On September 6, 1958, President Eisenhower signed the Food Additives Amendment into law and thus extended the concept of premarking clearance for drugs and pesticides to food and food additives. Congress was promulgating this legislation, defined any substance added to food as a food additive, except for two classes of food ingredients: substances that are generally recognized as safe (GRAS) among those scientifically qualified to judge safety and substances whose use(s) in food were sanctioned by the Food and Drug Administration or the U.S. Department of Agriculture prior to September 6, 1958.

No definition of GRAS was included in the legislation, so we have to try to determine what Congress had in mind by reviewing the legislative record. One can conclude that Congress considered that any new food ingredient thereafter developed would need a formal premarking clearance. Nevertheless, since Congress did not specifically say that an ingredient could not be GRAS after 1958, we must assume that such a thing could happen and make allowance for it. Predictably, the GRAS concept provided for continued use of most ingredients then in use. Our knowledge and understanding of toxicology at that time permitted the conclusion that a long and uneventful history of use in food established the continued safety of that ingredient.

To provide guidance for the affected industry, FDA published a series of documents in the Federal Register during 1958 and 1960, listing substances that were considered eligible for GRAS status. Ultimately these were consolidated into a single section of the food additive regulations as the “GRAS List.” This list was not intended to be all inclusive. It was clear that Congress recognized that anyone could introduce an ingredient into the food supply based upon his own judgement that the ingredient was GRAS. FDA did not have to be queried before the ingredient was introduced, and it was left to the agency to discover such use and challenge it if the Commissioner did not agree that the ingredient was GRAS.

**Original GRAS List**

The original GRAS list served FDA, the consumer, and the industry quite well until 1969, when the cyclamates were removed from the list because new studies found evidence that they were carcinogenic. Recognizing that there was little modern toxicological work available on many GRAS substances, President Nixon called for a review of the safety of all GRAS substances in his Consumer Message of October 1969.

Almost anyone who has had extensive dealings with food additive activities in the United States readily recognizes the need for guidance in deciding what is GRAS and what is a food additive under the law. Accordingly one of our first major acts in the GRAS review was to issue the criteria by which we would consider a substance as eligible for GRAS status. These were codified in our Code of Federal Regulations, Title 21, Section 121.3. We now think they may need some modifications in the interest of clarity.

Use of food ingredients as GRAS without the review and approval of the FDA often does not afford the opportunity for participation of qualified scientists and other interested members of the public. In addition, the law requires the FDA to monitor the use of all food ingredients, and to make certain that no ingredients are used which are not in fact GRAS, unless a food additive regulation is promulgated. Accordingly, the Commissioner has determined that it is in the public interest that the safety of ingredients used in food on the basis of GRAS status be reviewed through public procedures. In addition to the criteria by which a substance may be eligible for GRAS status, the Commissioner has promulgated procedures for submitting petitions requesting FDA affirmation of GRAS status or determination of food additive status.

The “affirmed GRAS lists” established in section 121.104 and 121.105 imply a complete list of substances, except traditional food items which do not need listing. Because of the wide scope of sections 201(s) and 409 of the Act, which encompasses all ingredients in any processed or fabricated foods, including raw agricultural commodities and substances migrating from food contact articles, an all-inclusive list of affirmed GRAS food ingredients will not be attained for some time.

Now let us briefly consider the GRAS criteria, to see how varietal developments have been encompassed. Our regulation divides all food ingredients into three categories, those that we can conclude are GRAS without listing, those that will be listed on an affirmed GRAS list after examination of available data as GRAS under good manufacturing practices, and those that are food additives, ineligible for GRAS listing.

**Safety based on published literature**

We are considering whether or not to indicate that general recognition of safety must ordinarily be based upon published literature. This would be consistent with the Supreme Court’s statement in the Bentex decision that whether a particular drug is a “new drug” depends in part on the expert knowledge and experience of scientists based on controlled clinical experimentation and backed by “substantial support in scientific literature”. Although the Supreme Court was there referring to new drugs rather than to food additives, and to effectiveness rather than to safety, the underlying legal issues are indistinguishable.

