REGULATORY STATUS OF MAILLARD REACTION FLAVORS

Lawrence J. Lin

Division of Food and Color Additives,
Center for Food Safety and Applied Nutrition,
Food and Drug Administration, 200 C Street, S.W.,
Washington, DC 20204

August 24, 1992

NOTE: Pending publication by the American Chemical Society.

When a food ingredient (new or old) is used as a component of food, a regulatory burden is associated with its use. The first question is whether the ingredient is a food additive under the definition provided in the Federal Food, Drug, and Cosmetic Act (referred to hereafter as the statute). If it is a food additive, it must obtain pre-market approval from the Food and Drug Administration (FDA) before it can be marketed for use in food. On the other hand, if use of the ingredient is generally recognized as safe (GRAS) or has been sanctioned by FDA or the U.S. Department of Agriculture (USDA) before 1958, the ingredient is not a food additive. The latter two categories of substances, GRAS or prior-sanctioned, are exempt from the pre-market approval required of a food additive.

Maillard reaction flavors are referred to here as processed flavors. They are produced from complex mixtures, which are converted to flavors (e.g., meat or chicken flavor) by a heating process. The recipes for the precursor ingredients vary from company to company but invariably include, as essential ingredients, specific amino acids, reducing sugars, and animal or vegetable fats or oils. Optional ingredients may include hydrolyzed vegetable protein, onion extract, thiamine, inositol monophosphate, meat extract, and other substances. All of these precursor materials are common food and flavoring ingredients. However, the safety of processed flavors centers around the heating process which allows these ingredients to develop a desirable flavor in the reaction mixture. Because of this

reaction, the review of the safety of processed flavors must be focused on the reaction products rather than simply on the precursor materials. There is no question that processed flavors so produced are flavoring ingredients and thus their use must be in compliance with the statute. The first question we will ask about processed flavors is, Is such a flavor GRAS, prior-sanctioned, or a food additive?

Before we try to determine the categories to which processed flavors may belong, let us discuss the legal definitions for food additives, GRAS substances, and prior-sanctioned substances, as well as some historical background related to the FDA's applications of the GRAS concept.

According to section 201(s) of the statute, food additives include any substance, the intended use of which results, or may reasonably be expected to result, directly or indirectly, in its becoming a component of, or otherwise affecting the characteristics of, any food. Food additives must be approved by FDA, based on a fair evaluation of the entire record available to the agency in accordance with section 409 of the statute. Food additives are deemed to be safe when there is a reasonable certainty that the additive is not harmful under the intended conditions of use.

Section 201(s) also gives a brief definition of GRAS substances. GRAS substances include any substance, which is generally recognized among experts qualified by scientific training and experience to evaluate its safety, as having been

adequately shown through experience based on common use in food before January 1, 1958, to be safe under the conditions of its intended use. GRAS substances also include any substance, which is generally recognized by the same experts as having been adequately shown through scientific procedures to be safe under the conditions of its intended use. The statute did not appoint FDA as the sole authority to determine which substances are GRAS and which are not. The statute, in fact, explicitly recognizes the scientific community's expert opinions on safety of food substances as a basis for determining whether they are GRAS. Because of this statutory definition requiring general recognition, it is quite obvious that any substance that is secret or not well-known to the scientific community cannot be GRAS.

On the other hand, prior-sanctioned substances include any substance approved by FDA under the statute or by USDA under the Federal Meat Inspection Act or the Poultry Products Inspection Act before September 6, 1958, as described in section 201(s)(4) of the statute. The purpose of the exemption was to make it unnecessary to seek approval of those substances that had been sanctioned by these two government agencies before the effective date of the 1958 Food Additives Amendment.

GRAS substances are an open group of substances tied to the current state of scientific information and expert opinions. In contrast, prior-sanctioned substances are a closed group of substances determined by pre-1958 FDA or USDA decisions.

