The safe use of flavors—update

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In the Federal Food, Drug and Cosmetic Act, a food additive is "any substance which is or may become a part of food." Section 210(s) provides an exception with respect to each substance which is "generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown . . . to be safe under the conditions of its intended use . . .". We call GRAS those substances which are generally recognized as safe by the experts.

In 1971, the FDA published its interpretation of that definition in 21 CFR section 121.3. You should expect in early 1976 a publication of a final regulation amending Section 121.3. Despite FEMA's protestations, the definition will be a narrow interpretation of the statutory provisions, roughly equivalent to the proposed regulation published September 30, 1974. You should expect the interpretation to be so narrow as to provide that while a substance may be considered as GRAS, any new manufacturing process for that substance must be cleared through the FDA with a food additive petition.

Shortly after the Food Additives Amendment was enacted in 1958, FEMA established an Expert Panel of distinguished scientists, who undertook to review the safety of flavors within the meaning of the GRAS concept. After 17 years, we find that no other organization has reviewed the thousands of flavor materials in use. During those years, the FDA was concentrating on more urgent matters, reviewing the food additives with higher priorities. The FEMA Expert Panel is the first body in the world to develop a comprehensive methodology for evaluating the safety of flavors. Neither the Food Additive Petition process nor the GRAS Affirmation Petition process of the FDA really relate themselves to the specific distinguishing characteristics of the flavor industry, namely that flavors are used in relatively small quantities in foods, the amount of each flavor used per year is relatively small, and flavors have for the most part been found naturally in foods.

A major advantage of the process used by the Expert Panel is the speed of its review and the relatively lower cost to the submitting company. The Expert Panel meets four to five times each year and leaves each meeting with no backlog. If a question of safety arises, the Panel makes specific requirements which may include feeding studies. From time to time, the Panel contacts others as consultants should any issues be raised which require further information.

In contrast, the FDA requires a minimum of a year to review a GRAS Affirmation Petition. If there is any question regarding the safety of the substance, the FDA will not clear it GRAS but will require that the substance satisfy the demands for a food additive petition. In the case of food additive petitions, the FDA requires a minimum of a 90-day study, and in the present atmosphere longer studies of 2-years in 2 species are becoming the rule rather than the exception.

The FDA is relatively slow in its food additive activities because one Division of the Bureau of Foods has responsibility for all food and color additive activities, which involves a great majority of all the current major food issues. They review all food additive and GRAS affirmation petitions. They are also supervising the progress of the comprehensive review of GRAS and food additive substances, all with only twelve people.

The historical relationship of FEMA's GRAS lists and the FDA's approved lists, briefly described, follows. The FDA took the GRAS lists 1, 2, and 3 in their entirety and placed them into food additive status, 21 CFR Sections 121.1163 and 121.1164, with only a few exceptions. The FDA has tacitly accepted all the subsequent GRAS lists up to and including GRAS list 9.

It is now appropriate to raise two questions: 1) If the Expert Panel continues to recognize new GRAS substances, will those determinations continue to be acceptable to the FDA? What is being done by the FDA to evaluate the safety of the FEMA GRAS substances including those contained in the GRAS lists as recent as GRAS nine?

As background, we should review the FDA's Comprehensive GRAS review. Through a Committee of the National Academy of Sciences, the FDA initiated around 1970 a survey of all non-flavor substances. The FEMA's Second Flavor Additive Survey took place simultaneously. The FEMA included in its Survey all the FEMA flavors up through GRAS list 4.

Right now, this same committee of the NAS is preparing for a second massive Survey of all food additives. FEMA is again working with that Committee to participate in the survey to the extent of FEMA GRAS lists five through nine. While the list of flavors to be contained in the survey is still being developed, there should be included in the list a few other flavoring substances which had been omitted from the previous survey but are nevertheless of interest to the industry. This new survey will be mailed to companies which are interested in participating, sometime in the spring of 1976.

