PROGRESS IN RESOLVING FOOD SAFETY PROBLEMS: SYSTEMATIC EVALUATION OF GRAS FOOD INGREDIENTS

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A purpose of this discussion is to give some illumination to the status of food ingredients known as GRAS. The word is an acronym for the term *Generally Recognized as Safe.* Of necessity the discussion will include my own participation, with others, in a comprehensive and systematic evaluation of the safety of the several hundred GRAS food ingredients that may be used in food such as the many listed on cereal boxes, bread wrappers, cans of soup, and other food containers.

In connection with this large scale and timely process there is reason to make reference to the problems created by the prevalence of pseudoscience and zealotry in matters of food processing, food additives, and concepts of nutrition. That false concepts and confusion abound, and affect the resolution of problems concerning food processing and food additives, should be understandable because a disturbing proportion of the public is misinformed and lacks basic knowledge concerning science and nutrition (1). Thus there is wisdom in the saying of the once-noted humorous Josh Billings that "It's better to know nothing than to know what ain't so."

Some of the current problems are not new. Long ago there was misinformation and flagrant and extensive practices of food adulteration, misbranding, and use of certain food additives scarcely without regard for their effects on health. Apparently the first protective law of note on food was by King John (of Magna Carta fame) in 1202. This was the Assize (ordinance) of Bread (2).

With the development of analytical chemistry in the last century it became possible to greatly enhance the detection of fraud in food processing. In the first quarter of that century the most noted consulting chemist and writer on food processing and adulteration was Fredrick Accum (1769-1838).

The best known of Accum's books was the work on adulteration of food in 1820 which became known as "Death in the Pot." The full title was "Treatise on the Adulterations of Food and Culinary Poisons, Exhibiting the Fraudulent Sophistications of Bread, Wine, Spirituous Liquors, Tea, Coffee, Cream, Pickles, and Other Articles Employed in Domestic Economy, and Methods of Detecting Them." As pointed out by the biographer of Accum, C. A. Brown (3), "This book is also a classic as it represents the first serious effort to cope with the difficult problem of food adulteration." It was a landmark in the beginning of the pure food movement. The action reached critical mass in this country in 1906 with the passage of the original Food and Drug Act.

The general commitment to food safety in the government was headed for more than 25 years by Harvey W. Wiley (1844-1930), a native Hoosier who was the first professor of chemistry at Purdue.

In 1902 Dr. Wiley inaugurated the first federal program "to investigate the

*Indiana Academy of Science 1980-81 "Speaker of the Year"

character of food preservatives, coloring matters and other substances added to foods." By current standards his organization and program for inquiry, as a scientific undertaking, would not gain the approval of the most lenient of any granting agency for research. For example, Dr. Wiley employed 12 men who served as his "poison squad." His general procedure in testing the safety of certain food additives was to restrict all 12 to the same diet for a short time, with half receiving one compound and the others being given the same substance in a different form—or an entirely different compound. The appearance and feeling of the men were observed, and some limited metabolic studies were made. Notably, experimental animals were not used. The testing program was largely employed for its publicity value. On that basis it had great effect. It focused attention on the need for actions to promote safety in food processing (4).

Of course some chemicals used as preservatives or for other reasons were clearly harmful and measures to prohibit or properly control their use gradually became effective. But it was not until the middle of this century that explosive changes occurred which enormously expanded the application of myriad chemicals in the food industry. With the advent of new pesticides and other chemicals that could get into the food chain, and the elevation of environmental concerns such as were expressed by Rachel Carson in *Silent Spring* in 1962, significant numbers of aroused people vigorously sought ways to avoid food that contained residual or added chemicals.

Although there was a basis for concern, pseudoscience and zealotry, as well as outright deception, soon mounted and there was a pyramiding of interest, much of it misguided, in the avoidance of chemicals in food. Many individuals and groups became fascinated by the idea of using so-called natural foods and organically grown foods.

So-called health food stores became economically successful enterprises and the demand for "chemical-free" foods became felt in various segments of the economy. Since 1970 the growth of health food sales has risen an average of 30 percent a year. It has caused major food manufacturers to consider acquiring health food businesses. Various large and well known food companies find it financially advantageous to emphasize the naturalness of their products.

