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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.

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.

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

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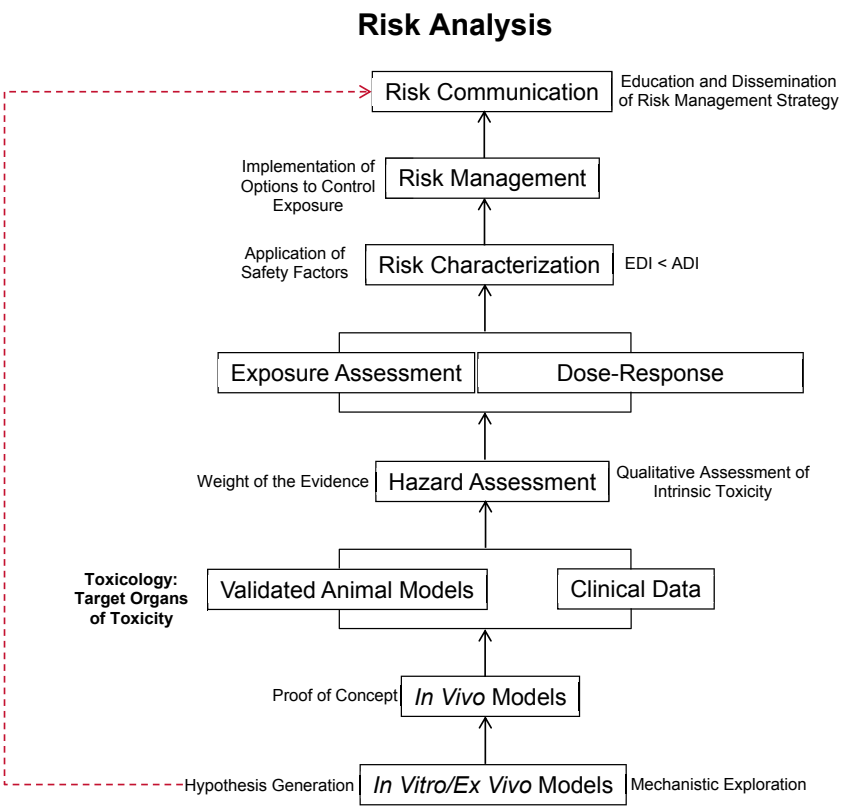

Fig. 1. Risk analysis.

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