Setting priorities for safety evaluation of flavoring materials

Dr. Jan Stofberg, Vice-President, Product Safety Assurance, PFW, Division of Hercules Incorporated, Middletown, NY, and Chairman, Committee of Experts, International Organization of the Flavour Industry, IOFI

Summary—A two step procedure is proposed to establish priorities for the evaluation of flavoring substances. It is based on quantitative evaluation of their occurrence in food and a decision tree safety evaluation. This provides a mechanism by which a group of toxicologists and flavor and food technologists can classify all flavoring materials consumed in decreasing order of potential hazard as recommended by JECFA.

Over the past few decades several attempts have been made, on national and international levels, to regulate the use of flavoring materials in the framework of the traditional legislation of food additives. Most legislators have been baffled by the size and the complexity of the project. Moreover, many have indicated that the regulation of flavoring materials is of relatively low urgency. The reasons for this situation include the following.

- The number of known flavoring materials is much larger than that of all other food additives combined.
- The levels at which flavoring materials occur, or are added, are relatively low. Their flavor impact limits the risk of an incidental overdose by making the food unpalatable.
- The vast majority of 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.

In the United States, FDA and the FEMA Expert Panel have reviewed a number of flavoring materials known to be used as flavor additives in food. This has resulted in the FDA GRAS (Generally Recognized as Safe) or safe additive status of a number of substances[1] and the FEMA GRAS lists. The criteria employed by the FEMA Expert Panel for the GRAS evaluation of flavoring materials have been reviewed by Oser and Hall.[2]

In the food laws of several countries (Germany, Italy, Spain, the Netherlands) regulation of flavoring materials added to food has been based primarily on whether such materials occur in nature. This can be understood to mean that they occur in natural products intended for human consumption, either processed or not. A number of harmful materials occurring in natural products have been quantitatively limited in these regulations, and a short list of artificial flavoring materials is permitted.

The Working Party on Flavoring Materials of the Council of Europe (Partial Agreement) reviewed a large number of natural flavoring materials and their active ingredients, as well as certain synthetic flavoring substances, for their potential hazards. The results of this study have been published for "urgent consideration by all interested parties."[3]

The Codex Committee on Food Additives has temporarily endorsed the use of natural and nature identical flavoring materials for many foods in the commodity standards of the *Codex Alimentarius*. The final judgment on the safety of flavoring materials in the *Codex Alimentarius* will be made by JECFA, the Joint Expert Committee on Food Additives of the *Codex Alimentarius*. In response to requests from the Codex Com-

 0272-2666/81/0004-6901$02.00/0

mittee on Food Additives, JECFA has actually reviewed the safety of a limited number of flavoring materials. It has either established ADIs (acceptable daily intake) for such substances or it has indicated in its reports what additional data would be required to come to a responsible decision.[4] The problem of flavor regulation in general has been discussed by the Codex Committee on Food Additives many times, and many times it has been stressed that in view of the size of the project any duplication of efforts should be avoided. At that same time, the delegates have agreed that the work of a national group, such as the FEMA Expert Panel, or of a multinational group, such as the Council of Europe ad hoc Working Party, cannot be accepted as an international standard without review by the sole judge of food additive safety for the *Codex Alimentarius:* JECFA. Special attention should therefore be given to the recommendation published in the 20th JECFA report.[5]

According to this recommendation, a group of toxicologists and flavor and food technologists should establish the order in which flavoring materials should be evaluated by JECFA, in decreasing order of potential health hazard. The exposure of the average consumer to every flavoring material should be estimated, and the total amount of each substance consumed by the average consumer should be considered. Several refinements of this total consumption, such as frequency of exposure and exposure by particular age or other groupings are recommended. In addition, materials should be evaluated based on toxicological data and on structural relationship to substances of known toxicological and biochemical properties.

Further, according to the JECFA recommendation the nature and the source of a substance should be considered. In this last respect a distinction is made by JECFA between artificial substances unlikely to occur naturally in food; substances occurring naturally in materials not normally consumed in food; substances occurring in herbs and spices and their derived products; and substances occurring in vegetable and animal products normally consumed as foods. In its recommendation JECFA clearly indicates that the *total* exposure to flavoring materials should be considered.

