



## The relevance of international assessments to GRAS determinations



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### ABSTRACT

A discussion of the risk assessment process as applied to the Generally Recognized As Safe (GRAS) determination of safety for new ingredients can benefit from an international perspective. When we think about how risk assessments are performed around the world it is critical to assess what can be learned. What are the similarities? What are the differences? What are the takeaways? It is important to talk about the similarities in processes, because it validates the approach taken by risk assessors who are charged with protecting the food supply. It is also instructive to evaluate the differences in order to determine where improvements can be made to our process.

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The scientific risk assessment process that is applied to GRAS ingredients is similar to the method used elsewhere for food additives and novel foods. There is good reason for the commonality in the risk assessment processes used globally. The risk assessment process can be used to characterize the nature and magnitude of health risks to humans from a myriad of exposures ranging from foods to drugs, environmental contaminants to consumer products. Risk managers use the information from assessments to help them decide how to protect humans and the environment from stressors. What makes the risk management approaches to evaluating safety of food ingredients differ? It is not the scientific process itself, but rather cultural and political influences during the times in which laws are enacted to protect public health that produce key differences in how risks are perceived and managed. And finally, the actual execution of the regulations and processes designed to manage risk can fail, even in the best of hands. So let's first look at finding common ground.

There are four steps to risk assessment. Risk assessments start out with a hazard identification, followed by a dose-response or characterization, exposure assessment, and, finally, risk characterization. When the full risk assessment process is not completed, there is the danger that hazard can be confused with risk. An identified hazard does not necessarily mean an identified risk. Hazard is intrinsic toxicity whereas risk is the probability of manifesting that hazard. Risk is the product of hazard under the conditions of exposure. The full risk assessment process is presented in Fig. 1.

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Safety is never an absolute but is the inverse of risk. As the first step in the risk assessment process, hazard assessment relies on the information gleaned from many sources including structure-toxicity analysis, *in vitro* testing, animal bioassays, and well-conducted clinical trials such as randomized placebo-controlled intervention trials. Hazard identification uses all of these tools to elucidate target organs, severity of intrinsic toxicity and reversibility in the identification of no adverse effect levels (NOAEL) and low adverse effect levels (LOAEL). Primary evidence of safety is gleaned from preclinical studies, however, human studies, when, can elucidate hazards that may not have been seen in an animal study or can confirm or corroborate that the animal model is, indeed, appropriate for extrapolation to human health. Good pharmacokinetic data for the substance of interest helps to confirm that we are appropriately bridging from animal data to human health assessment.

Dose response is the next step in the risk assessment process, and allows the determination of a quantitative relationship between the dose and the effect and establish a threshold for the toxic effect. Classic dose-response relationships for non-carcinogens describe the threshold below which no adverse effects are seen, and the slope of the response at levels higher than the threshold. Dose-response can express the dose in terms of administered dose, or systemic dose such as blood levels or dose reaching receptors or target organs of toxicity.

Exposure assessment is the third step in the risk assessment process. There are many ways to look at exposure and relate it to manifestation of the adverse effects that are manifested. Exposure assessment must evaluate amount, intensity, frequency, duration, and route, as well as internal dose such as how much gets to the

