

Food allergy and risk assessment: Current status and future directions

Benjamin C. Remington

TNO, Zeist, The Netherlands

Abstract. Risk analysis is a three part, interactive process that consists of a scientific risk assessment, a risk management strategy and an exchange of information through risk communication. Quantitative risk assessment methodologies are now available and widely used for assessing risks regarding the unintentional consumption of major, regulated allergens but new or modified proteins can also pose a risk of *de-novo* sensitization. The risks due to *de-novo* sensitization to new food allergies are harder to quantify. There is a need for a systematic, comprehensive battery of tests and assessment strategy to identify and characterise *de-novo* sensitization to new proteins and the risks associated with them. A risk assessment must be attuned to answer the risk management questions and needs. Consequently, the hazard and risk assessment methods applied and the desired information are determined by the requested outcome for risk management purposes and decisions to be made. The COST Action network (ImpARAS, www.imparas.eu) has recently started to discuss these risk management criteria from first principles and will continue with the broader subject of improving strategies for allergen risk assessment throughout 2016-2018/9.

Risk analysis is a three part, interactive process that consists of a scientific risk assessment, a risk management strategy and an exchange of information through risk communication [1]. In its purest sense, risk assessment is the scientific evaluation of known or potential adverse health effects resulting from human exposure to foodborne hazards. Risk assessment consists of four steps: hazard identification, hazard characterization, exposure assessment, and risk characterization [1]. Risk management is the process of weighing policy alternatives to accept, minimize, or reduce assessed risks and to select and implement appropriate options. In risk management, one accounts for the risk assessment results and other legitimate factors (political, technical, economical, societal, etc.) may be considered.

Risk communication is the interactive process exchanging information and opinion on risk among risk assessors, risk managers and other interested parties. As all manner of risks are evaluated with the same process, risk analysis for food allergens does not differ in concept from other risks associated with foods. However, while methodologies and principles of risk assessment in food safety have developed and become harmonized to a large extent worldwide over the past half century, the risks addressed are mainly those posed by chemical, microbiological and physical hazards.

Within risk assessment, hazard identification is the recognition of a particular component in foods associated with potential or known health effects [1]. The hazard in food allergy is a specific protein (or perhaps carbohydrate) that can cause sensitization and allergic reactions on subsequent exposures. Multiple proteins within a single food can be sensitizing agents and any of them can be the cause of an allergic reaction [2]. Additionally, proteins from one allergenic food can cross react with proteins in foods from a number of categories including fresh fruits, vegetables and legumes, as is known with the major allergen in birch pollen, Bet v 1 (3). Sensitivity to a cross-reactive carbohydrate determinant (CCD) can have broad implications and lead to reactions after consumption of multiple foods



previously allowed in the diet (i.e. alpha-gal in beef, pork or lamb) [4]. Food allergens and exposure to them are not a risk to the majority of the population; however, individuals within the food-allergic population risk potentially life-threatening reactions upon consumption and must take their avoidance diets seriously.

Hazard characterization is the qualitative and/or quantitative evaluation of the nature of the adverse effects. If data are obtainable, a dose-response assessment should be performed [1]. As commonly known and reported by others, a wide range of symptoms can be experienced by food-allergic individuals upon exposure to the offending food. It is important to note that not all allergic reactions are life-threatening. Some food-allergic individuals will never experience a severe reaction and their symptoms range from very mild, such as itching and flush, while others can experience a severe drop in blood pressure and bronchospasm. The reasons for the differences in reaction severity are not fully understood, but many factors are expected to play a role [5]. The minimal eliciting dose (MED), or threshold, also varies widely across foods and across the entire population of individuals allergic to any specific food [6–9]. Double-blind, placebo-controlled food challenges (DBPCFC) can be used to quantify an individual food allergen thresholds in a clinical setting, preferably with objective symptoms as the endpoint. Dose-response curve assessments can then be conducted by risk assessors using the DBPCFC results to determine the population threshold for a particular allergen. Data now exist to conduct quantitative, dose-response based risk assessments for a number of food allergens.

