Safety Evaluation and Regulation of Flavoring Substances

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What has preoccupied me most during several decades of involvement in food and flavor regulation is the proper perspective of all risks involved and the proper setting of priorities in evaluating the safety of flavoring materials.

We are constantly being exposed to influences from our environment. These may be of a physical nature, such as temperature or radiation; or of a chemical nature, via our food intake, skin absorption or inhalation. Many of the exposures to chemicals are practically unavoidable, others result from processing or from deliberate addition.

First let me consider the consequences of unavoidable exposure to chemicals via our food intake. I am referring to our consumption of basic and traditional foods.

What we eat, and how it has been prepared, is largely based on human experience. I know that the value of this experience has been questioned, and that it has been pointed out that human experience does not qualify as a scientific test result. In particular, it is impossible to run controlled experiments; the best that can be done is comparison of epidemiological studies. Moreover, human experience will not provide limits of safe use. However I maintain that its strong points are very convincing:

- the experience has been made with our own species, and not on one with a forestomach and no gallbladder

- the experience is with levels normally consumed, by eating in the normal way of administration. It avoids irritation effects by abnormal routes, such as gavage, and it also avoids the use of "overload" metabolic pathways which may be called upon to deal with higher than normal levels of intake.

Dr. Jan Stofberg, vice-president of the PFW Division of Hercules Incorporated, (right) was awarded the 1982 W.R. Littlejohn Memorial Medallion by Henry B. Heath, President of the British Society of Flavourists. Dr. Stofberg presented the Littlejohn Memorial Lecture, which is printed in full in this issue, in London in October 1982.

I am aware that many toxic materials have been identified in our basic and traditional foods. They are often listed to prove that those consumerists who expect everything natural to be particularly healthful are wrong. Potatoes contain the alkaloid solanin, and many other vegetables contain similar cholineesterase inhibitors.

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Oxalic acid and its salts occur in spinach, nuts, tea and cocoa. Myristicin, a known hallucinogen, occurs in nutmeg. This also contains another known hazardous material, a flavoring material this time, the carcinogen safrole.

I could also mention ethyl alcohol in wines and other alcoholic beverages, and hydrogen cyanide, another flavoring material, in almonds and in the lima beans I found in my new country of residence.

But this does not mean that all these foods are unsafe and unsuitable for human consumption. Our conclusion should be quite different. Obviously, the human body is a marvelous organism, able to deal with small quantities of an extraordinary range of chemicals. The best definition of a "safe substance" is that based on available data the risk of the consumption of such a substance is acceptable. Under this definition our basic and traditional foods are safe.

There is also consumption of chemicals other than the components of traditional foods, that is, of deliberately added materials, in particular, flavoring substances. I would like to discuss the relative impact of the flavoring substances from these two sources, the traditional foods and the added flavoring substances. For a quantitative comparison we should consider the quantity of flavoring substances consumed as unavoidable ingredients of traditional foods and the quantity of the same substances consumed as deliberate food additives. I have called the ratio of these two quantities the Consumption Ratio. This Consumption Ratio has considerable significance for setting priorities for the safety evaluation of flavoring substances.

Safety Evaluation of Flavor Substances

So far, problems associated with setting such priorities have been the main stumbling block for a systematic approach to the safety evaluation of flavoring substances other than those occurring on limitative lists.

An innovative approach to the safety evaluation of flavoring substances is needed because of their following characteristics:

- 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.

These facts have led to a number of safety evaluations of, and regulatory approaches to, flavoring materials.

In the United States, FDA and the FEMA Expert Panel have reviewed a number of flavoring materials known to be used as flavor additives, according to a series of well defined criteria. As a result a number of substances have obtained a food additive status, or a GRAS (Generally Recognized as Safe) status from FDA or FEMA.

In several countries, such as Germany, Italy, Spain and the Netherlands, the regulation of flavoring materials has been based primarily on whether such materials occur in nature. This should 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."

