



Salient features for GRAS status affirmation

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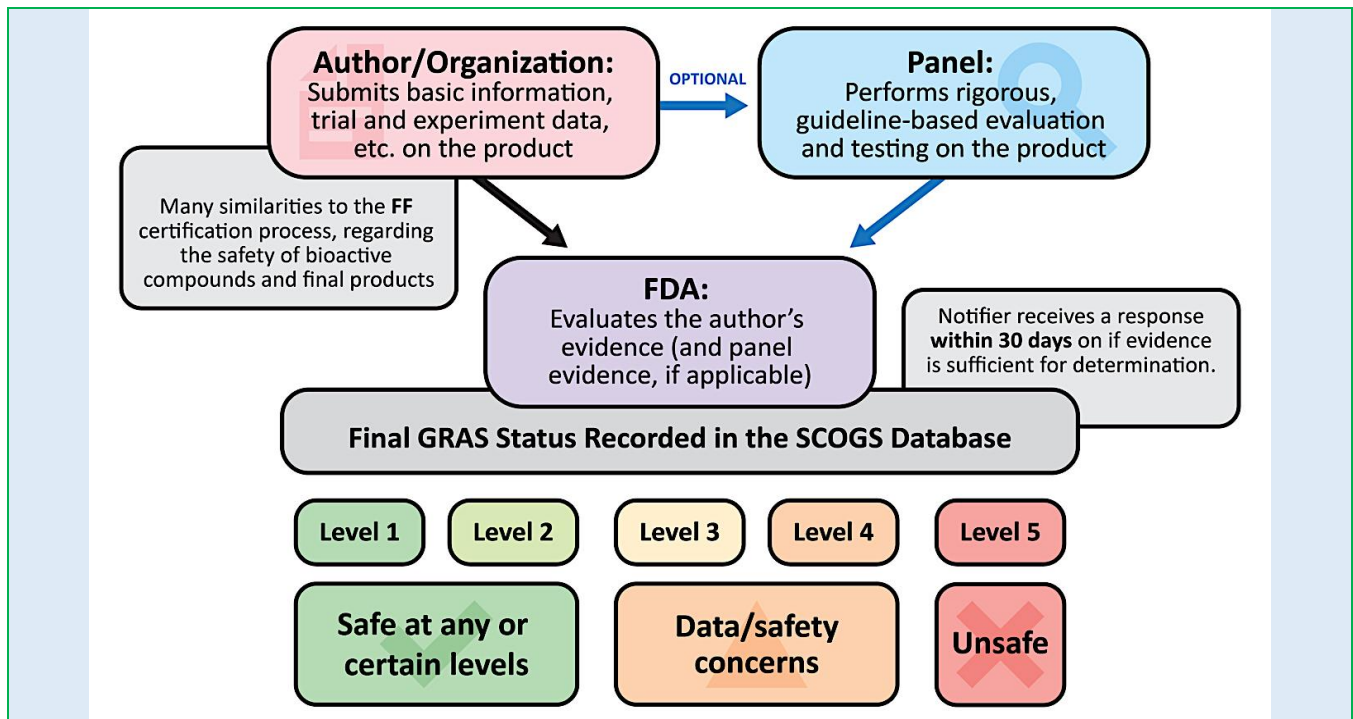
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ABSTRACT

Background: To satisfy the need for thorough yet flexible food safety guidelines, the GRAS (Generally Recognized as Safe) certification process was introduced in 1958, establishing a process for food products and additives to be considered safe for consumption. It involves a multitude of steps from multiple parties: the author advocating for their new food product, a group of panelists who will evaluate the safety of the product, and the FDA (Food and Drug Administration), who has the final say in the GRAS status of the product. The first step involves the author submitting documents with their basic information and product details, including lab trials and experimentation. Next, the panelists follow thorough guidelines to carefully evaluate the product and its safety in the context of its intended usage. The final step involves the FDA reviewing evidence from both previous groups and reaches a singular conclusion that will determine the GRAS status of the product at the end. Overall, the GRAS process established a concrete set of guidelines to determine the safety of food products. Different conclusions and safety levels were produced to set a general standard for companies and other organizations to abide by. These different groups and multiple safety procedures are all required to maintain the highly renowned status of GRAS certification and overall maintain a standardized level of quality for all food products that are exported to the United States. This article will also evaluate the candidacy of functional food products, comparing both processes with regards to sending a functional food product to market and the GRAS notification process overall. Functional foods proved to be an excellent candidate for the GRAS certification process, passing every component of the requirements and serving as a great example of exactly what authors should be expecting when putting their food products through the GRAS certification procedure.

