Insights on Food Safety Evaluation: A Synopsis\textsuperscript{1,2}

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The Life Sciences Research Office's Select Committee on GRAS Substances has completed a report entitled, "Insights on Food Safety Evaluation." The report, in conjunction with an earlier report of the Select Committee, reflects the opinions and experiences garnered from a decade of evaluating the health aspects of generally recognized as safe (GRAS) substances. This second report identifies and discusses the principal components of the evaluation process and offers a perception of the issues that are critical for effectively evaluating the safety of foods and other ingested substances. Specific suggestions stemming directly from the Select Committee's experience in the GRAS review are made for improvements in the safety evaluation of food ingredients. Suggestions include phaseout of the GRAS list, modification of the Delaney Clause, utilization of appropriate human testing in protocols for evaluating candidate food additives, development of improved animal tests for behavioral effects of food ingredients, and improvement in procedures for detection of hypersensitivity to food ingredients. General priorities for study of the contribution of food and food ingredients to major causes of mortality and morbidity are also discussed.

In 1969, as a result of a recommendation of the White House Conference on Food, Nutrition and Health, President Nixon directed that the Food and Drug Administration (FDA) evaluate the safety of the generally recognized as safe (GRAS) food ingredients. As a part of this effort the Life Sciences Research Office (LSRO) of the Federation of American Societies for Experimental Biology (FASEB), in 1972, at the request of FDA, undertook the review and evaluation of all available information on the health aspects of using each of more than 450 of the GRAS or prior-sanctioned substances as food ingredients. Central to the evaluation process was the establishment of a Select Committee on GRAS Substances consisting of 11 research scientists organized by LSRO. During the period 1972–1982, the Select Committee held 75 meetings and provided FDA with 144 comprehensive reports covering the safety of 468 food ingredients.

\textsuperscript{1} Prepared for the Select Committee on GRAS Substances by Frederic R. Senti.
\textsuperscript{2} Copies of the full report are available from the National Technical Information Service, U. S. Department of Commerce, Springfield, Virginia 22161 (PB83-154146). In early 1983, the Federation will make this second report and the previous report of the Select Committee (Siu et al., 1977) available in a publication entitled A Decade of Experience in Evaluation of the Safety of Food Ingredients.
At the completion of the GRAS review the Select Committee on GRAS Substances prepared a final report entitled, "Insights on Food Safety Evaluation" (SCOGS, 1982). The report, in conjunction with an earlier report of the Select Committee (Siu et al., 1977), reflects the opinions and experience garnered from a decade of evaluating the health aspects of GRAS substances. An appendix to the report lists the conclusions reached on each GRAS substance and identifies those that may require particular attention in regard to regulatory action or research.

The following paragraphs provide a brief summary of the major points discussed in the Select Committee's report. The Committee has attempted to generalize from its experience with GRAS substances and offer suggestions that may be of interest to other scientists who are, or may become, involved in similar evaluations. The report deals with the nature of the physical, chemical, and biological data needed for substances to be evaluated, pointing out where problems need to be recognized or improvements sought. The elements of sound scientific judgment and recommendations for future evaluation efforts are discussed.

IDENTITY OF SUBSTANCES ADDED TO FOODS

Official specifications are needed to identify and characterize substances added to foods. Such specifications are provided for many food ingredients by the Food Chemicals Codex (NRC, 1981) and assure that the material actually added to food is the same as the product on which the supporting biological data have been obtained. However, specifications are frequently lacking for complex natural products such as vegetable gums, waxes, flavoring materials, and for products derived by fermentation, distillation, extraction, hydrolysis, fractionation, or a combination of these processes. Such deficiencies await correction.

Identity of the substances consumed may be a problem when the substance added reacts with food components. Evaluation must then be concerned not only with the health aspects of the substance added, but also with reaction products as well. For example, hydrogen peroxide, added as a bleaching agent, can in some instances destroy methionine, cystine, or ascorbic acid, or result in the formation of toxic peroxides or epoxides from oxidation of unsaturated fatty acids, prostaglandins, fat-soluble vitamins, or sterols. Such possibilities should be carefully explored in assessing the health aspects of the consumption of foods so treated.

CONSUMER EXPOSURE DATA

Evaluators of the safety of food ingredients need to know, with varying degrees of accuracy, depending on the nature of the substance in question, how much is, or will be, typically consumed and whether there are atypical subpopulations. If the estimated consumer exposure is considerably less than the highest no-adverse-effect level determined in appropriate toxicological studies, there need be relatively little concern about the precision of human exposure data. However, when toxicological data indicate possible adverse effects at consumption levels near those of members of a subpopulation of consumers, the accuracy of the estimate of consumer exposure becomes particularly important. In the case of nutrient fortification of foods, subgroups likely to benefit should be identified and their intake of the nutrient in question
determined to permit fortification at the lowest level compatible with meeting the goal of adequate intake. In general, much more work is necessary in identifying the upper percentile of intakes by subgroups of the population.

