **23**(9), 857, 1985
4. J. Stofberg and F. Grundschober, Consumption Ratio and Food Predominance of flavoring materials, Third Cumulative Series, Perf. Flav. **12**(4), August/September 1987
5. H. Maarse and C. A. Visscher, Volatile Compounds in Food, Qualitative Data, Supplement 3, 1986, CIVO TNO, Zeist, the Netherlands
6. Federal Register, December 18, 1985, p. 51551-51559