Safety Evaluation of The Food Ingredients Called GRAS

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Background
This article briefly describes the evaluation of the Generally Recognized As Safe (GRAS) food ingredients, which was undertaken by the Life Sciences Research Office (LSRO), an operating arm of the Federation of American Societies for Experimental Biology (FASEB) six years ago under contract with the Food and Drug Administration. Additional details can be found in a paper published by LSRO in 1977.1

The acronym GRAS, meaning Generally Recognized As Safe, is a spinoff of the 1958 Food Additives Amendment2 of the Federal Food, Drug, and Cosmetic Act3. The amendment required that all substances intended for addition to food receive prior approval of the Food and Drug Administration (FDA). Approval was to be based on scientific data provided by the proposer which demonstrated the absence of hazard when the substance is used in the amounts and manner proposed. At that time, several hundred substances already in common food use were “grandfathered” by exempting them from the requirements of the Food Additives Amendment. A listing of these substances was first published by FDA in the early 1960’s under the title, “Substances Generally Recognized As Safe.” This particular category of exempted food additives came to be called the GRAS list and the substances on it, GRAS substances. Inclusion of substances in the original GRAS list was not determined by history of use alone. Prior to pub-

lication of the original list, FDA sought the opinions of many qualified individuals for the purpose of eliminating any substances thought to have questionable characteristics. Several substances were eliminated before initial publication and others have since been deleted. The 1977 revision of the Code of Federal Regulations4 lists the more than 600 substances currently considered to be GRAS.

Since 1958 the GRAS list has been augmented by FDA’s issuance from time to time of so-called GRAS letters. These letters have authorized requestors to consider certain substances as GRAS for specific food uses. The substances concerned have not always been added to the published GRAS list in the annual revision of the Code, but continue to be regarded by FDA as “unpublished GRAS substances.” A complete listing of such substances is not available.

The language of the Food Additives Amendment did not designate particular experts to judge GRAS status, requiring only that it be those “qualified by scientific training and experience to evaluate the safety of substances based on scientific data derived from published literature.” Almost immediately after enactment of the Amendment, the Flavor and Extract Manufacturers’ Association formed a panel of experts to evaluate the natural and synthetic substances and compounds used as flavoring materials in processed food.5 Results of the first of these evaluations appeared in 1960.6 As additional substances have been evaluated results have continued to be published, the most recent being in 1978.7 Of this group of substances, now numbering about 1400, about 800 are included in the Code of Federal Regulations8 under the title “Syn-

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thetic flavoring substances and adjuvants." While these substances are not GRAS substances in the strict sense, their use is administered by FDA as though they are GRAS. The safety of this group of flavoring substances is now undergoing re-evaluation.

There was no systematic attempt in the decade following the publication of the original GRAS list and the periodic appearance of GRAS letters, to make a critical evaluation of the available scientific information on these individual GRAS substances. However, with stimulus provided by a recommendation of the White House Conference on Food, Nutrition and Health, FDA was directed by the President in 1969 to conduct such an examination.

What follows is a summary of the steps taken, the procedures used in conducting this examination, and the current status of the evaluation effort.

 Procedures

In the early 1970's FDA took the following steps: (1) contracted with the Franklin Institute of Philadelphia to search the scientific literature, beginning in 1920, for references to all substances on the GRAS list, and to prepare and send to FDA bibliographies and abstracts; (2) the bibliographies and abstracts concerning each substance or group of related substances were then sent to one of several institutions* which, under FDA contract, prepared scientific literature reviews (monographs)** summarizing the salient information and providing reprints, and translations of foreign language articles when necessary, of all original articles cited in the summary; (3) contracted with the National Academy of Sciences, National Research Council (NAS/NRC) to survey*** the food industry to determine the levels of use in food of each of the GRAS substances and to estimate human daily intakes; (4) initiated studies in FDA and under contract in nongovernment laboratories to perform special tests, especially those for assessing the mutagenic and teratogenic potential of many of the GRAS substances; (5) contracted with FASEB to receive all of the documents indicated above, evaluate the information contained in them, and provide FDA with individual reports on the health aspects of using each of these substances (nearly 400 in number) as food ingredients. More than 200 natural and synthetic flavoring substances on the GRAS list were not evaluated by FASEB but are being evaluated separately by other means. Upon completion of its present contract, FASEB has been invited to undertake evaluation of some 30 additional prior sanctioned GRAS substances.