The misdirected enthusiasm for so-called natural foods could be corrected through much better understanding of simple chemical facts about foods and the principles of nutrition. Commonplace foods such as oranges, beans, and potatoes contain naturally scores of identifiable chemicals some of which are the very ones that some natural food proponents abhor. Through advertising and in other ways some of the chemical manufacturers and food processors are giving some effort to the correction of public misconceptions.

There is great justification for the widespread use of many food additives, including many classified as GRAS. Some reasons for their use are the following:

1. To *enhance and maintain desired consistency.* Examples include lecithin, methyl cellulose, and mono- and diglycerides.
2. To *enhance nutritive value.* Examples include various vitamins and inorganic salts.
3. To *enhance flavor.* Examples include amyl acetate, benzaldehyde, ginger, sodium chloride, and monosodium glutamate.
4. To *control acidity or alkalinity.* Examples are sodium bicarbonate, vinegar, citric acid, and lactic acid.
5. To *maintain appearance, palatability, and wholesomeness.* Examples in-

clude calcium propionate, ascorbic acid, and sodium benzoate.

6. To *give desired and characteristic color.* Examples include carotene, chlorophyll, and many other natural and unnatural dyes.
7. To *mature and bleach.* Examples include potassium bromate and iodate, hydrogen peroxide, and chlorine dioxide.
8. *Other functions.* These include moisturizing in some foods and to promote free-flowing in others. Examples respectively are glycerol and magnesium carbonate.

In this setting it is timely to consider the large current program on the evaluation of food ingredients identified as GRAS. The listing of such substances began in 1958 in response to major amendments that year in the Food, Drug, and Cosmetic Act. The amendments constituted evolutionary changes in a process that started with the passage of the original Food and Drug Act in 1906 (5).

Administration of the original Act was the responsibility of the Bureau of Chemistry of the Department of Agriculture. By 1958 the Food and Drug Administration (FDA) had been evolved from the Bureau and it was a part of the Department of Health, Education and Welfare, now Department of Health and Human Services. The GRAS ingredients are under the surveillance of the FDA. However, some jurisdictional complications exist in food additivies. The Department of Agriculture has a regulatory role concerning substances added to meat and other products of animal origin, and the Department of Interior has such responsibility concerning marine food products. There are even other federal regulatory agencies concerning the safety of food ingredients.

Until 1958 the food safety laws were rather simplistic. If a substance was apparently safe and nondeceptive in its use it was permitted, but if it was regarded to be "poisonous and deleterious" it was prohibited. The important differences made by the quantity ingested were not given sufficient consideration in the law. By 1958 the young science of toxicology and the status of analytical chemistry had advanced far enough to make rational and appropriate administration of the law impossible. It was necessary to understand that the possible beneficial effects or harmful effects had to be a function of the amount of a substance ingested. Even Paracelsus had recognized this in the 16th century, when he wrote, "it is only the dose which makes a thing a poison." That principle had to be recognized in establishing and implementing the new food safety laws.

The Food Additives Amendment required the fixing of the responsibility for demonstrating safety of the food ingredient on the industrial firm proposing its use in interstate commerce. However, for practical reasons the Act specifically exempted food additives in common use at that time which were generally recognized as safe as determined by "experts qualified by scientific training and experience," or "experience based on common use in food."

The first listing of generally recognized as safe additives was prepared by FDA scientists and without benefit of substantial input from other scientists. Shortly thereafter approximately 900 scientists in the academic world, industry, and government were requested by direct mailing to evaluate the list and suggest additions and deletions. The mailing list was prepared by reference to *American Men of Science* (at the time women were not recognized in the title) and several professional societies. I recall that I was invited to participate.

During the 1960s there were several changes in the GRAS list including those resulting from direct authorizations by letter from the FDA to food manufacturers or processors. Such statements of opinion or authorization became

known as "GRAS letters." I am not aware of any inappropriate decisions through this process of dealing with the Food Additives Amendment of 1958.