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 judgement on the safety of flavoring materials in the Codex Alimentarius will be made by its Joint Expert Committee on Food Additives of the Codex Alimentarius (JECFA). In response to requests from the Codex Committee 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. 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 agreed to rely only on the judgement of their Expert Committee, JECFA. 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 internationl standard without review by JECFA. Special attention should therefore be given to the recommendation published in the 20th JECFA report.

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.

For the execution of the program outlined in the JECFA recommendation I propose the following action, in two steps.

- Determine the Consumption Ratio of every known flavoring substance
- Evaluate the safety of every flavoring substance with a low Consumption Ratio

Step 1—The Consumption Ratio

First, I will discuss the determination of the Consumption Ratio in more detail. As I have stated earlier, the Consumption Ratio expresses the balance between the quantity consumed as an ingredient of traditional foods and the quantity consumed as a food additive of the same substance. If, for example, the quantity of one well defined flavoring material consumed by an average consumer as a natural ingredient of food is twenty times larger than the quantity consumed as a food additive, then the Consumption Ratio of such a material would be 20. If the consumption as an additive is twice the quantity occurring in food, the Consumption Ratio would be 0.5.

In actual practice, the Consumption Ratio is calculated using a fairly simple form to collect the necessary data (see Table I). On one sheet for every flavoring substance the name of the

Table I. Calculation of the Consumption Ratio

Flavoring substance:								FEMA No.
Occurring in:	Concentration	Ref.	Annual per cap. consumption of this food	Ref.	Annual per cap. cons. of this flav. subst. in this food	Annual total cons. of this flavoring subst. calculated for the population of the U.S.		CONSUMPTION RATIO:
						VIA FOOD	AS ADDED FLAVOR	

REFERENCES:

substance is filled in, as well as its FEMA GRAS number. In the various columns the foods in which it occurs are mentioned, the concentration present therein, a literature reference, the annual per capita consumption of the food, and the source of that information. In the next column, the annual per capita consumption of the flavoring substance as an ingredient of this food is calculated.

Two possible ways for calculation of the Consumption Ratio are open: either to calculate the intake per capita, as well as the per capita intake of the same material as a flavor additive; or to calculate these quantities for a given population, such as that of the U.S.A. or another large community. Since the figures calculated for a large population can be more easily compared to annual use by the flavor industry I have chosen that route. By addition of the previous column, and multiplication by the population of the U.S.A., estimated at 216 million people, we obtain the total annual consumption of this flavoring substance via food by the population of the U.S.A. This figure can be compared to the known reported quantity used per year in the U.S.A. as an ingredient of added flavorings. These quantities have been reported in several surveys held by FEMA among its members. The ratio of the last two figures is the Consumption Ratio.

I have filled out the values for one flavoring substance, 2,6 dimethyl pyrazine, as an illustration of the procedure (see Table II).

This is one example of the 89 substances for which Jan Stoffelsma and I have calculated the quantitative natural occurrence and the Consumption Ratio. The Consumption Ratio ranged from 0.05 to 80.700.

The result of the calculation of the Consumption Ratio for six flavoring substances as representative examples of the 89 determined so far is shown in Table III. It shows the wide variation in the Consumption Ratio. A large Consumption Ratio may be caused by the fact that a certain flavoring material originates from the same type of preparation of different foods, such as the roasting of such diverse materials as beef, grains and coffee.

In other cases a large Consumption Ratio is caused by the fact that a flavoring substance is predominantly present in a widely consumed food, such as onions or cucumbers.

These examples also show that in some cases the total consumption per population for the U.S.A. is only a hypothetical figure. In one case it is based on the consumption figure for a different population where a given food is traditionally consumed. For olive oil, data was

Table II. Calculation of the consumption ratio

Flavoring substance: 2,6-dimethyl pyrazine — FEMA No. 3273

Occurring in:	Concentration	Ref.	Annual per cap. consumption of this food	Ref.	Annual per cap. cons. of this flav. subst. in this food	Annual total cons. of this flavoring subst. calculated for the population of the U.S.		CONSUMPTION RATIO:
						VIA FOOD	AS ADDED FLAVOR	
coffee	19 ppm	8	4.8 kg	11	92 mg	22,246 kg	2.3 kg	9670
roasted beef	0.19 ppm	8	40 kg	9	7.7 mg			
beer	0.035 ppm	31	90 kg	10	3.1 mg			