The concept of "GRAS" is unique; no country other than the U.S. has such a category for food ingredients. The creation of the GRAS concept in 1958 by Congress was practical; the lawmakers recognized at that time that to subject a large number of GRAS substances to safety testing not only would disrupt the food supply but also would place an unnecessary financial burden on industry. However, there was considerable debate over the usefulness of the GRAS concept during the hearings held in Congress before it was finally adopted. Many people expressed concern that the term "GRAS" was imprecise and vague in not specifying how general the recognition of safety must be in order for a substance to be GRAS. Others envisioned that the GRAS provision could present a problem to food manufacturers in deciding whether a new food ingredient would be GRAS. Nevertheless, Congress adopted the GRAS concept with the support of FDA officials, who claimed that the GRAS provision had been working well with new drugs and with pesticide chemicals.

There was little activity up to 1971 on the part of FDA to define what "GRAS" meant. From 1959 to 1971, 21 CFR 121.3, which described GRAS criteria, stated that "... any substance added to food which has no history of common use as a food ingredient should be regarded as a substance that is not generally recognized as safe.....unless it has been scientifically tested and shown to be safe."

On June 25, 1971, 21 CFR 121.3 (based on a proposal of December 8, 1970) was revised to be more specific about "GRAS."

The revised version declared that any substance of natural biological origin (including those modified by conventional processing) consumed primarily for nutrient properties before January 1, 1958, without detrimental effect, would be considered GRAS and there was no need for a promulgation in the Federal Register for this type of substance. It also listed five categories of substances which were considered eligible for GRAS classification, provided that convincing evidence of their safety (including comments from qualified experts) was obtained by the agency.

> (1) Substances defined in subparagraph (1)(i) of this paragraph that have been modified by processes proposed for introduction into commercial use after January 1, 1958, where such processes may reasonably be expected to significantly alter the composition of the substance.
>
> (2) Substances that have had significant alteration of composition by breeding or selection and the change may reasonably be expected to alter to a significant degree the nutritive value or the concentration of toxic constituents therein.
>
> (3) Distillates, isolates, extracts, concentrates of extracts, or reaction products of substances considered as GRAS.
>
> (4) Substances not of natural biological origin including those for which evidence is offered that they are identical with a GRAS counterpart of natural biological origin.
>
> (5) Substances of natural biological origin intended for consumption

for other than their nutrient properties.

Four of these five categories were substances of natural biological origin and the remaining one was substances not of natural biological origin but identical to their natural counterparts that were GRAS. 21 CFR 121.3 also stated that substances that were neither of natural biological origin nor identical to GRAS substances of natural biological origin would not be eligible for GRAS status if they had no history of food use. The 1971 version of 21 CFR 121.3 for the first time marked the agency's attempt to define a boundary of eligible GRAS substances.

A more significant change in the FDA's interpretation of the GRAS concept occurred when the agency proposed to further revise 21 CFR 121.3 on September 23, 1974. The proposal, which was finalized with little change on December 7, 1976, represented a refined, restricted view of what the GRAS criteria were supposed to be from the agency's point of view. The new 21 CFR 121.3 (recodified in 1977 as 21 CFR 170.30) defined "GRAS" as:

> (1) General recognition of safety through scientific procedures must ordinarily be based on published literature, and requires the same quality and quantity of scientific evidence that would be required for approval of a food additive regulation.
>
> (2) General recognition of safety based on history of common use in food does not require the same quality and quantity of scientific evidence required of a food additive, but shall ordinarily be based on generally

available data and information.

This change was particularly significant in that it declared that any GRAS substance based on scientific procedures should be required to pass the rigid safety standards set for approval of a food additive, i.e., the same quality and quantity of scientific evidence.

Now let us return to the question regarding the regulatory status of processed flavors: Are processed flavors GRAS, prior-sanctioned, or food additives?

We know that processed flavors have not been regulated by FDA as food additives, and we are also certain that processed flavors are not sanctioned by USDA or FDA before September 6, 1958. Therefore, processed flavors must have been marketed for use in food on the basis of their manufacturers' determination that such flavors are GRAS. As stated earlier, the statute authorizes the scientific community, not FDA, to be the arbiter in deciding which substances are GRAS and which are not. Thus, a manufacturer may consider that a particular food ingredient is GRAS, based on its judgment that the scientific community has considered that particular ingredient to be GRAS. This type of determination is often referred to as an independent GRAS determination made by individuals outside FDA. However, such a unilateral determination is subject to the risk that FDA may object to it and may challenge its use in food on the ground that the ingredient is an unapproved food additive. An example is the

recent court cases on evening primrose oil, in which FDA challenged independent GRAS determinations made for the oil by its promoters. Once FDA and the companies contest the GRAS status of a substance in the court, the ultimate decision as to whether the substance is truly GRAS lies with the presiding judge.