Since July 1972, evaluation of the data on the assigned GRAS food ingredients has been underway by a group of qualified scientists chosen by FASEB with the concurrence of FDA, and designated as the Select Committee on GRAS Substances (SCOGS). The SCOGS has been supported by a full-time professional scientific and support staff within FASEB. Members of SCOGS were selected, for the most part, from nominations made by the constituent societies of FASEB. A committee of eleven members*** balanced with respect to the disciplines required for the task has proven effective. Disciplinary coverage has occasionally been augmented by making use of ad hoc consultants and the expertise of the FASEB staff. Members of SCOGS and FASEB staff are required to be free of conflict of interest and SCOGS members are expected to devote a minimum of 5 days of each month to the effort, including frequent two-day meetings of the full committee. During the 6 years of its existence, SCOGS has held 58 meetings. Members have been chosen for their breadth of knowledge as well as expertise in a particular discipline rather than narrow depth in a restricted specialty, for their demonstrated good judgement, and for their effectiveness in the "take" as well as the "give" in the collective reasoning of Committee deliberations. Tenure of one-year was established for members with option to continue by

*Principal contractors have been Informatics, Inc., and Tracor-Jitco, Inc., both of Rockville, Md.

**Monographs and the NAS/NRC survey reports are available from the National Technical Information Service, U.S. Department of Commerce, P.O. Box 1553, Springfield, Virginia 22161.

mutual agreement, making possible adjustments by addition or subtraction to maintain a panel having the characteristics desired.

The mechanics of SCOGS and staff operations and relations, evolved early, proved to be effective and have been continued. To assure that opinions and conclusions eventually reached are entirely those of SCOGS members, the initial draft report is written by members, usually by a subcommittee of two, assigned so as to match subject matter with the professional backgrounds of the individuals. Full Committee deliberations are then conducted with the draft as the point of departure. All members and staff are provided copies of the same raw data to permit study prior to full discussion which is continued until there is agreement among SCOGS members that the draft opinion, conclusions, and supporting data reflect adequately the thinking of all Committee members. A second draft report, prepared by staff, is marked-up by SCOGS members and substantive modifications are debated at a subsequent meeting. After agreement on additions and emendations, staff prepares a third draft report, verifying every statement and figure against the original articles cited and checking all calculations. Upon signed approval of this draft by all SCOGS members it becomes the tentative report of the Select Committee.

The tentative report is sent to FDA which makes an announcement in the Federal Register that the tentative report and all raw data used in its preparation are available for public inspection in the Office of the Hearing Clerk. The announcement also includes an invitation to those who wish an opportunity to present data, information and views concerning the tentative report to request a public hearing or provide the Committee with a written statement. When a public hearing is requested, a date, time and agenda are established by mutual agreement and announced in the Federal Register. The hearing is recorded and the hearing transcript is made available to the public. The data, information and views divulged at the hearing or the original SCOGS subcommittee, deliberated by the full Committee, and based on these deliberations, the FASEB staff prepare a revised draft incorporating any modifications agreed upon. After SCOGS approval, the revised draft is reviewed by the LSRO Advisory Committee* and after approval is submitted by the Executive Director, FASEB, as a final report of FASEB to FDA. Soon thereafter, the final report is made publically available through publication by the National Technical Information Service.

In due course, FDA considers the final report with attention to other relevant factors, and publishes in the Federal Register a proposed regulatory order with respect to the substance or substances concerned. Public comment on the proposed order is invited and after resolution of any questions that arise, a final regulatory order is published in the Federal Register. Any still dissatisfied with the final order may request a public hearing with FDA and/or initiate court action.

Conclusions with Interpretations

The Committee's evaluation report on each GRAS substance provides FDA with an analysis of all relevant scientific data and a judgment expressed as an opinion leading to one of the five conclusions stated below. Also indicated below is the manner in which FDA may translate each conclusion into regulatory action provided it concurs with SCOGS conclusions.

1. There is no evidence in the available information on _________ that demonstrates or suggests reasonable grounds to suspect a hazard to the public when it is used at levels that are now current or that might reasonably be expected in the future. (FDA interpretation: Substance continued in GRAS status with no limitations other than good manufacturing practice.)