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8 - PFW unpublished data
9 - National Food Review, NFR-7, 1979, p. 51 (data from USDA)
10 - American Dairy Review, June 1979, p. 8
11 - Advertising Age, April 30, 1979, p. 70 (data from USDA)
31 - R. Tressl, R. Renner, T. Kossa and H. Koppler, Proceedings of the 16th Congress of the European Brewery Convention (Amsterdam 1977), 693

Table II. Consumption ratio of 6 flavoring substances

FLAVORING SUBSTANCE	OCCURRING IN	ANNUAL CONSUMPTION OF THIS FLAVORING SUBSTANCE CALCULATED FOR THE POPULATION OF THE U.S.		CONSUMPTION RATIO:
		VIA FOOD	AS ADDED FLAVOR	
2-decenal FEMA 2366	potato chips olive oil	103 kg 30,186 kg	20 kg	1514
furfural FEMA 2489	roasted coffee	62,972 kg	2025 kg	31
methyl propyl disulfide FEMA 3201	onions	14,996 kg	25 kg	600
2,4-nonadienal FEMA 3212	potato chips	17.2 kg	42 kg	0.4
2,6-dimethyl pyrazine FEMA 3273	roasted coffee roasted beef beer	19,909 kg 1,666 kg 671 kg	2.3 kg	9670
2-trans, 6-cis nonadienal FEMA 3377	cucumbers	3,399 kg	1.4 kg	2428

used from Greece, Italy and Spain.

Flavoring materials that are almost exclusively consumed as ingredients of traditional foods, as indicated by a very high C.R., have a low priority for further safety evaluation. They 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.

The large number of food identical flavoring substances that are only synthetically produced on a small scale will end up in the low priority group with a CR >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. I have just calculated the Consumption Ratio of allyl isothio cyanate, and it comes to exactly 10—a good example of such a marginal substance.

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 evaluation in Step 2.

The C.R. of flavoring materials therefore also indicates, in a quantitative way, the nature and the source of a material, another aspect to be taken into consideration according to the 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.

Of the 89 flavoring materials we studied, as I mentioned earlier, 58 would be set aside in the "high Consumption Ratio class." The remaining 31 materials would have to be dealt with a priority as indicated by the evaluation of their safety.

The calculation of the Consumption Ratio for all known flavoring materials will require their quantitative identification in food. I am very happy that the flavor industry, in their national associations like FEMA and in their international organization IOFI, are actually undertaking the task to determine the Consumption Ratio for many more flavoring ingredients in many more foods than we have been able to cover so far.

The International Organization of the Flavor Industry (IOFI) has committed itself to pursuing this way of setting priorities for safety evaluation. It has contracted with CIVO/TNO to cover during 1982 the published quantitative occurrence of flavoring materials in twelve foods as the start of a continuing program. These foods are: oranges, beer, strawberries, tomatoes, bananas, lime and lemon, potato chips, rice, pineapples, nutmeg, cucumbers and coconuts.

Most of the data I have used came from unpublished PFW research. The research records of other major flavor companies most probably contain additional unpublished data. It is not uncommon that such data are only semi-quantitative, and that somewhere in the process of preparing distillates and extracts the exact quantitative relation has been lost. Both the national and international flavor associations are encouraging such companies to go back to their files and retrieve even semi-quantitative data that may well be sufficient to establish the order of magnitude of the Consumption Ratio for certain flavoring substances, in particular whether they are at the low or at the high end of the scale.

The priority ranking for safety evaluation based upon the Consumption Ratio will change continually as more data on quantitative natural occurrence becomes available. Also the decrease or increase of the quantities used as food additives will have to be reviewed on a regular basis. Once in a decade, a flavoring material takes off in importance and quantity manufactured. This has happened to maltol and ethyl maltol, 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 Consumption Ratio will move to the other end of the scale, and its priority will have to be changed.