Key Words: GRAS, GRAS notification, functional food product, FDA



Graphical Abstract:

FF- Functional Food, GRAS- Generally Recognized as Safe, SCOGS- Select Committee of GRAS Substances

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INTRODUCTION

After waves of health concerns with food products after Sinclair’s publication *The Jungle* and other issues found in meat-packing factories, a stronger regulatory system for food inspection was required. The FDA became significantly more stringent in its inspections, requiring that foods be “harmless per se”, meaning that they are non-toxic at every possible dosage [1]. These extreme measures are generally detrimental to both the consumer and the manufacturer as they significantly limit the number of foods that people can consume, even if certain products are safe at specific dosages. They would also place a financial burden on food industries, which would be required to conduct extensive tests. This would severely reduce the rate of innovation with food technologies and medicines. “Grandfathering” substances that were already in use by the public were

thoroughly vetoed by the majority. Grandfathering a substance involves using a substance as normal without any evaluation or approval if it has already been in use [2]. To mediate between completely inadequate food safety guidelines and inflexible provisions, GRAS certification was established as a compromise.

Congress introduced the concept of GRAS in the 1958 Amendment to the Federal Food Drug and Cosmetic Act [3]. This introduced the legal definition of a food additive and created a new class of substances. Substances generally recognized as safe were held separate from the category of food additives and not subject to pre-market approval. While this procedure isn’t as rigid as the previous “harmless per se” standard, GRAS still imposes thorough guidelines to ensure safety and security. Unlike grandfathering, GRAS requires every food additive and substance to be subject to unbiased reviews to be considered safe for consumption [4].

GRAS from the perspective of the author: Authors are the individuals that are pushing for their food product or additive to be sent out to market and labelled as GRAS. To begin the GRAS notification process, authors must submit a file containing all the detailed records of their

substance [5]. The figure below contains the various constituents of the record for the GRAS certification process from the perspective of the author. This includes signed statements and certification to the final step of a list of supporting data.

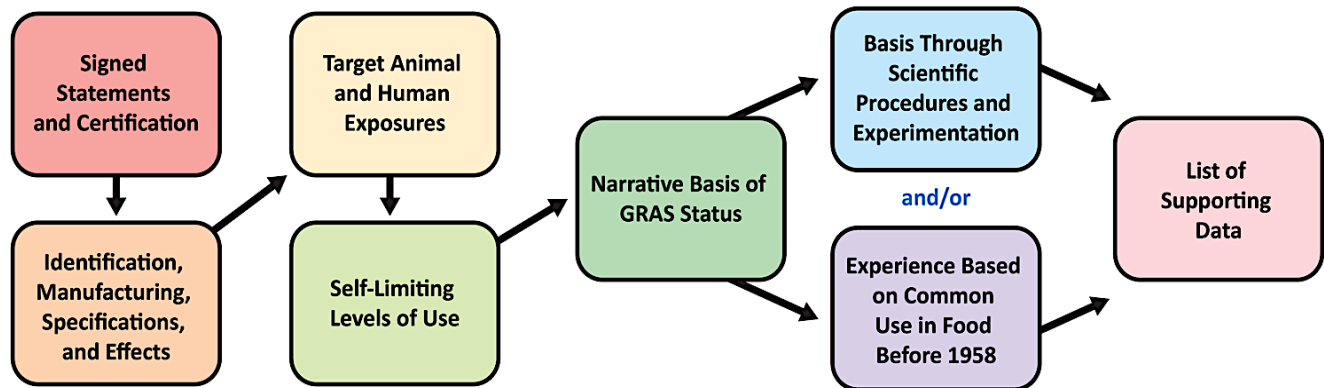


Figure 1: Steps in the GRAS Certification Process

Signed statements and certification: Signed statements and certification include the name and address of the organization promoting the substance and other basic demographic information. The file must indicate that you are submitting a GRAS notice, and specify the name, intended use, and target demographic of your substance (whether you will use it on animals, or indirectly on humans through livestock). Authors must also specify the basis of GRAS notification. This includes whether they are undergoing the scientific procedures with rigorous testing, or the common use pathway, where they must provide a history of common use in food before January 1, 1958. No matter the basis of the GRAS notification, authors must all consent to offer all their data to the FDA, as well as clarify which parts of the data, if any, need to be kept confidential. They must ensure that their data is truthful, complete, and to the best of their knowledge.