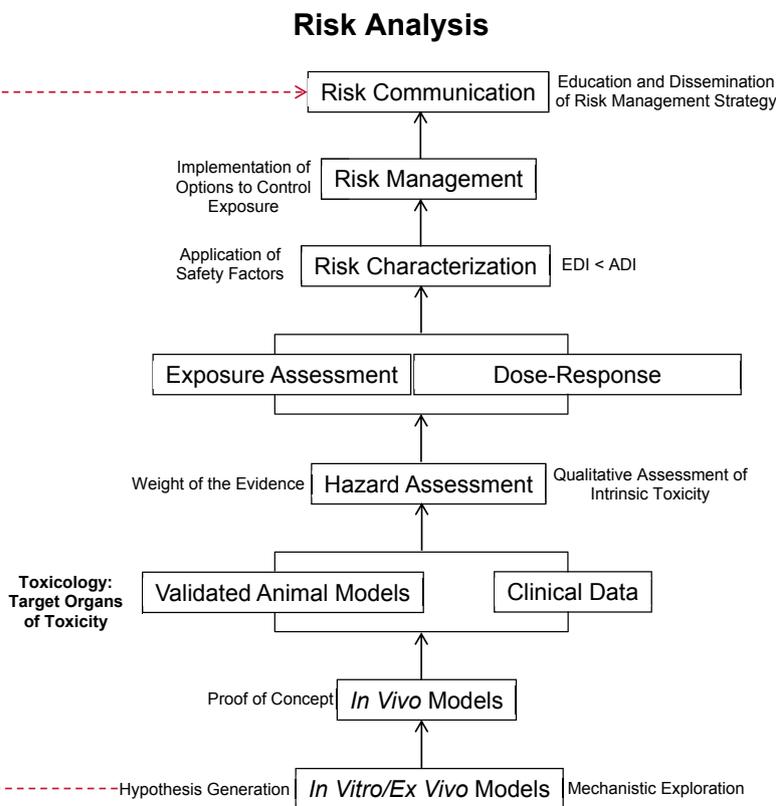


Fig. 1. Risk analysis.

receptors or target organs. An exposure assessment must utilize the knowledge of how much of an ingredient is being used in which products, how much a population is consuming from the intended uses, and what is the cumulative exposure. New uses of an existing ingredient must be added to background intake so that the risk of manifesting the identified hazard can be assessed at the new levels of exposure.

Risk characterization is the final step. All the information derived from the hazard assessment, dose response and exposure assessment is synthesized to determine risk. The risk characterization determines whether the estimated intake is lower than our calculated safe level. The integration of the steps in the process can be seen in Fig. 2.

The risk assessment process can frequently be miscommunicated in headlines that appear in newspapers and online. Risk communication that utilizes information derived only from the hazard identification step of the risk assessment process can mislead stakeholders. As just discussed, the four steps in risk assessment are pivotal to providing the right information for risk management and risk communication. Risk communication that confuses the results of the full assessment process with results from studies that are used for hypothesis generation, such as unvalidated *in vitro* bioassays, does a disservice because we do not yet know who to use these types of studies to extrapolate to human health. We all agree on the principles of risk assessment because it is process by which hazard information from validated bioassays can be used to complete the risk assessment needed for an informed management decision.

A comparison of the risk assessment principles from JECFA, EFSA, FSANZ, and FDA allows us to understand where consensus lies in the evaluation of safety for food ingredients. JECFA has opined that food safety risk assessment should incorporate the four

steps of the risk assessment, i.e. hazard identification, hazard characterization, exposure assessment and risk characterization. Risk assessment should be based on all available scientific data. It should use available quantitative information to the greatest extent possible. Risk assessment may also take into account qualitative information. Additionally, risk assessment should take into account relevant production, storage and handling practices used throughout the food chain including traditional practices, methods of analysis, sampling and inspection and the prevalence of specific adverse health effects. Constraints, uncertainties and assumptions having an impact on the risk assessment should be explicitly considered at each step in the risk assessment and documented in a transparent manner. Expression of uncertainty or variability in risk estimates may be qualitative or quantitative, but should be quantified to the extent that is scientifically achievable. Finally, risk assessments should be based on realistic exposure scenarios, with consideration of different situations being defined by risk assessment policy. They should include consideration of susceptible and high-risk population groups. Acute, chronic (including long-term), cumulative and/or combined adverse health effects should be taken into account in carrying out risk assessment, where relevant.

In the EU and Australia, regulatory guidance provides a framework for risk assessment applied to novel foods, nutritive substances and food additives is similar to that used in the US for food additives and GRAS ingredients. Technical information on the food needed includes: description of the food, ingredient or additive; physical and chemical properties; impurity profile; manufacturing process; specification for identity and purity that defines the food grade status, and; analytical method for detection of the ingredient. A list of the foods or food groups proposed to contain the food ingredient and the proposed use level for each food or food group allows estimation of the daily intake. Toxicokinetics and