Action leading to a thorough evaluation of GRAS substances was called for by President Nixon in 1969. Almost concurrently the White House Conference on Food, Nutrition, and Health was convened (6). The Conference concluded that

> "Traditional or long-continued use of any additive can no longer be considered to be sufficient evidence of safety. Thus it is necessary that a continuing re-evaluation be maintained of all compounds whose use in foods is relatively freely allowed."

The Conference "Recommended that the list of substances known as GRAS be systematically reviewed for safety in the light of new knowledge, experience, new levels, and new categories of food use."

Within the same general time period the need for changes in GRAS was manifested through mounting consumer activism, the media-stimulated fright over the use of cyclamates as sugar substitutes, and other media-produced alarms on the status of several GRAS substances.

The eventual action of consequence by the FDA was the establishment of a contractual arrangement with the prestigious and long established *Federation of American Societies for Experimental Biology* (FASEB) through which a comprehensive assessment of a large proportion of GRAS food ingredients would be conducted (7). The Federation, through its *Life Sciences Research Office*, established a committee and staff to carry out the large project. I became a member of the committee, the *Select Committee on GRAS Substances* (SCOGS), in 1973. The Committee was assisted through other contracts made by the FDA to provide extensive searching and compilation of the world's literature on each of several hundred GRAS food ingredients. Other assistance came from: (a) a contract with the National Academy of Sciences-National Research Council for surveys to estimate the human consumption of GRAS food ingredients, and (b) from other organizations to provide special information including mutagenic and teratogenic testing of relevance to the Select Committee.

The original Select Committee was composed of nine research scientists representing diverse backgrounds of importance. From 1972 through 1980 there were two resignations and four additions to the Committee. The expertise during most of the time included recognized persons in foods and nutrition, biochemistry, pharmacology and toxicology, pathology, and medicine including pediatrics and oncology.

An important consideration in the selection and functioning of the Committee was to assure professional competence and objectivity. To avoid even the appearance of any conflict of interest it was necessary for Committee members to be free from significant affiliation with industrial firms involved with food, governmental agencies, or "consumer-oriented" organizations with probable bias concerning GRAS food ingredients and the enforcement of food safety regulations. Initially there was considerable agitation from a limited sector of the public for the inclusion of consumer-oriented representation on the Committee. Capitulation to the effort obviously would have compromised the principle of high objectivity and limitation of activity to scientific evaluation of GRAS substances. The agitation subsided after two or three years.

A vital component of the system for evaluation was the supporting staff. During most of the program approximately six full time professional staff scien-

tists gave a substantial proportion of their time to the work of the Select Committee and they were assisted by several competent and responsible secretarial workers. Even though the staff personnel were not responsible in the formulation of Committee opinions and conclusions, all were required to be without conflict of interest. Even persons who conducted the extensive literature surveys were prohibited from expressing opinions on GRAS ingredients in the compilations of the findings.

To maximize independent and searching evaluation of basic information each initial draft report was written by Committee members assigned so as to match subject matter with the professional backgrounds of the individuals. Such drafts were individually reviewed by all members and then discussed in full committee meetings attended by the professional staff members. A serious attempt was made to gain input from all areas where searching inquiry and evaluation might be useful. In dealing with several substances scientists with special knowledge and background were consulted. Committee discussion and inquiry on a topic was continued at the initial meeting, or at subsequent meetings, until there was agreement that the draft content, opinion, conclusions, and available supporting data reflected adequately the views of each member.

At this point a new draft report was prepared by the professional staff and after thorough processes of individual review and criticism in the Committee a final draft report was written in which all statements and data were verified against the original articles and other sources. Such drafts upon signed approval by the Committee members became the tentative report of the Select Committee.

The tentative reports, after approval by an advisory committee of the Federation, were transmitted to the FDA. Announcements of the availability of the reports to the public were always made in the Federal Register along with invitations to request a public hearing or furnish the Committee with data, information or views (8). When requested, public hearings were held and submitted written data, information, or views were accepted and considered. The Select Committee submitted 143 final reports to the FDA. Table 1 lists representative GRAS food ingredients evaluated by the Committee.

