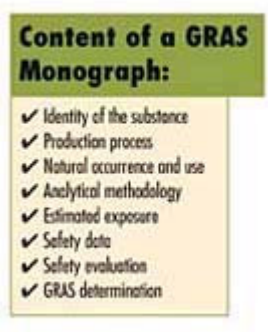
Prepared Foods, January 2004; pp. 123-129

GRAS Determination: A Short Guide

By James T. Heimbach, Contributing Editor

The GRAS concept often is misunderstood. The steps to GRAS self-determination are described, including preparing a GRAS monograph, setting up an expert panel, and introducing the GRAS substance into the food supply.

In principle, any food ingredient can be shown to be GRAS by demonstrating that it is generally recognized as safe for its intended use by experts qualified by scientific training and experience. If a substance is GRAS for its intended use, then it is, by definition, not a food additive and may be used in food without the Food and Drug Administration (FDA) having to review it or promulgate a food-additive regulation.



GRAS—A Higher Standard of Safety

Is it fair to regard GRAS determination as a shortcut to get on the market with ingredients that would not pass FDA review, a loophole that may afford a lower standard of safety? Indeed, a primary reason that GRAS determinations are so attractive is that they are a quicker way to market than food-additive petitions.

But GRAS status is not a lower standard of safety assurance, but rather a higher one. To find that a substance is GRAS for its intended use, the same safety information is needed as for FDA approval of a food-additive petition. There is no reduction in the breadth, quantity or quality of information required. This is referred to as the “technical element,” and the standard is the same for GRAS substances and food additives: reasonable certainty of no harm under the intended conditions of use.

To be GRAS, however, a substance also must meet a second criterion, the “general recognition” element. Demonstrating that general recognition is present has two components:

First, the information supporting the safety of the substance must be generally available, which usually means published in the peer-reviewed scientific literature, although in certain cases general principles from the secondary literature (such as textbooks) are appropriate, and limited use may be made of published abstracts or proceedings of scientific meetings. The rule of thumb is that “the ink must be dry” on publications; that is, they must have been in print long enough to have become available to the scientific community. Original study reports provided on government-sponsored websites (such as the National Library of Medicine’s PubMed) are regarded as generally available, but those on private websites are not because they could be removed at any time. Unpublished data may be used to support or corroborate the published information, but the primary data that establish the safety of the ingredient must be published.

Second, the information must be generally accepted among qualified experts as providing reasonable certainty of no harm. While perfect consensus is not required, serious disagreement among experts regarding the evidence supporting safety of the substance would not be consistent with its being GRAS. One of the key functions of an independent GRAS panel is to represent the scientific community at large, much as a trial jury represents the civic community, in order to demonstrate that there is general acceptance regarding safety.

Getting Started

Before starting on a GRAS determination, three things are needed:

1. A fully characterized substance. You must provide data showing the physical and chemical properties and composition of your product, including not only the principal constituents, but also any processing residues, contaminants, and impurities. There must be established product specifications that define the "article of commerce"—the product to be introduced into the market. You should have analyses of at least five lots of your product, not all consecutive, to demonstrate that the raw materials sourcing and production processes are in control and can produce consistent food-grade material meeting the established specifications. Complete information regarding the production process, including the sourcing of all starting materials, ingredients and processing aids must be available.

2. A technical function for the substance. That is, for what purpose will it be added? A listing of 32 technical effects may be found in Title 21 of the Code of Federal Regulations (CFR) at Section 170.3(o) (1-32); they include such effects as "emulsifiers" and "sequestrants." The only listed technical effect that covers substances added to foods for the purpose of providing a benefit to the consumer of the food is #20, "nutrient supplements" —not to be confused with dietary supplements. Note also that colors are not listed. (See sidebar, "Content of a GRAS Monograph.")

3. An idea of what foods you plan to add your ingredient to, and at what levels. Many substances are permitted for use in all foods, often at levels limited only by Good Manufacturing Practices, but this is less common for newer ingredients. A list of 43 food categories covering the food supply may be found at 21 CFR 170.3(n)(1-43). You may include complete categories as listed, or subsets of the listed categories. For example, yogurt is a subset of category #31, "milk products." Proposed maximum addition levels may be the same in all categories of foods, or they may be different for different foods. Addition levels are normally expressed as percentages by weight or in parts per million (ppm, equivalent to mg/kg).