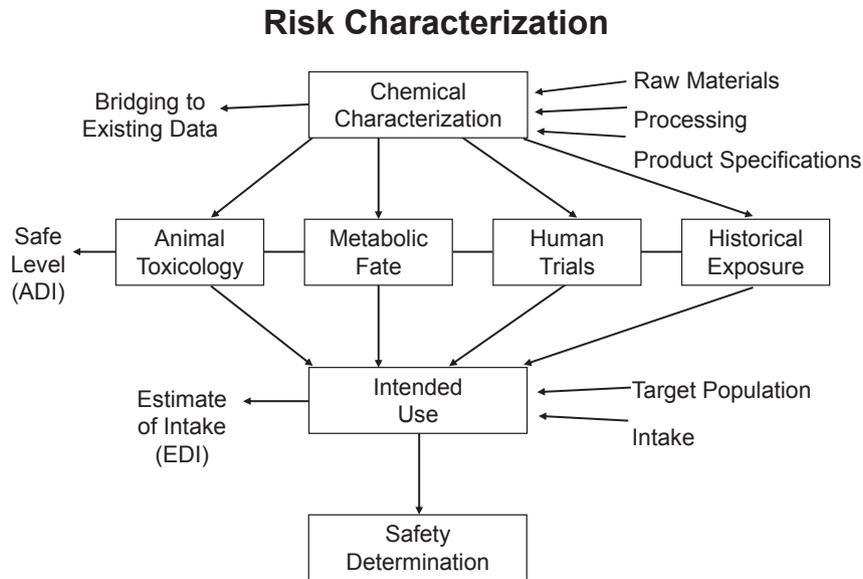


Fig. 2. Risk characterization.

metabolism of the food ingredient and if applicable, its degradation products and/or major metabolites should be included. Information on the toxicity of the ingredient and if applicable, its degradation products and major metabolites includes studies in animals or humans.

The EU has guidance on submissions of risk assessments for food additives, enzymes and food flavorings that mirror these principles that we have laid out. In case of an application for a new substance authorization a full package of data is required. Missing data must be accompanied by a verifiable justification. In case of an application for modification of the conditions of use of an already authorized substance, the data for risk assessment may not be required. However, a verifiable justification why the proposed changes do not affect the results of the existing risk assessment must be provided. In case of an application for modification in specifications of an already authorized substance the data may be limited to the justification of the request, the description of the proposed changes and a verifiable justification that the changes do not affect the results of the existing risk assessment.

The EFSA conceptual framework approach for re-evaluation of food additives, that assesses the burden for supplementary information in cases where an ingredient is already approved but new uses emerge, new levels are proposed, or the intent of the use is changed, is an important one in the concept of GRAS. These assessments build on the original and include the results from the reevaluation or reassessment process. Why does a change in level or use or intent matter? There are important examples of things used in our food supply like processing aids or flavoring ingredients, where original approvals may have been very narrow and innovation has expanded uses. Re-evaluation and documentation of the safety for the expansion of these uses is critical. Reassessment of safety is very important and amendments incorporating reevaluations of GRAS ingredients are a key step in assuring the safety of our food supply. There should have more discussion and additional guidance in the framework of GRAS evaluations on when and where and how to go back through what we have in the food supply to make sure that current uses are covered by the risk assessments that were done.

In the U.S., "Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food" originally

published in 1982 and revised in 2007 (Redbook, 2000), provides guidance to industry for: determining the need for toxicity studies, designing, conducting, and reporting the results of toxicity studies, conducting statistical analyses of data the review of histological data the submission of this information to the FDA as part of the safety assessment of food ingredients. However, it is critical to remember that Redbook does not provide this guidance as a checklist. The reason for the flexibility in approach is that science evolves. Thinking evolves. Risk assessments should incorporate and embrace these new advances. Nevertheless, the principles of risk assessment as defined in the step-wise approach apply.

This risk assessment approach has a commonality among regulatory agencies. And this is important to note, because when we look at the debate about GRAS, it is clear that some stakeholders have questions about whether this is the right process to protect the food supply. Are we missing something? Is there a better way to do it? Are safety evaluations being done in secret? How do we know that this is really a robust evaluation process and that we are utilizing all those principles that are needed to assure safety?