The basic principle of the Consumption Ratio as a tool for setting priorities has been favorably received at the 15th session of the Codex Committee on Food Additives (The Hague, Netherlands, March 16-22, 1982), and it is quite probable that it will be one of the mechanisms to be considered in the Working Group to be convened by WHO in 1984/85.

Step 2—The Decision Tree

Now I would like to discuss briefly the safety evaluation of flavoring substances with a low, Consumption Ratio. This evaluation will have to be done based on chemical structure, metabolic pathway, toxicological data and usage levels.

This kind of systematic safety evaluation was initiated by the FEMA Expert Panel in 1960. The properties of individual substances were evaluated in detail by a group of scientists of international reputation not affiliated to the flavor industry. The results of the evaluation were published, as the FEMA GRAS list, but it was not until many years later that the principles and rationale adopted in evaluating the safety of the substances were published in a presentation by Dr. Horace W. Gerarde.

In 1977, Oser and Hall published an updated account of the criteria employed by the Expert Panel. The considerations which led to the GRAS status of individual flavoring substances were never published. This may have led to other, independent reviews of the safety of flavoring substances, such as those by the Working Party of the Council of Europe. But this working group also never published the data and the criteria upon which their conclusions were based. We have a clear duplication of effort here which we hope to be able to avoid when the Codex Committee on Food Additives will request JECFA for safety evaluation of certain flavoring substances.

The drawback of all published results of expert panel evaluations is that they are usually inexplicit and subjective. This is why, as a further development of the criteria used by the FEMA Expert Panel, Cramer, Ford and Hall have designed a decision tree for the estimation of toxic hazard. The purpose was to make a significant part of the safety evaluation process rational, based on major chemical classifications. As a result of applying the decision tree, all chemical structures will end up in one of three classes of presumed toxicity, Class I with low, Class II with moderate and Class III with serious toxicity.

The decision tree consists of thirty-three questions, the answer to which can be only yes or no. Depending on the answer, the substance is either assigned Class I, II or III, or referred to the next question.

Yes to the first question, is the substance a normal constituent of the body? throws all such constituents in Class I.

All non-constituents proceed to question 2: does the substance contain an aliphatic secondary amine, cyano, N-nitroso, diazo, triazeno or quaternary nitrogen, with certain specific exceptions? Structures that contain elements or valency states often associated with enhanced toxicity are assigned Class III.

Substances without these functional groups go to the next question: does the structure contain other elements than carbon, hydrogen, oxygen, nitrogen or divalent sulfur? Structures containing such other elements go into the highest presumed toxicity class, III, unless they are simple salts—in which case they are referred back to the corresponding organic acids or bases.

If no other element other than C, H, O N or divalent S are present, the next question is whether the substance is a simply branched aliphatic hydrocarbon or a common carbohydrate—which go into the safest class I. If not, the chemical structure of the material is further analysed in a set of questions asking for the presence of:

- benzene rings with safrole structures
- heterocyclic structures, in particular lactones
- heteroaromatic structures with or without substituents
- whether the material is readily hydrolyzed, in which case both moieties are treated separately

It is obvious that this tree is heavily based on known data on metabolism and toxicity.

The total intake of a substance is another important factor in establishing the priority for doing further toxicological work.

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. I believe that in this way, a priority classification should be established for all flavoring materials with a Consumption Ratio of less than 10.

As an example of this procedure, Ford has provided the classification for the thirty-one materials referred to previously that have a Consumption Ratio of less than 10. None of these fall into the D category, and only two, diacetyl and indole, are classified as C.

The Importance of the Consumption Ratio

Now I would like to return to my main topic: the importance of the Consumption Ratio to establish confidence in the use of components of traditional foods.

With every new breakthrough in techniques for the analysis and identification of flavoring materials occurring in traditional foods, there will be a whole new generation of flavoring materials. Developments in gas liquid chromatography (GLC) and spectrometry over the last thirty years have made possible the discovery of thousands of new flavoring substances, characterized by their volatility. The current development of high performance liquid chromatography (HPLC) will provide us with large numbers of flavoring materials which are not volatile enough, or break down too easily, for detection by gas chromatography. Further refinement of such techniques will increasingly bring flavor analysis down from the ppm level to the ppb level—and many new flavoring materials will thus be identified that are essential at that level for further improvement or development of nature-like flavorings.