Identification, manufacturing, specifications, and effects: In addition to basic demographic information,

authors must also include a detailed file of all the data and the overall manufacturing process of their food product they wish to promote. This involves registry numbers, the product's quantitative composition, characteristic properties, and a taxonomic source if the substance contains any biological components. A quantitative composition is included to specify a specific metric dose or weight of an active drug substance contained in the food product or additive [6]. Any potential toxins that are associated with the food product or any of its byproducts must also be documented, as well as the intended effects of the food product.

Target animal and human exposures: To ensure safety, the intended use relative to the target audience demographics must also be evaluated. Food products are generally classified in two ways. It is either being used for animals and to never be consumed by humans, or it is indirectly consumed by humans through livestock consuming these food products. For non-human directed

animal targets, authors must provide the amount of substance that specific target animals are intended to consume. They must also report any byproducts that are naturally associated with the substance that the animals will also end up consuming. For indirect consumption by target humans through livestock, authors similarly must document potential residue quantities that humans may be exposed to of the substance through their consumption of livestock. Any byproducts that they may also indirectly consume must also be listed. To properly record the impact of the respective food product on target demographics, many panels are typically referred to as they provide guidelines to abide by. Particularly, the Panel of Contaminants on the Food Chain (CONTAM) provides scientific advice on potential risks to target demographics from particular chemical contaminants found in foods. Pesticide units offer guidelines on common impacts of pesticides in food products on animal and human health. The GMO (genetically modified organism) panel provides advice on the impact of GMOs in foods [7].

Self-limiting levels of use: Self-limiting levels must also be established. In line with the FDA's emphasis on guaranteeing food product safety, if the food is toxic at any dosage, the author is required to determine a threshold below which the substance is safe and effective. This is a large shift from the previous standard on safety determination. Instead of the "safe per se" approach, the FDA is now more lenient and allows for the use of substances at safe dosages. This benefits both the industries and the consumers by being less restrictive on the available ingredients that are considered safe and overall offers more food options for the public.

Experience based on common use in food before 1958: At this point of the notification process, if authors are

choosing the common use basis of GRAS notification, then they must provide evidence of significant use. In order to achieve GRAS status, a substantial history of common use of the food product or additive and significant consumption by humans or target animals must be demonstrated before January 1st, 1958. This generally entails existing evidence and the consensus surrounding the food during its consumption. This evades all the thorough scientific and experimental testing as it bases its evaluation mostly on the consensus of scientists regarding the food product [8].

Narrative basis of GRAS status: Authors must also acknowledge all the available data about their food product or substance. The FDA requires an explanation as to why the data the author provided serves as a basis for GRAS certification for a food product. Also, if there is any available data contradictory to the GRAS conclusion of the author, they must dispute that to effectively argue for the GRAS status of their product.

List of supporting data: At the end of the GRAS notification process, authors provide a list of all the supporting data for their GRAS notification basis. Authors must include confidential and public data, and specify which data is confidential. This is an overall compilation to provide the FDA's evaluation [9].

Functional food products and the GRAS procedure: Functional food products are defined as foods that contain bioactive compounds which, in certain dosages, provide a clinically proven health benefit [10]. Functional food products require an extensive pre-market approval process and are a good example to compare against the GRAS notification process step-by-step. The figure below contains a summary of the steps in this process [11].



Figure 2: Steps in the Functional Food Product Process.

Signed statements and certification: The first step of GRAS notification involves signed statements and certification, essentially all demographic information about the author as well as basic truthful data on the substance. Step 1 of the functional food process includes the establishment of the functional food product, with established methodology and precise preliminary research.

Identification, manufacturing, specifications, and effects: GRAS next requires the manufacturing method with the specific quantitative compositive and chemical properties of the substance. This is overall, a detailed record of the makeup of the proposed product. The functional food process goes into detail regarding the complete composition of a food product, as they also need to ensure safety at every level. Step 2 of the functional food process determines the relevant bioactive compound(s) in the functional food. Bioactive compounds are defined by the Functional Food Center as any natural or processed foods that contain biologically active compounds. Step 4 determines specific pathways and mechanisms of action. This specifically entails research on how bioactive compounds and other ingredients interact to determine the safety of the bioactive compound usage as a functional food. If the researcher finds any dangers, the functional food

development may be terminated. Step 5 establishes relevant biomarkers officially. Once the previous steps have been completed and the functional food's safety has been ensured, biomarkers are officially established and associated with their positive effect. Step 7 involves preclinical studies on efficacy and safety. Clinical trials with in vitro and in vivo studies with animals are conducted to determine what dosages don't produce adverse side effects before human clinical trials. This is a large precaution to reduce harm and maximize safety. Step 8 involves human clinical trials to access dosage, efficacy and safety. The dosage is further narrowed to determine viability of bioactive compounds, and these clinical trials abide by standardized regulations to ensure standard quality. Jumping to step 15, this includes epidemiological studies, which checks over the dosages and consumption by the general population compared to human clinical trials. This determines the safety and efficacy in a "real-world" setting, ensuring increased safety and quality usage of the product.

