

SPECIAL GUEST EDITOR SECTION: FOOD ALLERGENS ORGANIZATIONS AND PROJECTS

ILSI Europe's Food Allergy Task Force: From Defining the Hazard to Assessing the Risk from Food Allergens

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The International Life Sciences Institute (ILSI) Europe Food Allergy Task Force was founded in response to early public concerns about the growing impact of food allergies almost coincidentally with the publication of the 1995 Food and Agriculture Organization-World Health Organization Technical Consultation on Food Allergies. In line with ILSI principles aimed to foster collaboration between stakeholders to promote consensus on science-based approaches to food safety and nutrition, the task force has played a central role since then in the development of risk assessment for food allergens. This ranged from consideration of the criteria to be applied to identifying allergens of public health concern through methodologies to determine the relationship between dose and the proportion of allergic individuals reacting, as well as the nature of the observed responses. The task force also promoted the application of novel, probabilistic risk assessment methods to better delineate the impact of benchmarks, such as reference doses, and actively participated in major European food allergy projects, such as EUROPREVALL, the European Union (EU)-funded project "The prevalence, cost and basis of food allergy across Europe;" and iFAAM, "Integrated approaches to food allergen and allergy risk management," also an EU-funded project. Over the years, the task force's work has evolved as answers to initial questions raised further issues: Its current work program includes a review of analytical methods and how different ones can best be deployed given their strengths and limitations. Another activity, which has just commenced, aims to develop a framework for stakeholders to achieve consensus on acceptable risk.

The International Life Sciences Institute (ILSI) was formed in 1978 with the aim of providing a forum for scientific debate, bringing together academia, regulators, and industry and thereby helping to deliver a science-based consensus on issues of food safety and nutrition. ILSI Europe was founded in 1986. Its modus operandi was to deliver its mission through task forces focused on a specific broad area of science. ILSI Europe's Food Allergy Task Force was founded in 1995 at around the same time as the report of the Food and Agriculture Organization (FAO) Technical Consultation on Food Allergies was published (1).

Context

Food allergy has been long recognized as a clinical phenomenon, with numerous reports in the 20th century medical literature (2–4), but it remained largely a medical curiosity until the late 1980s/early 1990s. At that point, regulatory authorities, faced with increasing numbers of well-publicized incidents of severe and sometimes fatal reactions to allergenic foods, started to view it as a food safety issue. A key milestone was the initiative by the Nordic countries in the early 1990s to draw up a list of priority allergens and propose to amend the Codex Alimentarius's 25% rule. (The 25% rule allowed food producers to list a compound ingredient without mention of its individual constituents, provided it did not exceed 25% of a product.) This activity led to the FAO-World Health Organization consultation in 1995, which identified eight major foods or food groups as responsible for the majority of the food allergy burden (1). Although epidemiological data were scarce, studies supporting the authorities' new perception soon emerged (5). These began to reveal the true public health dimension of food allergy in terms of its prevalence and diverse manifestations. Allergens were (and remain) an increasing concern both for consumers and for food businesses of all types.

Recognition of food allergy as a public health issue led to initiatives by public authorities, and, subsequently, legislators, in response. At the start of the 21st century, legislation was introduced in many countries and regions, including Australia–New Zealand (6), Japan (7), the European Union (EU; 8), and the United States (9). At the time of this writing, 27% of countries, encompassing 44% of the world's population, have legislation relating to food allergens. In parallel, many food-manufacturing companies also recognized the importance of food allergy and their responsibilities to their food-allergic consumers.

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ILSI Europe recognized early-on the importance of food allergy as a food safety issue. It published its first Concise Monograph in 1994 on the topic, “Food Allergy and Other Adverse Reactions to Food” (10), before putting in place a task force on “Food Allergy and Intolerance” (simply “Food Allergy” since 1999) under the scientific guidance of eminent allergologist Jean Bousquet. Originally, the following challenging objectives were set:

(1) To establish criteria to identify allergens of concern based on scientific consensus and considerations, such as prevalence, severity of reaction, and exposure.

(2) To establish a list of true allergens.

(3) To determine the feasibility of establishing threshold doses at which allergens will not trigger a reaction in sensitive individuals.

Subsequent work by the task force has broadly followed the initial remit, illustrating the challenging nature, as well as the ambition, of the objectives. It also extended it to other areas where this was warranted by scientific and public policy developments, as illustrated in Table 1.

Overall, the history and work of the task force can be mapped onto the risk analysis paradigm described by the International Program on Chemical Safety (11). The different components of risk assessment have formed the focus at different times, starting with identification of the hazard, followed by hazard characterization, including a consideration of prevalence and exposure, and, finally, risk characterization. As the task has developed, the expertise required has changed and stakeholder involvement has broadened. In particular, moving beyond the strict tripartite model (academia, government, and industry), the Food Allergy Task Force integrated allergic patient organizations into many of its expert groups.