It is obvious that the JECFA recommendation shows the best way to international harmonization of the safety evaluation of flavoring materials by including those elements that have proven useful in various attempts at regulation or review of these substances. The flavor industry should therefore fully endorse this JECFA proposal, and provide all possible support, based on the available knowledge on the occurrence, use, and consumption of flavoring materials. Further information on this subject will have to be collected. With active contributions from all member associations of IOFI, the International Organization of the Flavor Industry, it would be possible to design a program that would enable an international group of toxicologists and flavor and food technologists to start classifying flavoring materials in decreasing order of potential hazard, for safety evaluation by JECFA.

Proposed procedure

The proposal for such a program is outlined below. It is a two-step program based on the following elements.

1. Determination of the consumption ratio
2. Decision tree safety evaluation

Both elements are expressed in a quantitative range that will determine the relative priority for safety evaluation of a material.

Step 1. *Determination of the consumption ratio of all flavoring materials.* In many cases, both the consumption of a flavoring material as a food ingredient and as an intentional additive to food contribute to the total amount of the material to which the average consumer is exposed. The balance of this exposure can be expressed as the consumption ratio (C.R.), defined as the ratio between the quantity consumed as an ingredient of traditional foods and the quantity consumed as a food additive. If, for example, the quantity of a flavoring material consumed by an average consumer as a natural ingredient of food is 20 times the quantity consumed as a food additive, the C.R. of such a material would be 20. If the consumption as an additive is twice the quantity occurring in food, this C.R. would be 0.5.

Stofberg and Stoffelsma have shown that, based on data available in literature and research centers, both the total consumption of a number of flavoring materials resulting from the consumption of traditional food, and their consumption as a result of industrial use of flavorings, can be calculated.[6] The C.R. of the 89 materials discussed in this publication ranges from 0.05 to 80,700.

Those flavoring materials that are almost exclusively consumed as ingredients of traditional foods have a very low priority for further evaluation. Such materials will have a very high C.R. Their priority is virtually unrelated to their chemical composition, their properties, or their per capita intake. The safety evaluation of flavoring materials with a very high C.R. would have the same priority as that of the traditional foods in which they occur. Because of the assumed practical safety of such foods, that priority is generally considered to be very low. Adding an insignificant amount to the total intake of the same flavoring material by using it as a food additive will not significantly change that low priority. In this context, the C.R. of a flavoring material becomes a measure of the confidence with which it can be used, with a low priority for further safety evaluation against the background of the safety of traditional foods.

I propose to consider a C.R. equal to 10 as the lowest value at which the use of flavoring materials as food additives could be considered insignificant compared to that caused by the consumption of traditional foods. This means a 10% increase in the total consumption of such flavoring materials. All flavoring materials with a

C.R. of 10 or higher can then be classified as "very low priority for safety evaluation" without further action. If for some reason the safety in use of a material in this category should become questionable, then the safety of the food containing such a material would also have to be reviewed. As an example, of the 89 flavoring materials reviewed by Stofberg and Stoffelsma,[6] 58 would be set aside in this class. The remaining 31 materials, with a C.R. of lower than 10, would have to be differentiated further according to the procedure of Step 2.

Determination of the C.R. for all known flavoring materials will probably lead to clear separation into two classes. Substances manufactured on a large scale will appear in the C.R. <10 category, whereas the large number of food identical materials that are only synthetically produced on a small scale will end up in the low priority group with a C.R. >10. Obviously, the proposed limit of C.R. $= 10$ is a guideline rather than a sharp cut-off point. The consumption of any material with a C.R. close to 10 should be reviewed in more detail. The experts involved in setting the priority for such a material may also want to take additional data into consideration.

Once in a decade, a flavoring material takes off in importance and quantity manufactured. This has happened to maltol and ethyl meltol, para hydroxy benzyl acetone, and more recently to 4-hydroxy-2, 5-dimethyl-3(2H)-furanone (pineapple ketone). From experience we know that this is a relatively rare occurrence. It is easy to spot, since such materials become fairly generally known. In such cases the C.R. will move to the other end of the scale, and its priority will have to be changed.