Unlike the definition of a “new drug” in section 201(p), however, under section 201(s) a food ingredient may become generally recognized as safe solely through common use in food if it was marketed prior to January 1, 1958. For such ingredients, scientific procedures are not required either to establish GRAS status or to obtain a food additive regulation to permit continued marketing. Accordingly, we are considering defining “common use in food” to mean a substantial history of consumption of a substance by a significant number of consumers in the United States, and explicitly to recognize that, under the law, GRAS status based upon such a determination does not require or involve the same quantity or quality of scientific evidence that would be required for approval of a food additive regulation.

This is a particularly important concept under the law. The current review of GRAS and prior-sanctioned ingredients used in food has made it clear that, for a large number of food ingredients marketed prior to 1958, scientific studies of the types now required for approval of food additives have never been undertaken. This includes virtually all raw agricultural commodities and other substances of natural biological origin. A requirement that all of these foods be tested according to modern standards for new food additives would be a substantial misallocation of the country’s testing resources and would represent a serious misordering of priorities. Where significant safety questions arise, immediate new testing can and will be required. Where no known hazard exists for pre-1958 ingredients, however, the full battery of tests for a new food additive is not to be required.

For substances introduced into food after 1958, GRAS status may not be achieved through experience based on common use in food. For such substances, GRAS status may be determined, if at all, solely on the basis of scientific procedures, i.e., the same quantity and quality of scientific evidence as is necessary to obtain approval of a food additive at this time.

Section 201(s) of the act does provide, however, that such GRAS status may be achieved for post-1958 food ingredients on the basis of scientific procedures even prior to any significant history of marketing and use. Unlike the definition of “new drug” in section 201(p) of the Act, section 201(s) does not require that a food ingredient be used “to a material extent or for a material time” before it may become GRAS.

**Scientific evidence necessary**

On the other hand, general recognition of safety through scientific procedures does require that the scientific evidence on the basis of which this status is achieved has been published in the literature or otherwise widely disseminated throughout the scientific community knowledgeable about the safety of food ingredients. This evidence must become common knowledge among such scientists. Accordingly, there will be at least some gap between the gathering of the scientific evidence necessary and the time when the ingredient may be considered GRAS.
knowledge its dissemination to and assimilation by the scientific community.

Some have raised the claim that a raw agricultural commodity is "food" and not a "food ingredient." We addressed this point, not in the original regulation, but in its preamble:

"6. The contention that the terms "food" and "food additive" are mutually exclusive is without basis. Sections 201(f) and (s) of the Federal Food, Drug, and Cosmetic Act, as well as section 402 (a)(2)(c) which provides that a food additive for which no regulation or exemption is in effect is an adulterated food, establish their equivalency."

As an illustration, meat and potatoes are frequently used as ingredients in a stew. We also have to recognize that the mission of the Food and Drug Administration is to monitor the use of all food ingredients, and the introduction of deleterious levels of alkaloids or other chemicals into a raw agricultural commodity through breeding or selection is just as significant as adding the alkaloid as a chemical entity to the cooking pot.

We think it is prudent to consider some of the changes that are taking place in our fresh fruits and vegetables as the breeding stocks are manipulated in order to develop a redder tomato, a shorter maturation time, or a variety more resistant to blight, mold, rust, or insects. In breeding to attain these desirable features, we need to monitor to assure ourselves that other, less desirable changes have not taken place.

The hazard of natural toxins is one that has received relatively little attention at the FDA through the years, but this situation is changing. Many have indicated that the policy of reviewing the safety of traditional foods is burdensome and perhaps ridiculous, even though their composition may have been significantly altered through breeding or selection. A very different impression is received by reviewing the literature on ipomeamarone, the toxin of sweet potatoes, which is produced when the plant is subjected to various kinds of insult. We are studying this problem but it is too early to tell where it will lead. Everyone recognizes the pressure that is being exerted to foster the breeding of plants resistant to pest attack in order to minimize the use of chemical pesticides. We should also speculate why a plant becomes resistant. Of course this may be due to the elaboration of some chemical agent repellant to the insect because of bad taste or smell, but it is equally possible that the chemical developed is toxic to the insect. And in either case, what about the toxicity to man? Likewise, we have been busy developing varieties resistant to plant diseases. We need to know whether this entails an increased risk to the consumer.