There are, of course, differences between GRAS and some of these other processes, because GRAS is unique in that it is not a premarket approval process. However, if we just look at the science, it is the same. And the validation for the scientific approach is that regulatory and authoritative bodies around the world articulate the same risk assessment principles that are used to evaluate the safety of GRAS ingredients. Products evaluated via the GRAS process, in principal and by regulation, are held to the same standard as are products that reviewed by FDA with a premarket approval process. The safety standard for both GRAS and food additives is reasonable certainty in the minds of competent scientist that a substance is not harmful under its intended conditions of use. GRAS ingredients and food additives are not different with respect to the science. The GRAS process is also not different with respect to the risk assessment process compared to food additives or novel food in the EU or Australia.

What does differentiate the GRAS process is the public availability of the pivotal information used, because for other premarket approval processes for food ingredients completed in other countries around the world, all of the animal studies, the human data, and the exposure assessment can be privately held. The studies do

**Table 1**  
Summary of the reasons given for FDA decision that notice does not provide a basis for a GRAS determination.

GRN	Reason for decision	Other information
328	Data do not support that substance is a new entity (not different from 21 CFR Part 184 listed component) Needs to submit a food additive petition or a citizen petition to amend substance Generally Recognized as Safe (GRAS) regulation	
108	Underlying data not generally available (failure to satisfy common knowledge element) Disagreement that substance is chemically and toxicologically similar to an established GRAS substance used as a surrogate	Subsequently submitted as a Food Additive Petition (FAP) and approved by the U.S. Food and Drug Administration (FDA)
100 (D-ribose)	Lengthy and complicated discussion of data having no relevance to safety Dismisses safety related findings without adequate support from the scientific literature	Notice resubmitted (GRN 243) with sufficient data to demonstrate GRAS ( <b>GRN 243 received a “No Questions” letter from FDA</b> )
96	Notice lacked all necessary information (conditions of use, use levels, basis for GRAS, identity of substance, source, manufacturing data)	
93	Insufficient information about composition and data relied on to establish safety not generally available	Resubmitted (GRN 125) and received a “No Questions” letter
92	Data relied on to establish safety not generally available	Resubmitted (GRN 129) and received a “No Questions” letter
66	Lack of information on composition No toxicology data	
42 (Milk-derived lactoferrin)	Did not address FDA concerns that some effects of the immunologically active substance could be adverse	Notice resubmitted (GRN 77) with sufficient data to demonstrate GRAS ( <b>GRN 77 received a “No Questions” letter from FDA</b> )
40	Insufficient data provided for FDA to reconsider its previous conclusion that pre-1958 use of the substance was not sufficient to demonstrate safety	Resubmitted (GRN 71) and received a “No Questions” letter
38	Insufficient data provided to allow for estimation of dietary exposure No toxicity data provided and no information on conditions of use	Subsequently submitted as a FAP and approved by FDA
35	Insufficient data provided to support claim of substantial history of consumption in food prior to 1958	
30	Insufficient data on dietary exposure No toxicology data in public domain	FDA informed of proprietary data supporting safety but still does not meet general recognition requirement
25 (Extract of <i>Garcinia kola</i> seed)	Lack of data provided on composition, physical properties, manufacturing, specifications No discussion of reports of adverse effect in publications identified by FDA	
14	Needs to submit a food additive petition or a citizen petition to amend substance GRAS regulation in 21 CFR Part 184	
13	Insufficient data provided to support claim of substantial history of consumption in food prior to 1958	
10	Notice lacked all necessary information (conditions of use, basis for GRAS, identity of substance, manufacturing data)	
7 arachidonic acid-rich single-cell oil (ARASCO) and docosahexaenoic acid-rich single-cell oil (DHASCO) as sources of the fatty acids arachidonic acid (ARA) and docosahexaenoic acid (DHA)	Studies showed treatment related effects that raised questions about safety of substance	Notice for ARASCO submitted separately (GRN 80) with sufficient data to demonstrate GRAS (received decision of “FDA has no questions”) Notice for DHASCO and ARASCO submitted (GRN 41) with sufficient data to demonstrate GRAS ( <b>GRN 41 received a “No Questions” letter from FDA</b> )

not have to be published which results in the release of redacted and sanitized versions of the information that is used in the risk assessments released by regulators. That makes it much more difficult for stakeholders because they are unable to look at all of that information and make their own independent judgment.