As I mentioned earlier, the approach to this new wave of flavoring materials will be quite different in various countries. Some will accept them just on the basis of their being nature-identical, others will want to put them individually through a safety evaluation after they all have been listed.

I sincerely hope that the setting of priorities according to the Consumption Ratio will lead to a more rational approach everywhere, and that it will facilitate the harmonization of the somewhat dug-in positions on "nature-identical" versus "positive list."

The basic idea of the nature-identical concept is that whatever occurs in our traditional "natural" food cannot be really harmful. In this concept the accent is more on the "traditional" aspect than on the "natural" origin of the food, as demonstrated by the fact that roasted coffee is generally considered natural. Every chemist knows that the result of the roasting process is a complex set of chemical reactions.

The main argument against the use of nature-identical as a criterion for safety has always been that the industry would be able to use far larger amounts of such nature-identical flavoring materials than occur in natural foods. The standard answer from the proponents of nature-identical has been that flavoring materials are self limiting by virtue of their sensory impact.

I am not sure this answer is adequate. How can we convince anybody that the amounts in which a material is used, limited by its flavor strength, are safe if the safe limits for such a material are unknown? And it certainly does not limit the total intake of a substance, as you will easily see if you compare the total consumption of synthetic vanillin to the quantity consumed in the form of vanilla beans. I have calculated the Consumption Ratio for vanillin to be no more than 0.02.

I think this is the main reason why the nature-identical concept for the permission of flavoring substances has not been generally accepted, not even by all scientists and regulators in those countries where it has force of law. In all other aspects it is definitely the only way to formulate a practical and enforceable flavor regulation. It avoids the practically impossible enforcement of a positive list regulation by analysing foods or flavorings for the presence of substances that do not occur on a positive list. In addition the enforcing agency will have to prove that such a substance does not originate from a natural and permitted ingredient in which it is known to occur. This is clearly an impossible burden especially if we are considering the enforcement of such a positive list regulation on flavors or foods imported from another country.

Qunatitative Food Predominance

If, however, the basic concept for a flavor regulation would be changed from "occurring in nature" to "occurring in traditional foods;" and in particular if the amount consumed in food would be larger than the amount consumed as additive, I believe that such a quantitative "Food Predominance" would be more acceptable as a criterium for practical safety.

Such a quantitatively limited use of substances occurring in traditional foods may also be acceptable within the framework of a positive list of materials that are GRAS. In that case the occurrence in food and the value of the Consumption Ratio could be the first steps in the safety evaluation procedure. In many cases it would make further safety evaluation unnecessary and would drop thousands of flavoring materials from the safety assessment by regulators.

The concept of quantitative Food Predominance as a criterium for the practical regulation of flavoring materials could become a successor, on a higher and more responsible level, to the nature-identical concept. It would have to be based on a limit for the Consumption Ratio of such a substance. I propose that, for the occurrence in food as the basis for permission to use the substance, the consumption as an ingredient of traditional foods would have to be larger than the consumption as a food additive. This is equivalent to a Consumption Ratio of more than 1. According to this proposal the meaning of Food Predominance would be "occurring in traditional food, with a Consumption Ratio of more than 1."

All other substances occurring in food and other natural materials, but with a lower Consumption Ratio, would be grouped together with substances not occurring in foods, and usually called "artificial." Such materials would have to be included in a list of permitted flavoring substances after further safety evaluation along the lines I have described earlier has been completed.

A regulation based on the Food Predominance of flavoring substances would protect public health even better than one based on whether they are nature-identical or not. It would dispel the doubts about the unlimited use by the industry of all substances occurring in nature. It would also allow flavor chemists to use the thousands of substances occurring in foods with confidence, and on an equal footing with Mother Nature.

Acknowledgement

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