For all flavoring materials, data on their quantitative identification in food as well as data about the quantities used by the industry, as well as for certain large populations, should be collected by flavor industries, their associations, and scientific institutes. This data collection will result in assigning C.R. values to all known flavoring materials, such as those referred to in "Volatile Compounds in Foods," also known as the C.I.V.O. Report,[7] the FEMA GRAS list, and the Council of Europe Report. At the moment, lack of data will probably prevent calculation of refinements in the C.R., such as frequency of exposure and consumption by certain social, age, or other subgroups. However, such refinements at this stage will only be of significance for materials with a relatively low C.R. value.

The C.R. of flavoring materials also indicates, in a quantitative way, the nature and the source of a material, another aspect to be taken into consideration according to JECFA recommendation. All artificial flavoring substances not consumed as ingredients of traditional foods will have a C.R. $= 0$, which classifies them for setting further priorities based on their chemical structure in Step 2.

Ingredients present in materials not traditionally consumed as foods, such as rose, jasmine, and other

essential oils and extracts, will have a very low "consumption as food ingredient." The C.R. will generally be a very low figure, and this will lead to further setting of priorities in Step 2. Flavor ingredients present in staple foods will generally have very high C.R.s. Such materials should be classified as having very low priority for safety evaluation, and be temporarily endorsed as food additives if used according to good manufacturing practice.

Step 2. *Safety evaluation according to the decision tree of flavoring materials with a low consumption ratio (<10).* Cramer, Ford and Hall have published a method by which, after following a set of 33 questions through a decision tree procedure, the potential hazard of a chemical structure can be established.[8] Materials with a C.R. <10 in Step 1 should be run through this decision tree. In addition, their daily per capita intake should be estimated.

The combined result of the toxic hazard, based on the evaluation of the chemical structure according to this decision tree and the estimated daily per capita intake of a material, will classify a flavoring material according to its presumable risk, expressed in its Protection Index (P.I.). For practical reasons, these P.I. values have been grouped in categories A, B, C, and D. A represents the lowest presumable risk; D the highest. In this way, a priority classification, can be established for all flavoring materials with a C.R. of less than 10.

As an example of this procedure, Dr. R. A. Ford has provided the classification for the 31 materials referred to by Stofberg and Stoffelsma[6] that have a C.R. of less than 10. None of these fall into the D category, and only two, diacetyl and indole, are classified as C. The priority for evaluation of these flavoring materials can, of course, only be established after many more substances have been submitted to the proposed procedure. It is obvious that further quantitative identification of flavor ingredients in foods may change priority rankings, as well as the increase or decrease in the quantity of those used as food additives. In addition, the setting of priorities will have to be reviewed at least every ten years, as intake patterns and C.R.s may change over time.

Conclusion

Application of the two-step procedure described above is in accordance with the JECFA recommendation for setting priorities. It will result in a classification in decreasing order of potential hazard for all flavoring materials consumed as food ingredients or food additives. It will allow JECFA to proceed with the evaluation of those flavoring materials that have been given the highest priority. It would also lead to the recognition that many flavoring materials, normally and predominantly consumed as food ingredients, should be assigned very low priority for further safety evaluation. Their use as food additives should temporarily be permitted, pending the safety evaluation of flavoring materials with a higher priority.

References

1. 21 Code of Federal Regulations 172.510, 172.515, 182.10, 182.20, 182.30, 182.40, 182.50, 182.60
2. B. L. Oser and R. L. Hall, Criteria employed by the Expert Panel of FEMA for the GRAS evaluation of flavoring substances, Fd. Cosm. Toxicol. **15,** 457, 1977
3. Natural Flavouring Substances, their Sources, and Added Artificial Flavouring Substances. Council of Europe, partial agreement in the social and public health field, Strassbourg 1973
4. 11th (1968), 18th (1974), 20th (1976), 22nd (1978), 23rd (1980) Report of the Joint FAO/WHO Expert Committee on Food Additives
5. 20th Report of the Joint FAO/WHO Expert Committee on Food Additives, 1976, page 20
6. J. Stofberg and J. Stoffelsma, Perf. Flav. **5** (7), 19, 1980
7. Volatile Compounds in Food, S. van Straten, ed., Central Institute for Nutrition and Food Research T.N.O., 1974, and Supplements 1 (1977), 2 (1978), 3 (1979), 4 (1980), 5 (1980)
8. G. M. Cramer, R. A. Ford, and R. L. Hall, Fd. Cosm. Toxicol., **16,** 255, 1978