2. There is no evidence in the available information on _________ that demonstrates or suggests reasonable grounds to suspect a hazard to the public when it is used at levels

*Consists of one member of each of the six constituent societies of FASEB and three ex-officio members. Members as of June 1978 were: E. S. Vessell (ASPET); F. P. Ferguson (APS), J. S. Ram (AAP), W. R. Beisel (AIN), P. J. Van Alten (AAI), vacant (ASBC), E. L. Way (President, FASEB); G. B. Pierce (Vice President, FASEB), E. L. Hess (Executive Director, FASEB), and K. D. Fisher (Director, LSRO).
that are now current and in the manner now practiced. However, it is not possible to determine, without additional data, whether a significant increase in consumption would constitute a dietary hazard. (FDA interpretation: Substance continued in GRAS status with limitations on the amounts that can be added to foods.)

3. While no evidence in the available information on demonstrates a hazard to the public when it is used at levels that are now current and in the manner now practiced, uncertainties exist requiring that additional studies be conducted. (FDA interpretation: Issue an interim food additive regulation requiring commitment, within a stated period, that necessary testing will be undertaken. Substance continued in GRAS status while tests are being completed and evaluated.)

4. The evidence on is insufficient to determine that the adverse effects reported are not deleterious to the public health when it is used at levels that are now current and in the manner now practiced. (FDA interpretation: Establish safe usage conditions or rescind its GRAS status. Interested parties may submit a petition establishing conditions of safe use.)

5. In view of the deficiency of relevant data, the Select Committee has insufficient information upon which to base an evaluation of when it is used as a food ingredient. (FDA interpretation: Provide interested parties opportunity to submit relevant data for evaluation or rescind its GRAS status.)

In considering revision of regulations with respect to each GRAS substance, the FDA regards the SCOGS reports and conclusions as but one factor in their decision-making process. Such other factors as benefits versus risks, idiosyncrasies of special consumer groups, and possible interactions of GRAS substances with new drugs, are also considered by FDA in arriving at regulatory decisions. It is to be emphasized in this regard that the Committee's deliberations are restricted to a scientific evaluation of potential health hazard posed by each GRAS substance for normal individuals, and, while it is constantly aware of such factors as indicated above, it has taken pains not to permit them to interfere with the scientific soundness of its conclusions.

Some Lessons Learned

It was the intention of those in FDA who planned the GRAS substances evaluation exercise to have practically all of the required data assembled in monographs that were furnished to the Committee. The SCOIS was only to analyze and evaluate it. Such a clean separation of function was not realizable. The Committee found that assuring itself that all of the relevant data on each of the GRAS substances had been assembled was a formidable task, requiring regular searches for additional sources of information to fill gaps in the assembled data. The monographs were helpful but in many cases they served at best to permit the Committee to start part way up the mountain and thus, undoubtedly, shortened the time required to reach the summit. However, it is highly probable that no advance search, no matter how exhaustive, can anticipate the supplementary needs that inevitably arise during the evaluation process.

Because level of consumption is an essential factor in assessing potential for adverse health effects of ingested substances, it has been necessary to have or derive estimates of average daily intakes of the GRAS substances. The Committee has relied heavily on the report of a subcommittee of the NRC which surveyed the American food industry in 1970 to obtain data on the levels of addition of each of the GRAS substances in a number of food categories. With these and other data, the NRC subcommittee was able to derive estimates of the daily human intake of most of the GRAS substances. However, it was recognized by the subcommittee and later apparent to SCOIS that the daily intakes obtained thereby for various age groups were usually overstated often by considerable margins. Obviously, accuracy of such estimates is less crucial with substances found to have little or no toxicity than with those found to elicit adverse responses at dose levels approaching those estimated to occur as the result of usual consumption habits. It was therefore necessary, in many instances, for SCOIS to use other means to derive intake estimates it considered more realistic. In
surveys currently being undertaken by the NRC, methodology has been improved and more readily interpretable responses are expected from a larger proportion of the industry than was the case in the first survey. The resulting new and better intake estimates will strengthen a weak link in the chain of data necessary for evaluation of the safety of GRAS food ingredients.