Exposure assessment is the qualitative and/or quantitative evaluation of the likely intake via food and other sources if relevant [1]. For a food allergen risk assessment, two main variables shape the exposure patterns: likelihood of consumption and the amount eaten. First, exposure will only be relevant if the allergic individual at risk consumes the particular allergen-containing product of interest. Second, the outcome of the risk assessment will be influenced by the amount of food eaten by the individual and thus the amount of allergen. Population-based dietary intake surveys exist for a number of countries and are regularly used by risk assessors in all fields but there is no consumption database available solely for food-allergic consumers. Until food allergy specific surveys are completed, with proper controls, risk assessors must assume that if an allergic individual chooses to consume a product, they consume it in the same amount as non-allergic individuals. Assumptions regarding frequency of consumption are more difficult as it is well known that allergic consumers are brand loyal, share experiences and will avoid perceived “risky” products and product categories. Additionally, some allergic consumers will ignore warning labels and purchase products that have allergen advisory statements [10]. While uncertainty exists regarding the consumption patterns of allergic consumers, use of the overall population consumption patterns is considered a suitable surrogate until dietary surveys are designed specifically for the allergic individual. However, as with all parts of a risk assessment, the assumptions involved during the exposure assessment must be stated and understood.

Risk characterization is the integration of hazard identification, hazard characterization and exposure assessment into a qualitative and/or quantitative estimation of the adverse effects likely to occur in a given population, with the attendant uncertainties [1]. Food allergy was a relatively late arrival to the field of food safety hazards and real progress in method development to ensure consumer protection is fairly recent in comparison to other fields (chemical, microbiological and physical hazards). In the past 30 years, true progress has been made regarding analytical methods for detecting the presence of allergens in foods and a deeper understanding of food allergy has been obtained through clinical research. In the past 15 years, knowledge has begun to accumulate regarding the sensitivity of food-allergic individuals from observed thresholds during large scale, structured clinical food challenges (DBPCFC) [6–9]. This growth of knowledge has enabled the development of methods for assessing the risk to food-allergic consumers from oral exposure to known allergenic food proteins already present in the diet [11–14]. Quantitative risk assessment methodologies are now available and widely used for assessing risks regarding the unintentional consumption of major, regulated (EC 1169/2011) food allergens [15,16]. Similar combinations of DBPCFCs and quantitative risk assessment methods may also be applied to assessing potential allergenic risks due to cross-reactivity

between new or modified proteins when the new protein will likely to be a risk for persons with food allergies to similar known allergens, e.g. the novel food mealworm cross-reacting with shrimp [17,18]. However, new or modified proteins can also pose a risk of *de-novo* sensitization, leading to the development of new food allergies. The risks due to these possible new food allergies are harder to quantify.

Adaptive immune responses, such as allergy, consist of two phases: sensitization and elicitation, which must be analysed separately. An expert panel of ILSI Europe recently published a framework allowing for the categorisation and prioritisation of allergenic foods in accordance with their importance to public health. Within that framework, the expert panel also proposed a scheme to also systematically apply the terms and principles to the interconnected risk analysis processes for the distinctly separate sensitization and the elicitation phases of IgE-mediated food allergy [19]. The first phase to be analysed in the risk analysis process is that of sensitisation to the allergenic food. The prevalence of allergy and the sensitivity of the allergic population (i.e. individual thresholds during DBPCFC) are the outcomes from the risk analysis for the sensitisation phase and are also the hazard input for the elicitation phase risk analysis (figure 1). During the sensitization phase, an allergenic food's sensitising potency, in combination with the pattern of exposure, determine the prevalence of sensitisation, subsequent prevalence of allergy and the sensitivity of the allergic individuals. During the elicitation phase, the prevalence and sensitivity of the allergic individuals, in combination with exposure, determine the frequency and severity of allergic reactions. During the elicitation phase (after the risk has been identified), exposure is not an independent determinant, as risk management measures (labelling, education) could influence the level of exposure in the allergic subpopulation. Thus, the frequency and severity of allergic reactions may be a reflection of risk management techniques and not only the potency of the allergen. Quantitative approaches to assess the risk posed by substances in the eliciting phase (reactions in already sensitized individuals) are proving very successful [15,20,21]. However, dose-response relationships in the sensitization phase are harder to study. Sensitization seems to be a non-linear response, as similar levels of exposure can lead to either tolerance or sensitization. To complicate matters further, the relationship between sensitization and elicitation is complex in allergic individuals. Additionally, the form and route of exposure to new proteins also impacts sensitization and allergenicity risks.