Together, the technical function(s), target foods, and addition levels constitute the "intended conditions of use" of the substance. It is extremely important to understand that no substance is simply GRAS; rather, it is GRAS under its intended conditions of use. If you do not include baked goods as a target food when you perform your GRAS determination, for example, your substance is not GRAS for addition to baked goods unless you do a new GRAS determination to expand its uses to include this category.

Steps to a GRAS Determination

1. Carry out a complete review of the relevant published literature. This includes all studies of your substance and may include studies of related substances. The literature review must include all findings, positive or adverse. It also should include any case studies, adverse reaction reports, evidence of history of safe use, or other information bearing on the substance's safety.

2. Critically review the body of data you have assembled—what is often termed the "information package"—and compare what is available with what is needed to adequately demonstrate safety of the substance under the intended conditions of use. Obviously, expert judgment is needed for this assessment. Some guidance is available on the FDA website, but bear in mind that this is indeed guidance, not a hard and fast set of rules. Determine what additional information is needed and develop a research plan to obtain the needed data.

3. Develop any needed data, including performing chemical analyses, in vitro testing, metabolic and toxicological studies and human studies. This step is likely to be on your critical time path, because the key studies must be designed, conducted, analyzed, written up for publication, submitted to a scientific journal, peer-reviewed and accepted for publication, and published. This process probably will consume at least two years.

4. Assemble all of the appropriate information regarding the safety of your product into a GRAS monograph, which summarizes the information package. The GRAS monograph should include the following sections:

- Identity: Review of chemical and physical characteristics of the substance: specific chemical structure(s), specifications, characterizations, quantitation of impurities, chemical stability and degradation products. Also, any other information on its identity, properties and composition should be included.
- Production Process: Characterization of all starting materials and the manufacturing process for the substance; description of the quality assurance/control program for the manufacturing process; and results of analyses of five or more non-contiguous lots of product.
- Occurrence and Use: Natural occurrence and/or previous history of use of the substance and related substances in foods; and proposed conditions of use(s) of the substance, including any directions for its use as well as proposed labeling.
- Analytical Methodology: Methods for determining the quantity of the substance in or on food, and any substance formed in or on food, because of its use.
- Estimated Exposure: Daily intake of the substance or related substances from natural occurrence or existing ingredient uses; estimated daily intake from the proposed new uses of the substance; total cumulative estimated daily intake (EDI) at both the mean and the 90th percentile of intake for the total population and appropriate population subgroups (including age/sex breakouts).
- Safety Data: Discussion of all information pertaining to the safety of the substance under its intended conditions of use; metabolic and pharmacokinetic characteristics, in vitro testing, pre-clinical (animal) toxicity, clinical (human) toxicity and tolerance; adverse-reaction reports and case studies; and evidence of history of safe use.
- Safety Evaluation: Derivation of an acceptable daily intake (ADI) of the substance, based on all data available, at which a reasonable certainty exists that no harm will be caused; and comparison of the ADI with the EDI to demonstrate that the intended use of the substance will not result in exposure above a safe level.
- GRAS Determination: Demonstration that the safety of the substance under its intended conditions of use is based on generally available information; and demonstration that there is general scientific agreement that the information presented provides reasonable certainty of no harm.

5. Convene an independent Expert Panel to review the information package and the GRAS monograph. This GRAS panel should comprise individuals with recognized expertise in the areas that are germane to the safety of the substance, usually based on publication record and peer recognition. They must be individuals with no stake, financial or otherwise, in the outcome of the evaluation. Commonly needed areas of expertise are toxicology, chemistry, human metabolism and physiology. Normally, three is the minimum number of members on the expert panel, and a greater number may be needed if the substance requires consideration of a wider variety of

scientific disciplines (as is often the case with biologically active or "functional" ingredients). In addition to providing independent assessment of the safety of the substance, the members of the panel represent the scientific community at large, and their unanimous conclusion regarding safety demonstrates that general scientific agreement exists.