Surveys of the food processing industry such as conducted by Committees of the National Research Council (NRC, 1979) to identify the foods to which each GRAS substance was being added, the level of addition, and the poundage used have provided the most extensive data available on the quantitative use of the substances added to processed foods. However, the problems associated with collecting data of this kind and translating it into intakes of added substances by various subpopulation groups tend to result in substantial overestimates of consumption. Efforts to improve methodology for estimating food ingredient consumption by subpopulations are continuing and should be encouraged.

**Efficacy of Substances Added to Foods**

There were a number of GRAS substances evaluated for which efficacy had not been demonstrated and, in the view of the Select Committee, these deficiencies should be corrected. Occasionally, the very purpose for the addition of a particular food ingredient is inseparable from overall judgments of health hazards. Examples include fortification of foods with certain nutrients, e.g., iron, for which the level of fortification meeting nutritional requirements depends on the bioavailability of the iron in the particular iron compound added. In such cases, the efficacy (bioavailability) of the added ingredient cannot be ignored in the assessment of its health effects.

**Biological Information**

A sound assessment of safety must be based on adequate and reliable biological data. The search continues for rapid and inexpensive experimental approaches including tests with single-cell systems and submammalian models. However, serious questions about the relevance of results of such tests to human subjects must still be answered. At present, toxicity evaluations rely heavily on nonhuman mammalian models for obtaining physiological, biochemical, and pathological data. In theory, categories of required data can be developed before the safety evaluation is undertaken. In practice, it is inappropriate to specify a precise list for rigid application because a multiplicity of factors will affect the need for and adequacy of such data. Instead of requiring all of the more commonly used tests and models for obtaining biological data, some rational combination may be sufficient for a particular substance being evaluated. For example, sound judgments regarding the safety of a substance added to foods can be made in some instances with data from a relatively limited range of toxicological testing. The instances in which this is the case are largely confined to substances commonly considered as foods and those present in the body as normal metabolites.

**Observations on Human Subjects**

Any study of human subjects must be preceded by accumulation of evidence that the circumstance of testing is not unduly hazardous. Such evidence may be available
in some instances because the ingredient in question is already consumed as a naturally occurring component of certain foods. When the ingredient is a novel product, extensive animal testing will be necessary before human studies are undertaken. If the human feeding studies then demonstrate that physiological handling of the substance differs between human subjects and the animal model(s) initially chosen, it will be necessary to carry out animal testing with more appropriate animal models before undertaking further observations on human subjects. Exposure of the public to a new food ingredient under largely uncontrolled conditions should be preceded by observations made under carefully controlled circumstances. However, the place of human testing in protocols for candidate food additives should be thoroughly aired with open participation of all interested parties before any regulatory actions are taken.

BEHAVIORAL AND HYPERSENSITIVITY REACTIONS TO FOODS AND FOOD INGREDIENTS

Improved testing procedures are needed to detect possible behavioral and hypersensitivity reactions to foods and food ingredients. Behavioral pharmacology and toxicology are expanding in scope and importance and behavioral tests can no longer be ignored in stratagems for assessing food safety. At present, testing procedures for behavioral effects are less developed than is true of many other areas of toxicology. Much effort is needed in the development of animal tests of relative simplicity that may provide quantifiable and reproducible information on behavioral effects in animals at levels of intake relevant to human exposure.

Approximately 66 million adults in the United States believe they have experienced adverse reactions to foods (MRCA, 1977). No credible estimate is available on the number of individuals who actually exhibit such adverse reactions. Data on this point, particularly on immunologically mediated reactions, should be obtained and should become a consideration in evaluation of food ingredient safety. Classical anaphylaxis-induction tests on animals should be extended and various techniques for establishing the existence of hypersensitivity reactions to specific food ingredients should be explored.