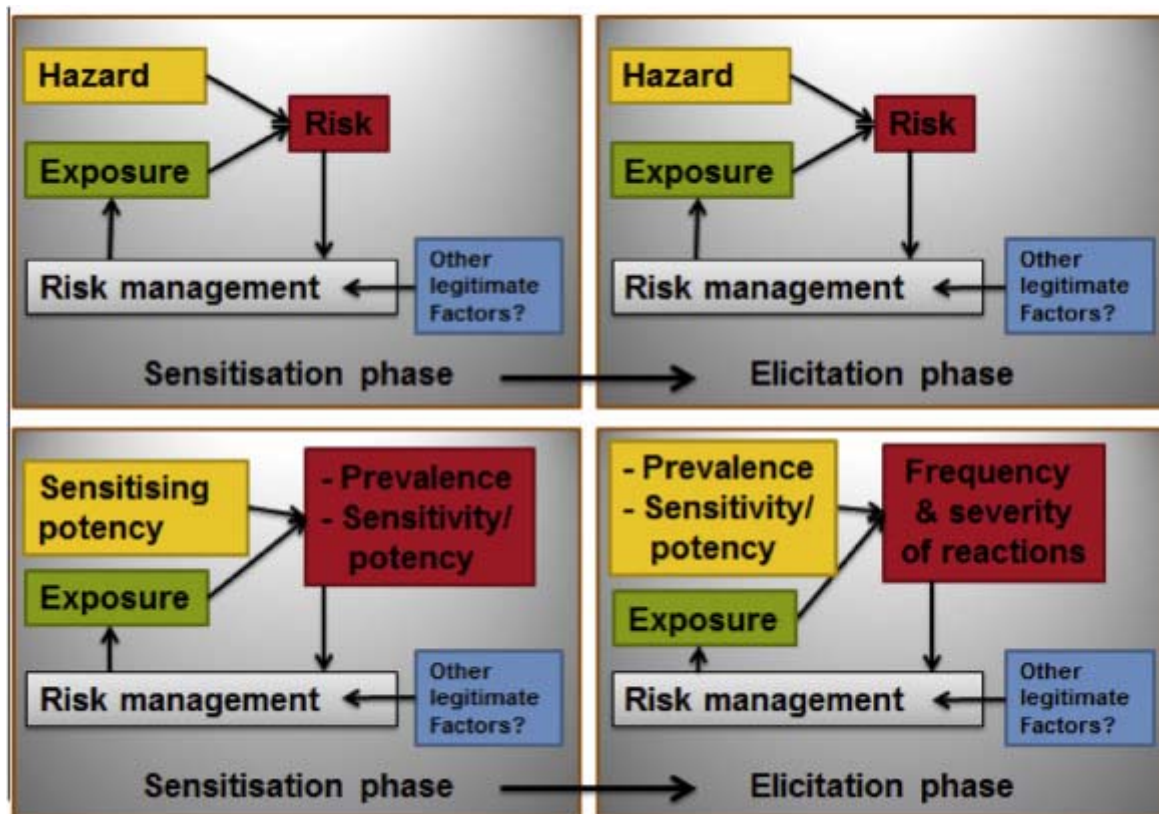


Figure 1. Reproduced from Houben *et al.* [19]. The generic risk analysis cycle (top) applied to food allergy (bottom). The prevalence of allergy and the sensitivity of the allergic population (i.e. individual thresholds during DBPCFC) are the outcomes of the risk analysis for the sensitisation phase and are also the hazard input for the elicitation phase risk analysis.