The Early Years: Hazard Identification and Preliminary Characterization

In the Food Allergy Task Force’s seminal 1998 paper, Bousquet et al. (12) articulated their objectives to (1) propose scientific criteria to define allergens that would require the foods containing these substances to be labeled, (2) evaluate the suitability of the criteria upon review of the scientific literature on food allergy, and (3) determine which food allergens meet the criteria of objective 1. The authors considered that, at the time, only two criteria could be used to establish whether specific foods should be on a list of allergens: double-blind placebo-controlled food challenge (DBPCFC) data on the food of interest and evidence that the food can cause anaphylaxis. They recognized that further criteria, such as prevalence of allergy, could be added later, but available data were inadequate at the time. They reviewed the FAO priority allergens, critically analyzed the evidence, and found that those allergens merited their listing, with the possible exception of molluscs included

under “other shellfish” in the absence of DBPCFC data. Among other allergens they examined, only sesame seed also met the criteria. In the present work, the task force set out a baseline for defining foods for allergen management purposes, and, significantly, endorsed the DBPCFC as the key element for identifying the nature of the hazard in contrast to approaches that had prevailed until then that relied on more anecdotal evidence. The initial work defining criteria in the 1998 paper was developed and refined through a series of expert groups up to the present day (13–16). Taken together, this body of work evolved not only clear criteria for identifying priority allergenic foods, but also established a framework for transparent decision making based on additional criteria, such as the quality of data, allergenic potency, and prevalence.

Approaches to Hazard Characterization

Hazard identification is a key initial step in assessing and managing risks generally, but its value is limited if the hazards are not characterized, leading to the misallocation—and potential waste—of resources. The Food Allergy Task Force’s objectives recognized this issue, identifying the definition of thresholds as critical to this characterization and a vital step in developing benchmarks against which the dangers posed by unintended allergen presence were to be evaluated. Experience with DBPCFC showed that it was possible to establish maximum nonreactive doses, i.e., minimum eliciting doses, in individuals under carefully controlled conditions. However, the conventional toxicological approach of using such data together with an uncertainty (safety) factor to define benchmarks for allergen management soon revealed itself to be impracticable. Benchmarks derived using this approach proved far below those that could be practically applied, and, in many cases, adherence to them could not be assured as they were also well below the limit of detection (LOD) of available analytical assays. In an attempt to manage such uncertainties and communicate them, the food industry started to use precautionary allergen labeling, which is often referred to colloquially as “may contain” labeling. Although initially welcomed by organizations representing people with food allergies, the disadvantages of such labeling rapidly became apparent through its excessive and indiscriminate application, mushrooming into a major issue for allergen management (17). Also, in the absence of generally agreed-on standards and benchmarks, allergen management performance varied considerably across industry (and continues to).

These developments sharpened the need to characterize the hazard posed by allergens so that the risk could be assessed and managed properly. Expert opinion concurred that DBPCFC, with the correct design, could serve to characterize the hazard even though the test could only be applied under highly controlled conditions, often far-removed from those under which allergic people were exposed in day-to-day life. The approach pioneered

Table 1. An overview of some of the activities of ILSI Europe’s Food Allergy Task Force

To validate the established criteria for identifying allergenic foods of public health importance.

To define action levels for allergenic foods and for allergen management purposes.

To determine whether food processing may alter the allergenicity of the foods.

To develop a plan for a pan-European registry of allergic reactions.

To participate in the global dissemination of new data and approaches to risk assessment for allergenic foods.

by the Food Allergy Task Force asked whether DBPCFC threshold data could be modeled statistically, with a view to predicting the proportions of the at-risk population that would be likely to react to specified doses. This resulted in a proof-of-concept paper on dose-distribution modeling by Bindslev-Jensen et al. (18), which is illustrated in Figure 1.

This approach shares many features with the benchmark dose approach (19), which has gained support in the wider toxicological risk assessment world (20). Interestingly, the work also illustrates the use of this approach with data from human beings, i.e., the species of interest, in contrast to most other types of toxicological safety data. An expert group set up by the task force further refined the concept and its application, elaborating on its strengths and limitations (21) and setting out considerations around implementation. Dose-distribution modeling became the preferred method for characterizing allergen hazard and was adopted for major projects, such as European Union-based projects, “The prevalence, cost and basis of food allergy across Europe” (EUOPREVAL; 22) and “Integrated approaches to food allergen and allergy risk management” (iFAAM; 23). However, probably the most significant impact came from the development by the task force of the work of the Voluntary Incidental Trace Allergen Labeling (VITAL) Scientific Expert Panel (24–26), which concluded that application of these models has provided valuable insights, leading to further refinements and generating testable hypotheses.

Impact of this work, initiated by the Food Allergy Task Force, has been wide. The concept of dose-distribution modeling remains largely unchallenged as the methodology for defining allergen benchmarks for risk management, even though translation into practice has been slower than anticipated. Together with consideration of exposure, it illustrates well the quantitative risk assessment-based approach of the type that the U.S. Food and Drug Administration Threshold Working Group recognized and provides “the strongest, most transparent scientific analyses to establish thresholds for major food allergens” (27).