We cannot afford to make too many assumptions unsupported by scientific evidence either that there is no problem or that we have an insurmountable problem. A single example will suffice. Several years ago FDA was approached with data establishing that gamma radiation in doses about one tenth those approved for inhibiting sprouting would break the dormancy of seed potatoes and thus more or less double the yield from a given field by delivering two crops. We were asked to agree that there was no food additive problem. We inquired what would happen to the crop grown from the irradiated tubers: would the solanine increase? The proposal was abandoned when the laboratory results on a controlled experiment showed a 60% increase in solanine in the crop grown from the irradiated tubers compared to the crop grown from unirradiated stock.

Production of undesirable changes

We should not overlook the possibility that certain desirable modifications may produce undesirable changes in the nutrient composition of widely consumed foods. Our general dietary regime is predicted on the basis that certain foods produce, on the average, a given amount of vitamins, minerals, and other nutrients that contribute significantly to the recommended dietary allowances. A particular food widely consumed as a good source of Vitamin C, for example, might become less than a good source if replaced by a new variety containing much less of the vitamin. Tomatoes are considered a nutritionally significant source of Vitamin C. Data show that a recently developed new variety intended for mechanical harvesting, and the concomitant marketing technique developed for this variety, delivers to the consumer a tomato having about 15% less Vitamin C content.

The need to keep a close watch on this kind of development is evident. It is not beyond the realm of possibility that a borderline deficiency could develop unless these changes are closely monitored. By requiring the submission of data where decreased nutrients have occurred, corrective measures can be applied if a significant trend seems to be developing.

FDA created a great deal of concern by the wording of the original regulation, which called for data on significant increases in toxicant levels and significant decreases in nutrients. Subsequently "significant" was defined as an increase of 10% or more in toxicant and a decrease of 20% or more in nutrients. As a result of this initial action, the U.S. Department of Agriculture, FDA, and interested members of the affected industries formed a task force to further define what nutrients should be monitored and what toxicants measured. The results of the study to date have been discussed elsewhere. However, FDA expects to amend this regulation in the near future to call for monitoring of only 9 food crops for 7 nutrients.

Progress on toxicants is not as far advanced as that on nutrients. We will consider the concentrations of toxicants either in the whole variety or fractions thereof, provided the basis for choice is reasonable. If the processing concentrates the toxicant into a certain fraction, and that fraction is consumed, then this might dictate the choice. Similar possible concentrations of nutrients in a particular fraction should also be considered in choosing what should be compared.

Costs

Obviously, one of the major concerns of the industry is how this will affect costs of doing business. We hope that the requirement that the GRAS criteria imposes will not affect horticulture significantly. It should require that any new variety be analytically compared with any commercially used "parent." If no "parents" were in commercial production, a commercial variety in significant production would provide a suitable baseline.

In order to do this adequately, the developer will have to arrange for toxicant analyses and nutrient analyses. This, of course, can be done by laboratories of the developer or by consulting laboratories. An increase in toxicant(s) of 10% or more compared to the parent containing the least toxicant (if both are commercially used) or a decrease in principal nutrient(s) of 20% or more will require that the analyses be supplied to FDA in a GRAS affirmation petition in accordance with §§121.40 and 121.41 of the Food Additive Regulations. If we agree that the new variety can be considered GRAS with or without enrichment or labeling requirements, we will list the new variety with appropriate qualifications. If we cannot conclude that it is eligible for GRAS affirmation -- a seemingly unlikely possibility -- it might be eligible for a food additive regulation.

With proper scheduling on the part of the developer, this requirement should not significantly delay the introduction of the new variety. This is true because the affirmation of GRAS procedure does not prevent the proponent from introducing his new variety while FDA is considering the affirmation petition and because the analyses of the new varieties will be conducted by or for the developer.

As far as costs are concerned, some preliminary estimates have been made on the basis of FDA's experience in performing the analysis required. We estimated that if a laboratory were to be set up and equipped to analyze 300 samples of wheat annually for protein, B6 thiamine, niacin, and magnesium the cost would approach $60,000. On the other hand, the number of samples that might need to be run could be less than one third of the amount used in our calculations. Other estimates have been obtained that the costs for screening of tomatoes would cost only between $1,000 and $7,000 annually, depending upon how comprehensive the screening might be. Indications are that at least one U.S. firm has been running almost all of the nutrients for some years as a matter of quality control.

We in FDA are very pleased that we have had the cooperation of the industry and USDA in developing the information needed to perform a better service to all consumers. Truly this is the way to make the GRAS list grow in the interest of the consumer.