When the NAS received the data from its first survey as well as that of FEMA's, the FDA asked the NAS to collate the data and establish average use levels, maximum use levels, and estimates of consumption of the surveyed substances by the average person in the United States. Once presented in this form, it became obvious that the values were considerably overstated because of several inherent defects in the assumptions made by the Committee. There are a few basic differences in the new questionnaires, the main one being the establishment of more categories of food into which the uses are divided.

As another step in the GRAS review, the FDA contracted with FEMA to prepare Scientific Literature Reviews of the flavors included in the first survey. The SLRs were intended to be summaries of all information in the literature relating to the safety of those substances for use in food. The first SLR covered 276 simple aliphatics. SLRs covering smaller groups of more complex substances were delivered to the FDA this fall, and others are in preparation. It is anticipated that the preparation of the SLRs will continue for several years, until eventually all flavors have been subjected to this close scrutiny.

As the next procedural step in the comprehensive GRAS review, the FDA entered into a contract with the Select Committee of Flavor Evaluation Criteria, known as SCOFEC, of the Federation of American Societies of Experimental Biology, known as FASEB. The assignment, as given to SCOFEC, is to prepare criteria for the evaluation of the safety of flavors. The members were handed FEMA's first SLR to assist them in their determinations. Part of their assignment is to indicate whether the information in the SLR is sufficient on which to base a decision of safety.

SCOFEC held two hearings during 1975 at which witnesses were invited to provide advice and comments. After one of the hearings, the committee issued its only public pronouncement to date of its thinking. The subsequent activities of the Committee have been kept closed and confidential.

In the published minutes of the Committees' May 29-30 meeting, the Committee stated "Combinations and permutations of chemical substances in foods constitute a toxicological question not addressed by the FEMA Expert Panel." Indeed this is true. Historically, the Expert Panel has endeavored to limit its determinations to individual substances rather than mixtures. The only exceptions to the Panel's rule of thumb, so far, have been the few natural substances which were reviewed in connection with GRAS three. However, the FDA follows the same pattern. The FDA, when it considers a food additive petition, does not consider all the combinations and permutations of uses of that substance before issuing its determination. The terms of the Federal Food, Drug and Cosmetic Act are addressed to the use of a food additive or a GRAS substance as an individual substance, not as a part of a vast system of combinations and permutations.

At the first hearing of SCOFEC, Dr. Oser stated that unless there is a genuine reason, based on chemical or pharmacological considerations, to question its safety under conditions of use, it is neither reasonable nor practicable to place on any substance, used to the extent of only a few hundred pounds annually, the cost burden of chronic toxicity studies. In response, the Committee stated, the "true evaluation of economic worth should be placed on the value of the final food products if one wishes to equate this with the cost of obtaining toxicity data to protect the consumer of the product." In effect, the Committee was staing that the GRAS concept is scientifically unacceptable. As you know, the GRAS concept is based on the principle that a substance is safe unless it is proven otherwise. Hopefully, the Committee will change that view before it issues its final report early in 1976. When the report is issued, FASEB will create another committee which will be charged with actually evaluating flavors based on the criteria established by SCOFEC. Following the final evaluation by FASEB, the FDA, with respect to each flavor, will either affirm the GRAS status, publish a prior sanction, establish an interim food additive regulation, establish a permanent food additive regulation, or eliminate it from food use.

The FDA has published regulations based on the GRAS review with respect to certain non-flavor GRAS substances. Where the FDA concluded that it would affirm the GRAS status, it published a proposed regulation setting the level of use, specified as being good manufacturing practice, for each use reported in the course of the NAS survey. The levels published were intended to be the highest reported uses in those categories of food. Where the FDA concluded that a food additive regulation was in order, it published proposed maximum use levels for each category of food and for each function in that category. The categories of food and the functions of use were taken directly from the NAS survey. As you see, the FDA cast in concrete, in regulatory concrete, the data received in response to the NAS survey. Any subsequent uses or any changes in category of food or changes in function will apparently not be permissible without changes to the regulations. Such additional uses would have to be justified by a demonstration that they would not adversely affect the health of the consuming public. You should bear these comments in mind as you contemplate whether or not to participate in the survey and especially as you respond to the survey questions. The data that you supply will have long-lasting effects on the industry.