Previous and current guidelines developed for food allergy focus on hazard analysis in already sensitised individuals and rely mainly on structural characteristics of the protein involved. Similarly, the available tools to predict allergenicity of a new food or protein analyse cross-reactivity due to their reliance on properties of known allergens. Current testing of new proteins assesses risks due to cross-reactivity/co-sensitization, but fewer options are available to identify and characterise the risks from *de-novo* sensitization. No single test is currently available, nor is one expected in the near future, for predicting and characterising *de-novo* sensitization potencies of new proteins. To date, there are no *in-silico* or *in-vitro* approaches that could be used to identify the sensitization potential of a protein or the subsequent potential to elicit a clinical reaction. The only tests currently fit to identify induction of specific IgE from a new protein are *in-vivo* models, either in animals or humans, although many limitations exist both scientifically and ethically with regard to these tests. Additionally, uncertainties in characterising differences between tolerance and allergenicity are present in these *in-vivo* models. Allergic responses in the human body are extremely complex and an overall mechanistic model (or adverse outcome pathway, AOP) for food allergy does not yet exist, despite extensive research. Arguably, the development and use of novel protein sources is restricted due to the limited ability of current testing strategies to predict sensitization. However, for the safety of our future food supply, it is critical to find more sustainable protein sources. Thus, there is a need for a systematic, comprehensive battery of tests and assessment strategy to identify and characterise *de-novo* sensitization to new proteins and the risks associated with them. This overall strategy should incorporate all relevant intrinsic protein properties, aspects of exposure and matrix/processing effects.

New potential allergenic hazards are currently managed through avoiding exposure. Risk managers can avoid exposure of an allergen to the population by not authorizing the introduction of a protein

identified as a new allergen into the marketplace or possibly earlier in the process by identifying potential allergenicity early in development and cancelling the project. Labelling can be utilized to alert consumers with existing sensitivities to the presence of a potential hazard (e.g. rapeseed protein isolate and individuals with existing mustard seed allergies potentially at risk for reaction). However, food proteins with a high sensitizing potency cannot have their public risks mitigated through labelling alone. Post-launch monitoring exercises should be considered and are expected to provide an early indication of any unexpected development of allergy after introduction of a novel food to a new population or market. Any indication of allergenicity should then trigger the initiation of risk management measures. While resource intensive, post-launch monitoring is viewed as a necessary tool and others have previously discussed the possibilities and limitations in the context of novel foods and unintended health effects or allergenicity have been critically discussed [22,23].

Development of a comprehensive, coherent risk assessment strategy would benefit greatly from a clear definition of criteria for distinguishing between proteins of high and low allergenicity (i.e. ability to induce IgE, potency to induce IgE, expected prevalence of IgE-sensitization, expected prevalence of allergy, expected exposure, expected eliciting potency, expected frequency of reactions, expected frequency of severe reactions). It is important to establish first what we need to test for in order to define the requirements of new methods, and this is, in turn, dependant on what risk we want to manage. Do we want to prevent only the extremes (i.e. that no people die or that no single individual is sensitized) or could we accept a certain level of risk regarding sensitization and allergic reactions? As indicated above, the risk analysis outcome is based on an interactive process between risk assessment and risk management. These are not independent of each other, as a risk assessment must be attuned to answer the risk management questions and needs. Consequently, the hazard and risk assessment methods applied and the desired information are determined by the requested outcome for risk management purposes and decisions to be made. Likewise, if new methods for hazard and risk assessment are to be developed, then the methods, the information needed and the requested outcomes all depend on the information that is going to be requested for the risk management goal or decision to be made. It is an important step in the coming period regarding novel food allergen risk assessment and it is critical that parameters and criteria for risk management decision making are clearly outlined. Once risk management criteria are defined, risk assessors could apply or develop the appropriate tests as needed to investigate the relevant protein characteristics. The COST Action network (ImpARAS, www.imparas.eu) has recently started to discuss these criteria from first principles and will continue with the broader subject of improving strategies for allergen risk assessment throughout 2016-2018/9.

It is important to demonstrate a proof-of-principle for any chosen approach, to establish that the methodologies are able to distinguish between, and rank allergens of different potency appropriately. As scientific knowledge progresses, improvements to the methodologies used in allergenicity risk assessment should be possible. New development of biologically relevant *in-vitro* or *in-silico* methods should open new possibilities, and reduce animal and human testing while improving the safety and risk management of introducing novel foods into the diet. It is going to be crucial to identify those approaches, methods and technologies on which future research efforts should be focussed and a better understanding of AOPs could guide the development of better *in vitro/vivo* allergenicity testing methods. As the perfect tests have not yet been identified, it is, therefore, important to leave flexibility within any regulation or guidance to account for improvement of methodologies regarding food allergy and allergen risk assessment.

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