GRAS is held to the same scientific standard as for food additives and novel foods that must undergo premarket approval. The breadth and quantity, the quality of information must be the same. The only difference is that the risk assessment is done utilizing the added burden of proving general recognition and consensus of opinion. So it is an even more robust a process because not only is the standard for the science the same, but the evaluation must

include proof that there is no significant disagreement in the public domain over the conclusion. To do this, one must show that all of the pivotal information is made publicly available so that if someone did disagree, they would have had the opportunity. It makes consensus of opinion quite difficult to achieve and adds to the comfort level that the GRAS process is protective of the food supply.

Notification of a GRAS determination gives us a public record. Notification is a very powerful tool to assist regulators in understanding and helping keep track of exposures and calculating cumulative exposure. Nevertheless, it is important to note that exposure assessment is typically very conservative. It assumes that the presence of the additive or ingredient is at the maximum level

allowed in the foods. It also assumes that the product has saturated the intended market. It is designed to provide a safe level of consumption for the highest consumer (90% percentile) and assumes that the additive is going to be consumed every day over an entire lifetime.

What are some of the concerns about the GRAS process? One of the first issues, of course, is a concern that GRAS is “dated”, having started back in 1958. What we are eating is very different today than back then and the science of risk assessment has evolved. Is GRAS still relevant? The answer is yes, because the safety evaluations that are used for GRAS are not a static checklist. The scientific tools we use and how we apply them to incorporate new science into looking at the kinds of ingredients that were not even envisioned back in 1958 have evolved.

Another issue that has been brought out is that GRAS is not a pre-market approval process. Is this a process that relies on industry policing itself, as opposed to a transparent process that allows stakeholders to understand actually what was done to make sure that their food supply was safe? Is the GRAS process not transparent enough? Transparency itself is actually a complicated issue. What should be transparent? What should be known? What should not be? How do we make sure that stakeholders have the right amount of information and enough information, and yet commercial and proprietary interests of those companies who must go through this process in order to be successful in the marketplace are protected? And yet we could argue that, from a transparency perspective, even without Notification, GRAS actually qualifies as one of the most transparent processes that are available, because, as we previously discussed, all of the pivotal information has to be published.

Many times, GRAS determinations rely on evaluations by Expert Panels who opine on basis for the consensus of safety that is derived from the risk assessment. The use of Expert Panels for evaluating the safety of ingredients in our food supply has a long history. European Food Standards Agency (EFSA) is an example of an expert panel that opines on the safety of foods. Flavor Extracts Manufacturing Association (FEMA) has used expert panels for decades to evaluate the GRAS status of flavors. It is very important that panel members do not have conflicts of interest, that they represent the expertise needed, and that there is a balance of bias,

because no one comes to a discussion completely neutral on any particular subject. JECFA has articulated useful guidance on some of the key elements of how expert panel members should be selected to avoid conflict of interest and assure effective communication and deliberation. This guidance is useful to embrace in selecting Expert panels for GRAS deliberations (see [Table 1](#)).

## 1. Conclusion

In summary, GRAS is not unregulated. It relies on established scientific principles articulated by regulatory and authoritative agencies around the world for risk assessment. There is a way that every stakeholder can check the results of this process because pivotal information is published. Most critical is the knowledge that the risk assessments applied to the GRAS process are not static. Both science and regulation are never static, nor should they be. We must constantly question old paradigms, test new methodologies, and incorporate better strategies. But we must do this in a thoughtful, deliberate and unbiased fashion. The process must allow us to keep the processes that work well while incorporating innovations that add to their value. Eliminating processes that have served us well for 50 years with no evidence that there is a compromise in the assurance that we are protecting public health is unconscionable. The GRAS process is a robust, rigorous, peer review process. It is a process that can satisfy consumer concerns about food ingredient safety that articulates what was done, how it was done, and why we can conclude that the ingredient is safe.

## Transparency document

Transparency document related to this article can be found online at <http://dx.doi.org/10.1016/j.yrtph.2016.06.010>.

## Reference

Redbook 2000, U.S. Food and Drug Administration, July 2000. Guidance for Industry and Other Stakeholders, Toxicological Principles for the Safety Assessment of Food Ingredients revised July 2007. <http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm2006826.htm>.