In the light of this regulatory status of flavors, a related significant issue is the question of labeling of flavors as it relates to existing and future GRAS lists.

While the FDA does not prevent the FEMA Expert Panel from carrying on its activities by a direct confrontation, it appears that indirectly the panel's activities have been affected through FDA's flavor labeling regulation. Pursuant to 21 CFR Section 1.12 (g), the label of the bulk flavor product need not identify the flavors that have FDA acceptance. In the preamble to the December 31, 1973 version of that regulation, the FDA gave the same exemption to substances which were in published FEMA GRAS lists as of that time, namely, GRAS lists one through six. At the FEMA Convention in Florida, May 1975, Dr. Angelotti, Associate Director for Compliance of the Bureau of Foods, stated that GRAS lists seven and eight would be considered exempt as well, except for those simple aliphatic substances which had not been included in the first SLR prepared by FEMA. With respect to those 22 simple aliphatic substances, Dr. Angelotti stated: "We believe that we are justified in seeking a GRAS or food additive petition for these 22 compounds before we should properly consider them as part of the GRAS review or exempted from specific label declaration. A Scientific Literature Review has already been prepared in flavors of this simple aliphatic structure, and we believe that it is now the responsibility of the FEMA, or members of the flavor industry, to seek GRAS or food additive clearance for those or any additional compounds of similar structure.

"Because we cannot leave the list of substances to be exempted from specific label declarations open ended, we believe that we are also justified in seeking petitions for any flavors that may be included in any future industry association approved lists."

FEMA acted quickly in response to this speech and held several meetings with Dr. Angelotti in order to minimize the impact on the industry. Following these discussions, the FDA published in the Federal Register of February 3, 1976, a notice which extended to July 1, 1979, the effective date for the requirement of ingredient labeling of flavor ingredients on an industry association list of flavor ingredients but which are not approved for use in a regulation of the FDA. The notice establishes the following procedures. FEMA has prepared SLRs on all the simple aliphatic substances in GRAS lists 7 through 9 and these are being incorporated into the SLR filed with the FDA last year. Because FEMA did this, all the flavors listed in GRAS lists 7 through 9 are to be considered as exempted from specific identification on the bulk package.

When GRAS list 10 is published, the substances will be treated as follows: 1) The substances which would fit into the categories which have already been covered

in SLRs submitted to the FDA will not be considered approved by the FDA until after an appropriate petition is filed by industry at industry's expense. The methodology of petitioning has not been established. These substances will not be exempt from labeling until FDA approval occurs. 2) The substances which would fit into the categories that are being covered in SLRs then in preparation by the FEMA will be incorporated into the SLRs at the expense of the FDA. They will be exempt from labeling pursuant to the notice. 3) The substances which would fit into catgories which have yet to be covered by SLRs will remain exempt from labeling and will be included in the appropriate SLRs as prepared at the expense of the FDA.

Certain aspects of the FDA comprehensive survey, as it related to flavors, have yet to be resolved. For one, we do not know what the evaluation criteria of the FASEB will be nor do we know whether or not the FDA will accept FASEB's criteria. We do not know what the final form of the GRAS regulations on the individual flavors will be nor do we know what FDA's final general regulation on this matter will be. I am sure that you question from time to time whether all this effort will ever prove worthwhile. We should recognize the benefits of a completed review of all flavors, which includes an end to the need for constant defense of your uses of flavors and a uniform international acceptance of flavors.

Literature

ODOR CONTROL AND OLFACTION. J. P. Cox, PhD, edited by Ralph B. Duclos. Researched and compiled by Florie Cox Illustrated by R. G. Johnson Pollution Sciences Publishing Company P.O. Box 175; Lynden, Washington 98264

John E. Amoore in his book "Molecular Basis of Odor" has defined the main task of any "Unified Theory of Olfaction" to "Bridging the gap between stimulus and sensation." This definition is illustrated with the "Bay Bridge Analogy for Odor Research" in which a suspension bridge reaching from "Chemistry" to "Physiology" is supported by four major piers: Molecular conformation, Molecular Biology, Electrophysiology and Psychometrics.