JUDGMENT OF SAFETY

Judgment of safety of a food ingredient by a scientific panel entails an evaluation of all the data available from animal and other testing systems and consideration of its applicability to the human population under consideration. Several factors must be considered in making a reasoned judgment on the basis of the available data since they may bias the conclusions reached. Foremost are the credibility of the data and its relevance to humans. Second is the recognition that interpretation of data is influenced by a host of subjective and subconscious factors. It is necessary, therefore, for an evaluation panel to be aware of the nonscientific components of its deliberations and to take special pains to reduce the effects of emotional and idiosyncratic biases and fancies on sound collective judgments. Subjective factors include personal leanings concerning what constitutes “safety,” perception of what constitutes adequacy of data by the same individual for different situations, scientific popularity (the “conventional wisdom”), and personal weighing of the significance of adverse findings based on unconfirmed studies and/or less than rigorous experimentation.
MODIFICATION OF THE DELANEY CLAUSE

The Delaney Clause of the 1958 Amendment of the Federal Food, Drug, and Cosmetic Act does not apply to GRAS substances and the Select Committee’s assessments were not constrained by it. Nevertheless, the existence of the Clause in the law resulted in discussions of its perceived importance in overall food safety during the Select Committee’s consideration of evidence related to possible carcinogenicity of GRAS substances. The Clause makes no distinctions among the types of chemicals or physical agents involved in cancer induction or promotion. Similarly, the law has no provisions for consideration of evolving knowledge of carcinogenic processes. As written, the Delaney Clause does not permit investigators to apply reasoned judgment in the interpretation of long-term animal studies which may employ high dosages to reveal toxic potential, if any. Another incongruity of the Clause is that it applies only to direct and indirect food additives and not to GRAS or prior-sanctioned food ingredients, or to naturally occurring food contaminants. The Select Committee joins others in recommending modification of the Delaney Clause to allow for the necessary flexibility in the interpretation of scientific and medical data by knowledgeable experts and responsible health authorities.

PHASEOUT OF GRAS LIST

GRAS substances should be merged with other food ingredients into a single system for evaluation of potential hazards that may be associated with them. Exemptions from contemporary criteria of safety were probably necessary for some food ingredients as a pragmatic administrative matter during the evolution of regulatory mechanisms, but there now appears to be little scientific basis for perpetuating these exemptions. Many of the current GRAS substances might well be judged as having fulfilled the minimal requirements for clearance as food additives, or could be considered as food per se.

RISK/BENEFIT

Relating benefits to risks in considering matters of safety has become prevalent in recent years. While a risk/benefit assessment is not feasible as a mathematical relationship and its application in specific cases may be difficult, the concept has value with respect to food and drug safety in cases where health benefits can be compared with health risks. Vitamins and other essential dietary ingredients fall into this category. A scientific evaluation panel can assess their benefit to the health of the consumer at a given exposure level and weigh the benefit against the risk of harm to the same individual. Although there are potential risks from food fortification with iron, vitamin D, and vitamin A, the Select Committee believed such risks to be outweighed by the widespread public health benefit and, in the case of vitamins A and D, the risk is actually small.

FUTURE PRIORITIES

In addition to the foregoing specific recommendations, the Select Committee identified several general priorities for emphasis in the decade of the eighties.
The relationships between food constituents and the leading causes of illness and death are ill-defined and need to be explored with intensity and imagination. There are many claims, suggestions, coincidences, and apparent links between diet or dietary habits and cardiovascular disease and cancer, but limited scientific data. Much research is needed in these areas, as well as on the effects of food and food constituents on the behavioral and psychological status of normal and disturbed people. There is a paucity of scientific evidence that food ingredients constitute a major contribution to psychiatric and behavioral problems. Nevertheless, food and food ingredients have been suggested as causative or aggravating factors in some disorders. The way in which food and food constituents may modify defense against infective agents, is recognized as an important, emerging field of study.

Another criterion for the determination of priorities is the degree of reversibility of the potential hazard, coupled with the proportion of the population to which the episode in question may apply. According to this rationale, the development of predictive model test methods for teratogenicity, for example, should receive much greater attention. Teratogenic malformations are often noncorrectable and teratogenic tests should be a component of safety evaluation tests.

An issue that calls for continuing attention concerns the perennial conflicting tendencies toward progressively simpler, less time-consuming, and inexpensive model systems for testing the toxicity of a substance on the one hand and progressively more complex and comprehensive batteries, including human studies, on the other. The systematic sorting-out of relevancy needs more deliberation, and explicit recognition in the regulatory process of weighing evidence than it has in the past. Otherwise, the development and adoption of particular test methods run the risk of being unduly influenced by the happenstance availability of a method, by economy, and by expedience.

The Select Committee has advocated consistency in rationale, though not uniformity in specific test methodologies, for all food ingredients. Consistency in rationale also suggests a comparability in approach across agencies in safety evaluation of all substances ingested by human beings, including drugs and environmental pollutants.

REFERENCES