Target animal and human exposures: Step 3 of the GRAS process requires target animal and human exposures, including the amount of substance and any possible byproducts that the target organism would be consuming or exposed to. Step 6 of the functional food product process involves determining the food vehicle that the

functional food product would be applied to. Different common foods are considered and tested to observe their interaction with the functional food product and its bioactive compounds to ensure that food is an appropriate and safe application. Step 9 is to label and inform consumers how to consume the product. This label contains the finalized therapeutic dosages (the dosage that is considered safe for consumption and effective) for human consumption after the human clinical trials are completed, as well as specifying the ingestion method.

Self-limiting levels of use: Step 4 for GRAS Notification requires self-limiting levels of the substance if it is unsafe at certain levels. The functional food product process thoroughly satisfies this requirement with step 3 of its respective process, which involves the establishment of the appropriate dosage of bioactive compound(s). Through their substantial clinical and animal trials, a therapeutic range is established within which the compound exhibits positive effects, while also remaining safe for consumption by the intended organism or individual.

Experience based on common use in food before 1958: GRAS Notification's 5th step asks for evidence of experience based on common use of the food product or additive. This is optionally applicable, and the functional food process does not have a directly connected procedure for this step as their process is much more scientific and conducted through clinical testing. This serves as the alternative step in the GRAS certification process.

Narrative basis of GRAS status: Step 6 of the GRAS process requires the author to explain the basis of their GRAS proposal, why their substance is GRAS, and they must address all the data on their substance. If any data happens to be inconsistent with their proposal, they

must dispute that, and explain why some of their data is kept private, if any. Step 10 of the functional food process requires that publications be submitted to (preferably open-access) peer-reviewed journals. Publishing findings to public journals gives the public greater access to information and establishes the legitimacy of the functional food to the consumer and government agencies. Therefore, the functional food process doesn't leave any of their data confidential for the benefit of the public. Step 16 is after-market research. This analyzes the wider population to monitor the well-being of the public with the product and ensure that it is remaining effective in its everyday use. The functional food process leaves the data on their product to the review and analysis of other credible scientists and the public. Additionally, even after extensive clinical trials and research, the functional food process still conducts research on the consequences of the product after it is released to the public, ensuring the product's efficacy.

List of supporting data: The final step of the GRAS notification process is a list of supporting data provided by the author. This is a list of all the data that was discussed in the GRAS notice and the specification of which parts are public and which are private. Step 11 of the functional food process involves the education of the public. The specifics of the functional food product and its bioactive compounds are accessible to the public and explained to increase transparency for consumers to make more informed decisions. Step 12 sends the information to credible governmental agencies, such as the FDA [12].

Overall, the functional food process on its own is substantially thorough as, like the GRAS process, its focus is to ensure safety of food products when being consumed by living beings [13-17]. Therefore, the two processes side-by-side contain a lot of direct proportional similarities, making functional foods good GRAS certified

candidates and an excellent example of how to go about GRAS certification.

GRAS from the perspective of panelists: Panelists are a group of diverse experts certified in their respective fields. When judging the safety and efficacy of a food product or food additive, panelists abide by the standard scientific procedures for GRAS determination. These guidelines involve properties of absorption, distribution, metabolism, and excretion along with testing. This testing includes acute toxicity testing, and reproductive, developmental, and carcinogenic testing if deemed necessary.

The amount of testing is generally dependent on the concern level of the product. Concern level 1 (low) requires genotoxicity and acute toxicity testing. Concern level 2 (intermediate) additionally requires sub chronic, reproductive, and development toxicity testing. Concern level 3 (high) requires all of the above testing as well as one year of non-rodent and carcinogenic testing [4].

The panel will evaluate all the required tests and collaborate on the new product, and if the information included is accurate, they must develop a consensus statement. This would involve specifying the intended use of the ingredient. To create the consensus statement, a unanimous agreement is not required. However, a major conflict between the panelists will inhibit the general recognition process and raise further questions about the proposed food product [18].