Work on three of these piers has made great progress in the past. "Molecular conformation" has topped out: whatever we need to know about conformational changes of monomeric stimuli and biopolymers involved in chemoreception in general and olfaction specifically is well understood. "Electrophysiology" has made rapid progress and has been tremendously refined by progress in solid state electronic and electronic data processing —like "Psychometrics" it is a well established pier very well suited to support the bridge from chemistry to physiology.

The fourth pier however—the central one—"Molecular Biology" is still missing and has not progressed much beyond an increasing recognition of the fact that without it the bridge could never be finished. It is recognized though that there is a solid foundation available and that the techniques necessary for the construction—enzymology, structure and function of biological membranes, electrophysiology, molecular pharmacology, molecular neurochemistry to name a few—are in rapid development themselves and ready for attempts to close the gap. But only a few sketches and blueprints based on available data have been proposed.

All of this is conspicuously missing from this "Handbook." It is a unique assembly of facts and fiction, mystique of odor and established facts of odor perception in its first thirtytwo pages dealing with the deduction of a new "Unified Theory of Olfaction." Unification of the well researched older odor theories and their inputs is achieved by accepting the salient features of nearly all of them. Intrinsic incompatibilities force the author to resort to very broad and cryptic formulations, such as:

"Olfaction is a complex sense dependent upon specific, multi-specific and/or composite stimuli of diverse natures"

"Olfactory epithelium is responsive to osmogenes exhibiting a variety of energies by

a. A series of extended resonators tuned to a range of osmic frequencies (that takes care of the theories of G. M. Dyson and R. H. Wright)

b. Potentiometric sensitivity between the lipomucosal layers (that extends the umbrella to J. T. Davies "Penetration and puncturing Theory") and by chemical reactivity (Echoes of H. Hellers Mechanical-Chemical theory of odor and T. H. Durrans' Residual Affinity Theory of Odor) on active sites (Here come the Stereochemical Theories of Odor by R. W. Moncrieff, J. E. Amoore and L. J. Mullins)."

The result derived is for all practical purposes useless and constitutes a serious case of disinformation. It reduces this first part of the book to a collection of interesting, sometimes amusing and in many parts quite informative reading.

Odor classification is the next topic. After a well researched review of older systems a new one is added, based on a "photo-functional osmogenic taxonomy." It is just another attempt to use semantics and linguistic creations to achieve the impossible: A precise odor description. In this light the merit of this chapter remains questionable.

The best part follows: pp. 54 to 124. This is a very good, well written introduction to the problems of odor pollution and methods of odor control. It covers the "state of the art" methods, sources of industrial malodors, and regulations for the control of malodors issued by 52 agencies. An excellent patent index (pp. 363-401), well researched, abstracted and commented gives the practitioner of state of the art odor control methods very valuable additional information which cannot be found in any other source in this handy and compact form.

A list of Natural Plant and Animal Odors (pp. 125-136) and an "Osmogene Index" (pp. 137-348) give a sketchy odor description of a large number of odorants and irritants. It may make a useful complement to a set of S. Arctander's "Perfume and Flavor Chemicals" and the "Riechstoffkodex" by Arno Mueller.

A collection of conversion formulas, odor/structure correlations, a glossary, Bibliography and Index account for the remaining pages.

Overall, this book is an unusual mixture of competence and pseudo-competence; well researched and documented information and less than convincing speculation; quite up to date in the odor control section and hopelessly obsolete in the section dealing with olfaction. It may not offer much to scholars and researchers in the field of olfaction, is almost certainly not contributing new informations to practitioners of modern creative perfumery, but can be recommended highly to those who have to deal with problems of odor control.

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