TABLE 1. *Representative GRAS Food Ingredients Evaluated by the Select Committee on GRAS Substances**

Gum arabic	Ascorbic acid and various ascorbates
Butylated hydroxytoluene (BHT)	Magnesium salts
Benzoic acid and sodium benzoate	Silicates
Sorbitol	Sucrose
Sulfiting agents	Bioflavonoids
Nutmeg, mace, and their essential oils	Propionates
Certain zinc salts	Pectin and pectinates
Alginates	Caffeine
Phosphates	Vitamin D, vitamin D_2, and vitamin D_3
Iron and iron salts	Pyridoxine and pyridoxine hydrochloride
Certain glutamates	Potassium chloride and sodium chloride
Protein hydrolyzates	Lecithins
Choline chloride and choline bitartrate	Niacin and niacinamide
Aluminum compounds	Thiamin, thiamin hydrochloride, and thiamin mononitrate
Certain calcium salts	Carotenes
Dextrose, corn syrup, and invert sugar	Riboflavins
Butylated hydroxyanisole (BHA)	Activated carbon (charcoal)
Gelatin	Vitamin A, vitamin A acetate, and vitamin A palmitate

*Copies of all the final reports may be purchased from the National Technical Information Service, Springfield, VA 22161. Order number, PB 80203789

The heart of the reports were the opinions and the conclusions. These were derived from the comprehensive analysis of the literature made by the Committee and reviewed in the body of the reports.

It was possible to reduce the basic conclusions to five categories as follows:

1. The food ingredient should continue in GRAS status with no limitations other than good manufacturing and handling practices and levels of use that might reasonably be expected in the future.
2. Same as No. 1 except that without additional supporting data the level of use should not be increased.
3. Same as No. 1 except that uncertainties exist requiring that additional studies be promptly conducted, and evaluated.
4. There is evidence of adverse effects and safe usage conditions should be established or the GRAS status should be rescinded.
5. There is insufficient information upon which to base an evaluation.

A large majority of the GRAS substances were found to present no hazard to health when used at levels that are now current and in the manner practiced. Substances in this category include sodium benzoate, calcium salts and certain other inorganic salts, and all the vitamins except A and D.

Substances recommended to be restricted to the current level of use include vitamins A and D, glutamates, zinc salts, propionates, hydrogen peroxide, and many gums such as gum arabic, and gum ghatti.

Several GRAS substances were found to be questionable when used at levels that are now current and in the manner practiced. These include oil of nutmeg, BHA (butylated hydroxyanisole), BHT (butylated hydroxytoluene), and caffeine.

Sodium chloride is the only GRAS ingredient of widespread interest which the Committee concluded is being used at such high levels, both discretionally and in processed foods, that the health of a significant proportion of the people is being jeopardized.

Several food ingredients were considered concerning which there is insufficient information upon which an evaluation can be made. In general there is little if any commercial interest in using any of these substances in food.

Benzoic acid and sodium benzoate were among the earliest GRAS ingredients reviewed by the Select Committee. These long-used food preservatives were found to be without evidence of being harmful when used at current levels or that might reasonably be expected in the future. It is of interest that Harvey Wiley had fed these compounds to his "poison squad" at the turn of this century. Although his testing gave no evidence of harmfulness, he persisted in his belief that they should not be used in food.

The evaluation of 415 GRAS ingredients was time-consuming and difficult for the Select Committee. Some that required the greatest amounts of time included caffeine, sucrose, glutamates, sodium chloride, and iron and iron salts. What were some of the considerations and actions? This may be illustrated by a discussion of caffeine (9).

It is common knowledge that caffeine is a prominent constituent of coffee and tea. Also, it is present, as *required* by the Code of Federal Regulations, in all cola-type beverages. However, the caffeine concentration in such beverages must not exeed 0.02 percent by weight. Less than 10 percent of the caffeine present in these beverages is from extracts of kola nut; all the remainder is added caffeine.

It is not clear whether caffeine is added to cola-type beverages for its stimulatory effects or for the enhancement of flavor. The substance is without nutritive value.

In its evaluation of caffeine the Select Committee focused attention on its use as commercially added to food and beverages. Coffee, tea, and cocoa are not in the GRAS category, but their contribution to the total consumption of caffeine was considered.