In most cases, the GRAS certification for a product won't require an entire panel to determine a conclusion for its GRAS status. If there is well-substantiated and published evidence vouching for the safety and efficacy of a product, secondary and direct peer literature is generally enough to determine the GRAS certification of

a product. Therefore, the panel's conclusion doesn't confer an official consensus on the product's safety, but rather just serves as more confirming evidence in favor of the food product [19].

GRAS from the perspective of the FDA: The FDA has the final say in a product's GRAS certification and is a crucial part of the GRAS process. To develop a systematic method by which they evaluate different food products' safety and efficacy, the FDA's newest system is the GRAS notification process.

First, the FDA Office of Food Additive Safety receives a GRAS notification from the individual or author, and potentially a pre-submission meeting request. Within 30 days of receiving this notice, the FA will notify the author whether the information in the notice is substantial for determining whether the substance is GRAS. They may require the consultation of other expert agencies if extra confirmation is deemed, such as the U.S. Department of Agriculture (USDA). The FDA specifically defines "safe" as a reasonable certainty of multiple competent scientists that the substance is not harmful under the conditions of its intended use. Also, general recognition of safety through common use experience (substantial history of consumption for food by many consumers before January 1, 1958 is acceptable without scientific procedures) [20].

Once the FDA reaches a conclusion on the GRAS status of the food product or additive, they record this into the Select Committee of GRAS Substances (SCOGS) database. This database is essentially a reference point for already existing GRAS products and substances and the conclusions that they received. The figure below illustrates a brief overview of how the levels are generally sorted.

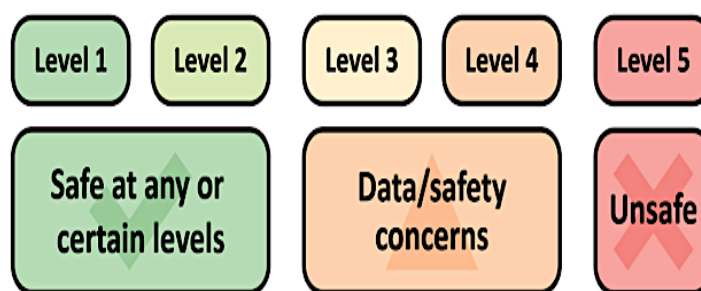


Figure 3: Brief illustration of concern levels.

Level 1 indicates no evidence that the product poses harm used at current or expected levels. Level 2 indicates there is no evidence that the product poses harm used at current or expected levels, but an increase may cause a dietary hazard. Level 3 entails no evidence that the product poses any harm used at current or expected levels, but it is uncertain and additional studies are required. Level 4 indicates there is not enough evidence on the substance to substantially determine its safety when used at current or former levels. Level 5 states there is nearly a complete lack of evidence/studies, so this substance cannot be determined as safe [21].

While the FDA plays a significant role in the GRAS status determination of a food product, they do not intend to thoroughly analyze every single aspect of every GRAS determination received. After the initial evaluation, the FDA will simply send the notifier 1 of 3 letters: 1 indicating the FDA doesn't question the basis of GRAS determination, 2 indicating the notice does not provide sufficient basis for GRAS determination either because it doesn't have enough data and studies or the information provided raises safety questions, or 3 the notifier has requested the FDA to cease GRAS determination process.

CONCLUSION

In conclusion, the GRAS certification process has proven to be thorough and a stringent process to establish a higher standard for food safety. It was made flexible

enough to benefit both the consumer and companies that produce these food products. This multi-faceted process is necessary for the food industry to remain effective and to set a standard for all food products.

Functional food products were concluded to be an excellent candidate to fulfill all the steps within the GRAS certification process. As the functional food product process is also a complex procedure with various steps, it neatly aligns with the steps in the GRAS procedure.

The novelty of this work: This review article demonstrates how the thorough steps of the GRAS Certification process maintain a high-level standard of safety for food products. These steps provide a beneficial policy for both organizations of the respective products as well as consumers who rely on the safety of these food products. These standards ensure safer foods and a general standard for all organizations to abide by in order to satisfy the consumer.

List of abbreviations: FDA: Food and Drug Administration, GRAS: Generally Recognized as Safe, CONTAM: Panel of Contaminants on the Food Chain, GMO: Genetically Modified Organism, SCOGS: Select Committee of GRAS Substances

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revising this manuscript and editing. JS provided the rough content, searched for literature and formatted the article.

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