Risk Assessment

Risk assessment takes place at both individual and population levels. Although both levels need to be taken into account, the remit of the Food Allergy Task Force has always rested clearly with the public health dimension. Determining risk from exposure to allergens requires consideration of the hazard, as already characterized, but needs to integrate quantified exposure. One critical aspect revealed by experience with dose-distribution modeling, although suspected even in the early years, was the near-impossibility of defining, for practical purposes, an amount of any allergen below which it could be confidently stated that all those susceptible would be protected against any reaction. It thus became critical to understand how many people could react under different exposure scenarios. An expert group was designated to study this problem “from thresholds to action levels,” holding a stakeholder workshop in late 2012 in Reading, United Kingdom (28), and publishing its findings in three key papers in 2014 (24, 25, 29). Key features discussed at the workshop and in the publications include the establishment of appropriate benchmarks for allergen management, such as the reference doses of the Australia–New Zealand VITAL 2.0 program (26) and the application of probabilistic risk assessment techniques (25). These approaches provide a sound scientific basis for managing allergens with due regard to the different and often conflicting requirements that must be balanced.

Evaluating whether prioritization and any further risk management measures have been successful requires data to be collected, and another expert group made a proposal for a pan-European registry of severe reactions (30). This initiative has been followed through by clinician members of the expert group as a project ultimately aimed at integrating and harmonizing separate national allergic reaction registries in Europe.

Both risk managers in industry who are responsible for food production, including management of allergens, and authorities who are responsible for verifying that foods are produced to a safe standard require tools and methods for validating and

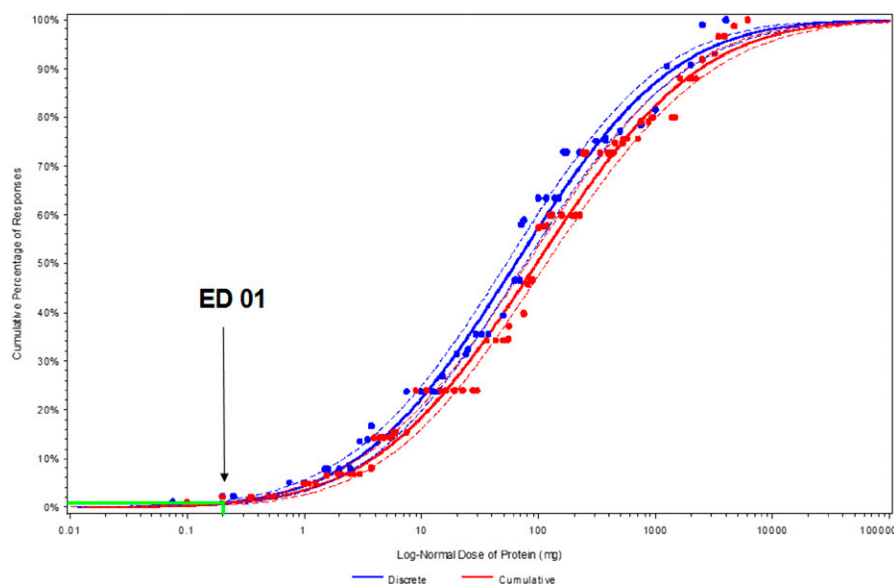


Figure 1. Dose distribution for peanut protein, based on 750 challenges (18). ED01: eliciting dose to trigger reactions in 1% of the allergic population.

verifying processes or checking that products truly do not contain specific allergens. Another expert group was recently commissioned by the Food Allergy Task Force to critically review available analytical methods and develop good-practice guidelines for their effective application, focusing on reliable measurement of allergen concentrations of the order implied by adherence to VITAL 2.0 reference doses. This work complements elements of the major projects actively supported by the task force, EUROPREVAL and iFAAM, which aimed to improve food allergen risk management and, therefore, the protection of people with food allergies.

However, currently, the quantitative risk assessment methodologies detailed in those publications (and elsewhere) can only describe the risk in terms of the number of reactions that may occur under the conditions of the assessment. An important dimension of risk is the nature of the adverse outcome, i.e., how severe a reaction is likely to be. The task force thus formed an expert group to review knowledge on the contribution of the amount of allergen (exposure) to severity and determine whether such knowledge could be used to refine the risk assessment and determination of appropriate benchmarks. The findings of this review were discussed at a stakeholder workshop in late 2016 in Brussels, Belgium (31), and will soon be published.

Conclusions and Future Directions

The Food Allergy Task Force has made a significant and enduring contribution to risk assessment and management of allergens over two decades. Its work has helped demystify allergic reactions and provided a sound basis for quantitative risk assessment, which can now be performed with confidence. Recent single-dose challenge studies have begun to confirm the eliciting dose to trigger reactions in 5% of the allergic population (ED05) in wider and more diverse populations, as well as establishing safety in relation to the symptoms provoked (32). Nevertheless, allergic reactions are still feared, and both their occurrence and outcome are considered by many to be unpredictable. Acceptance of quantitative risk assessment approaches remains suboptimal, hindering the adoption of generally agreed-on allergen management principles. The Task Force plans to address this knowledge gap by developing approaches that foster a better understanding of these issues across different groups of stakeholders. In line with this, the task force has started a new expert group to consider how different stakeholders could work effectively together to generate consensus on what risk can be considered acceptable or tolerable, building on earlier work in EUROPREVAL.

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