It is established that the dose of caffeine required to stimulate central nervous system activity in humans is approximately 3 mg per kg of body weight and the effect is observable at about 2 mg per kg. A substantial proportion of cola drinkers consume about 0.3 mg of caffeine per kg per day from this source with a few in the less than 5 year age range consuming as much as 1.8 mg per kg per day. As stated in the Select Committee's report on caffeine, "the consumption of a 12-ounce container of cola beverage containing 0.01 percent caffeine represents a dose of about 0.9 mg per kg for a 40 kg child, for example, or about 0.6 mg per kg for an adult. It is to be noted that these figures represent the amount of caffeine solely from cola drinks."

Another consideration is the possible adverse effect of frequent selection of cola drinks and other soft drinks in preference to milk, particularly when the diet is marginal in the nutrients which milk abundantly supplies.

The Select Committee concluded that "it is not appropriate to continue to consider caffeine as a generally recognized as safe substance for addition to cola-type beverages." It pointed out that in support of this conclusion "The amount of caffeine consumed as cola-type beverages borders on the dose known to produce central nervous system stimulation in animals and man. Whether such stimulation constitutes an adverse effect or whether a potential hazard may exist for the segment of the population, particularly children, that is exposed to stimulating doses of caffeine, cannot be answered on the basis of the evidence available."

In response the FDA proposed regulations that would encourage the production of caffeine-free cola beverages and require the industry to conduct new caffeine studies.

Prior to the response the Bureau of Foods of the FDA conducted a study which indicates a significant proportion of birth defect in the offspring of female rats that had ingested relatively large quantities of caffeine.

A representative press release, by the Associated Press, in October 1980 stated the following (10):

> "One of the regulations put forward by the Food and Drug Administration would make the continued use of caffeine as a food additive contingent upon the industry's funding of studies showing how caffeine affects children and human fetuses.
>
> "Both the National Coffee Association and the soft drink industry already have indicated willingness to pay for additional research. Among the studies they propose is one comparing rates of birth defects with caffeine consumption by pregnant women.
>
> "The other proposal would remove caffeine from the agency's list of substances generally recognized as safe, a step that ordinarily would lead to prohibition of its use (as an additive). The agency would allow an exemption permitting the current uses of caffeine to continue while the studies are conducted."

Throughout the long period of evaluation by the Select Committee and the subsequent deliberations and limited research by the FDA, the Center for Science in the Public Interest acted vigorously to promote the limitation of caffeine consumption among children and pregnant women. This consumer-oriented action group has strongly criticized the FDA for not going further in withdrawing caffeine from the GRAS list. The Center wanted the limitation to start at once, on the basis of the present evidence, and it wanted the labeling of coffee to be initiated with a warning that would advise pregnant women to avoid it during pregnancy. I believe the FDA's response to the Select Committee's report was correct.

Moderate use of coffee, tea, and cola drinks by adults not under stress presents no cause for concern, if such use does not result in the exclusion of milk or other food that may be needed. Granted that caffeine has a clearly stimulating effect on the central nervous system at about 3 mg per kg of body weight, an adult weighing 70 kg, or about 150 pounds, should be cautious about ingesting more than approximately 200 mg per day. At 85 mg of caffeine per cup of coffee the consumption of more than about 2 cups of coffee, a cup of tea, and a cola drink or two per day can be assumed to be disadvantageous.

In retrospect, over the years that the Select Committee reviewed, evaluated, discussed, and worked toward the completion of the reports on caffeine and many other GRAS food ingredients, I believe there was no improper action or interference of any kind by the advocates of change and the advocates of the status quo.

From the perspective of 1980-81 the methodology and guidelines used to evaluate the GRAS ingredients have stimulated new concepts and actions in the assessment of food safety (7).

It is hoped that this will be followed in other problem areas where the objectivity and methodology of science can be used in providing information and judgment through which public decisions can be made. This could be applicable at the state level as well as the national level. I believe the talent in the Indiana Academy of Science should be utilized in studying and reporting on some of the problems important in this State.

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