To date, we are not aware of any significant adverse effects associated with processed flavors used as food ingredients. Processed flavors may be GRAS for the following reasons. (1) The manufacturing of processed flavors mimics high-temperature cooking such as barbecuing. The major difference between the flavors in cooked meat and processed flavors is that the latter are a mixture of selected food ingredients rather than a raw agricultural commodity. Also, most processed flavors are produced at temperatures below 150°C, much milder than those used in barbecuing. (2) When preparing a gravy, a chef mixes selected food ingredients and cooks at a certain temperature for a specified period of time. Such a gravy is in fact similar to a processed flavor, although the temperature used for the gravy is lower. (3) The use level of processed flavors is low, as is true with other flavoring ingredients.

However, many studies reported that meats cooked at high temperatures contain heterocyclic amines. Some processed flavors may also contain small amounts of heterocyclic amines, which are present as by-products or impurities. The following nine such heterocyclic amines have been isolated from cooked meat or fish.

(1) 2-amino-3-methylimidazo[4,5-f]quinoline (IQ),

(2) 2-amino-3,4-dimethylimidazo[4,5-f]quinoline (MeIQ),

(3) 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx),

(4) 2-amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline (DiMeIQx),

(5) 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP),

(6) 3-amino-1,4-dimethyl-5H-pyrido[4,3-b]indole (Trp-P-1),

(7) 3-amino-1-methyl-5H-pyrido[4,3-b]indole (Trp-P-2),

(8) 2-amino-6-methyldipyrido[1,2-a:3',2'-d]imidazole (Glu-P-1),

(9) 2-aminodipyrido[1,2-a:3',2'-d]imidazole (Glu-P-2).

These compounds were found to be mutagenic by the Ames test. Moreover, dietary exposure to all of these compounds, except DiMeIQx, increased the incidence of tumors in mice and rats. The principal site for tumor induction was the liver. Malignant lesions following exposure to these compounds were also noted in the forestomach, intestine, blood vessels, and the zymbal and clitoral glands of rats. Furthermore, in an ongoing study conducted by the National Cancer Institute, IQ caused liver tumors in monkeys. After 5 years, 8 out of 20 monkeys with an intake of 10 mg IQ/day and 16 out of 20 monkeys receiving 20 mg IQ/day developed liver tumors, beginning from 21 months to 40 months. Studies in monkeys, sponsored by National Cancer Institute, with MeIQx and PhIP, are also under way. After 3.5 years, no tumors have been observed in the study with MeIQx. The same is true with the study using PhIP, which has been ongoing for 2 years.

At this time, most information on heterocyclic amines in foods relates to cooked meat products. We do not have comparable information on processed flavors. Therefore, new information must be generated to show whether processed flavors contain heterocyclic amines in amounts sufficient to affect their safe use in food. An analytical method working group, started by FDA and the Flavor and Extract Manufacturers' Association (FEMA) in 1990, involving government and industry laboratories is developing a protocol for quantification of heterocyclic amines in processed flavors. FEMA has also conducted a survey of the industry to estimate the types and amounts of processed flavors made by the industry. The analytical method developed will then be used to determine the amounts and identities of heterocyclic amines present in randomly selected processed flavors. We hope that this information will make it possible to see the patterns in which heterocyclic amines are formed in the manufacturing of processed flavors. If so, manufacturers will be able to control their manufacturing conditions to minimize the presence of heterocyclic amines in processed flavors.

Reliable information on the identities and amounts of heterocyclic amines in processed flavors will also make it possible to use risk assessment procedures to estimate the upper-bound limit of risk presented by any of these compounds present in processed flavors. By using risk assessment procedures, the scientific community will be in a better position to render a more informed judgment on the safe use of processed flavors.