6. Revise the GRAS monograph as needed. It is not unusual for an expert panel to suggest a number of changes; some changes may be minor, but others may be critical to the panel's opinion.

7. Working with members of the expert panel, prepare a "Consensus Statement" that summarizes the information considered in reaching its decision that the substance is both safe and generally recognized as safe. The document should end with a page containing a one-paragraph "Conclusion of the Expert Panel" that states the panel's determination that the substance is safe under its intended conditions of use; this page should be signed and dated by all members of the panel.

This final step completes the GRAS determination per se; you are now free to introduce the product into the food supply. However, your work is not quite complete. Before you close out the project, you should catalog and file all of the documents in your information package, as well as the final GRAS monograph and the Consensus Statement. Finally, your work is never really done. As FDA points out, it is your "continuing responsibility to assure that food ingredients that your firm markets are safe." It is worth recalling that calcium- and sodium-cyclohexyl sulfamate—popularly known as cyclamates—were regarded as GRAS until data emerged that called their safety into question and led to their removal from the market. It is a good idea to plan to update your information package periodically.

The FDA's Role

The FDA's Office of Food Additive Safety staff is knowledgeable and helpful, and it is worth seeking their counsel at any time before, during, or after the GRAS-determination process. Second, you may choose to submit a GRAS notice to the FDA, informing the agency that you have determined that your substance is GRAS and summarizing the basis for this determination. If FDA agrees the information cited does provide an adequate basis for the determination, you will receive a letter stating, "FDA has no questions at this time regarding [your] conclusion that [your substance] is GRAS under the intended conditions of use." If FDA does not agree, it will provide a detailed explanation of the deficiencies of the submission, which can help determine how to improve the information package.

With one exception, this GRAS notice is optional, and many experts suggest you submit such a notice only if you have one or more key customers who will not accept your product without an FDA review. However, filing a GRAS notice is mandatory if you intend to add your ingredient to food products regulated by the U.S. Department of Agriculture (roughly, any product containing more than 3% meat or 2% poultry); you need prior approval from USDA's Food Safety and Inspection Service (FSIS). FSIS reviews your ingredient for suitability, not safety, but will not approve any ingredient as suitable for use in meat or poultry products unless FDA has reviewed its safety. Thus, you must file a GRAS notice, and FDA will coordinate its review with FSIS.

There is nothing mysterious about the GRAS-determination process. Fundamentally, it is a pure application of the scientific method in which we seek truth by presenting our evidence to the scientific community, permitting it to reach an informed conclusion. The outline provided above can help you apply the scientific method in an orderly fashion and, not incidentally, comply with Section 201(s) of the Food Drug and Cosmetic Act to get your ingredient to market.

Website Resources:

wwwww.cfsan.fda.gov — Home page for FDA's Center for Food Safety and Nutrition:
www.cfsan.fda.gov/~dms/opa-frgr.html — FDA Guidance on How to Submit GRAS Notices:
www.cfsan.fda.gov/~dms/opa-cg4.html — FDA Guidance on Chemistry Data
www.cfsan.fda.gov/~redbook/red-toca.html — FDA Guidance on Toxicology Data
www.cfsan.fda.gov/~dms/opa-cg8e.html — FDA Guidance on Exposure Estimation
www.fsis.usda.gov/OPPDE/rdad/FRPubs/00-022N/ApprovalofIngredients.htm — Guidance on Joint FDA/FSIS Approval of Ingredients Used in the Production of Meat and Poultry Products:

Jim Heimbach served with FDA for 10 years and with USDA for four years before beginning a consulting practice. As head of JHeimbach LLC and a founding partner of FunctionalBiotics LLC, he assists clients in meeting regulatory requirements for new food and dietary-supplement ingredients and probiotic microorganisms as well as for health and structure/function claims. He has directed GRAS determinations for more than 90 substances and served on numerous GRAS panels. Contact 804-742-5548, jh@jheimbach.com, www.jheimbach.com.