Once all available information was assembled and SCOGS addressed itself to the evaluation task, it recognized that a conclusion concerning safety was to be drawn, ultimately, from these data alone. Hence, great care was required in assessing the scientific rigor of data reported and the credibility of investigators, in weighing and extrapolating indicative studies, and the adjudication of conflicting findings. It was learned that much of the available data was contained in studies made for purposes other than to demonstrate presence or absence of hazard, with substances not clearly typical of those presently used in food, or by laboratory techniques that have since been improved or replaced by better ones. Considerations of relevance, validity and significance became increasingly important the more incomplete the data. It came to be recognized further that exercise of reasoned judgment rather than simple analysis and summation of data was often necessary in reaching conclusions and that consistency in applying such reasoned judgment was important in view of the large number of substances to be separately evaluated. Because of possible adverse effects due to interaction of some of the many food components and additives in biological systems, it was imperative to keep the total problem in view as the individual pieces were examined.

It is obvious from the preceding paragraphs that the evidential adequacy for the evaluation of health hazards varied widely among the GRAS substances. Conventional criteria for judging safety could only be used as an elastic framework and each substance had to be evaluated within its own context and with what data were available. The principal thread of consistency in rendering opinions was the “reasoned judgment” referred to in the Food Additives Amendment of 1958. For many GRAS substances, the narrow base of experimental information has had to be supplemented with empirical experience and judgments as to permissible inferences.

Many considerations point to the imperfection of evaluation methodologies and the fallibility of expert panels in deriving interpretive values from available tests. As a result, some toxicologists are pressing for standard protocols for safety evaluation, to be followed across the board for all substances to be evaluated. SCOGS has come to believe it is more sensible to tailor the kinds of definitive tests to the nature of the substance and the uses envisioned. Rather than rigidly standardized protocols what is needed is a set of generally accepted and officially approved guidelines and principles, continually updated by scientists and other interested parties. In the meantime, we need to focus attention on getting the maximum interpretive value from a reasonable body of controlled experimental data for each case at hand.

New technologies are on the side of the future evaluator. As they are applied to the GRAS substances and other “environmental chemicals,” less will need to be left to judgment in deciding questions of safety. It is to be hoped in this regard that enthusiasm for demanding new tests simply because we are able to perform them, will be tempered with reason so that the greater possible threats to human safety will get priority attention in the competition for limited facilities and resources. SCOGS' reports provide such a priority list. Together they also constitute a base upon which to build a continuing fund of information on the GRAS substances as new data emerge. The availability of such a current data base should make it possible for FDA to reflect new knowledge more promptly in its regulatory actions.

Current Status of the Safety Evaluation of the GRAS Substances

By mid-1978, final evaluation reports on 262 GRAS substances had been submitted to FDA. In addition, tentative evaluation reports on 89 GRAS substances were awaiting completion of hearings or were in the hands of FDA awaiting announcement of invitations for hearings. Tentative reports on the remaining 48 GRAS...
substances, still undergoing evaluation, are expected to be submitted to FDA before year's end. All of these, and the tentative reports already submitted are expected to become final reports early in 1979 as hearings are completed.

Of the 351 GRAS substances covered in final or tentative evaluation reports:

Seventy-one percent were found to be without hazard when used in food at current levels or at levels that might reasonably be expected in the future (Conclusion 1).

Fifteen percent were found to be without hazard if use is limited to levels of addition now current (Conclusion 2).

Six percent were found to be without hazard when used in food at current levels, but due to uncertainties in the existing data, specific studies need to be conducted promptly (Conclusion 3).

Four percent were found to exhibit adverse effects when used in food at current levels requiring that safer usage conditions be established (Conclusion 4).

Four percent were found to be unevaluable due to the inadequacy of available data (Conclusion 5).

FDA has proposed regulatory action on 60 GRAS substances and has taken final regulatory action on 28 others, based in part on the Committee's reports. FDA actions have consistently reflected the conclusions reached in SCOGS reports.

Subsequent articles will present the results of the evaluation of several specific GRAS substances. □


2. Food Additives Amendment of 1958: An Act to Protect the Public Health by Amending the Federal Food, Drug and Cosmetic Act to Prohibit the Use in Food of Additives Which Have Not Been Tested to Establish Their Safety. 72 Stat. 1784


5. R.L. Hall and B.L. Oser: Recent Progress in the Consideration of Flavoring Ingredients Under the Food Additives Amendment. II. Food Technol. 15:20, 22-26, 1961


