

EDITORIAL

How allergenic is food?

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There is much confusion concerning food allergy. The true prevalence of food allergy is unknown, although most researchers and clinicians would agree that documented IgE-mediated food allergy is most common during the first 3 years of life. Estimates are around 1–2% of the adult population and about 6% in young children [1]. Perceived intolerance or idiosyncrasy to various foods are much more common, however, and often referred to as 'food allergy' by lay people, while the term 'food allergy' is medically defined as an immunologically mediated hypersensitivity to a defined food [2]. Thus, there is a large gap between patient perception of 'allergy' or intolerance to food and what the Medical Community accepts as food allergy.

The risk of suffering an allergic reaction is a function of the potency of the allergen to elicit a reaction, the manufacturing process, the amount of ingested allergen and the sensitivity of the individual. Sensitivity in turn may vary considerably over time, even in the same individual. As current labelling of manufactured foods is often not reliable and the food may contain allergenic components, many food-allergic individuals have imposed strict limitations on what food products they dare to buy. Adequate labelling would alleviate this burden on their daily lives, particularly for the majority of food allergic individuals who are only moderately sensitive. Such labelling would, however, also help many more than those who have a documented food allergy. The stress of coping can be substantial also among individuals with merely a fear of food allergy [3]. Unwarranted restricted diets [4] and failure to thrive in children as a consequence of unnecessary dietary restrictions [5] are well known among paediatricians and would be less common if the labelling of foods could be generally trusted.

The most allergenic foods worldwide are egg, milk, fish, crustaceans, peanut, soybean and tree nuts. In a recent analysis of the literature, foods with confirmed allergenicity were listed and suggested to be included in product labelling of manufactured food products [6]. All proteins in a certain food are not allergenic, however, and allergenicity can therefore not be expressed merely by declaring the amount of the food. Unfortunately, currently available information on potency and thresholds of food allergens is insufficient to allow a systematic ranking for all, but the most potent allergens. There is a need to find methods to define the allergenic potential, i.e. the biologic activity in sensitive individuals. Such methods require access to patients who are highly sensitive and representative for those who are clinically sensitive to the food in question. By selecting a representative panel of such individuals, it would in principle be possible to identify threshold levels, below which the risk for a clinically significant reaction to a certain food is low. Identifying such threshold levels would be of major significance for food-allergic individuals and for the food industry.

Standardized diagnostic procedures and well-defined diagnostic criteria are essential if we are ever to know the incidence and prevalence of food allergy, to recognize different pathophysiological mechanisms and to identify and protect individuals at a high risk of suffering severe reactions to certain foods. Standardized double-blind, placebo-controlled food challenge (DBPCFC) is currently the only universally accepted procedure to confirm the presence of a food allergy, and several procedures have been published [1, 7, 8].

Avoidance of the offending food is currently the treatment of choice. While this is easy for some uncommon foods and for the offending food in a pure form, it may be difficult to achieve for certain highly allergenic foods that may be present in an invisible form in places where they are not expected. For example, while it may not be too difficult to recognize and avoid eating an egg or drink a glass of milk, low amounts of egg and milk proteins may be invisibly present in, e.g. sausages and bread, or inconspicuously labelled as 'high protein flour' or 'caramel flavouring'. Soy protein is widely used in processed foods and it can be hidden under label ingredients like 'vegetable starch' or 'vegetable broth'.

There has been much discussion regarding to which extent the content of processed food products should be labelled. The decision is not always easy to make. On the one hand, trace amounts of a highly allergenic protein in a food may cause severe anaphylaxis if eaten by a very sensitive person. Failure to indicate the presence of the allergen on the label may result in a liability suit. On the other hand, routinely labelling all processed foods with, e.g. 'may contain egg, milk or soy protein' would be unnecessarily warning for the wolf. Therefore, it is important to recognize threshold doses for various allergenic foods, which would be safe for the vast majority of individuals who are allergic to the food in question. It is not reasonable, however, to set the levels so low, as to exclude that any individual under any circumstances could react. Obviously, there is a trade-off between practically important information for almost most patients, and safety for the single most sensitive individual in the population.

Against this background, an important step has been taken by a group of experienced and internationally respected clinicians and scientists, who have developed a practical protocol for the determination of the threshold doses for allergenic foods. The consensus protocol developed by the group, and which is reported in the current issue of the journal [9], is an important starting point for defining standards for the amount of allergens that could be accepted in processed foods without labelling. If we could find such a tolerance level

suitable for all patients, patient care and food avoidance measures would be greatly improved. Unfortunately, we are not yet there.

There are already published standardized protocols for how DBPCFC should be conducted in a clinical setting [1, 7, 8]. They are essential tools in the diagnosis of food allergies. However, the lowest doses of food allergens used in the diagnostic tests are not standardized, but based upon the judgement of the clinicians for each patient. The novelty of the consensus protocol published in this issue of *Clinical and Experimental Allergy* [9] is the effort to design ways to define reasonably safe threshold levels. This would have considerable practical and legal aspects, and it would certainly meet a need on the market.

For several reasons, the consensus protocol would and should not be used in clinical practice in an unmodified form and it certainly does not replace currently employed DBPCFC protocols. Rather, the consensus protocol could be used in multi-centre research projects in order to define reasonably safe threshold levels. The definition of 'reasonably safe' in the general public is a delicate balance between safety to the overwhelming majority of allergic individuals, yet being reasonable from a practical point of view. If food manufacturers would routinely label too cautiously and hide behind a sentence stating that the product 'may contain' a certain allergen, then allergic individuals will be excluded from eating that food and unnecessary limitations are imposed upon their life. It would also exclude many more than those who are truly food allergic, as perceived adverse reactions to certain foods are considerably more common [10].

The outcome of studies defining threshold levels for allergen content food products will have major medical and economic consequences, as they will guide manufacturers, authorities and the public. They have to meet strict criteria with regard to standardized methodology and documentation. Such studies should therefore only be conducted in a limited number of highly qualified centres. The centres could collaborate closely in a network, adhering to the strict standards of Good Clinical Practice and provide authorities and industry with the information. Once the threshold levels are biologically defined, future quantitation of allergen content in various foods can be carried out with sensitive immunochemical assays in the laboratory.

Several issues have to be adequately addressed when identifying threshold levels for allergenic foods. First, the food allergens have to be characterized and be possible to quantitate. This is now the case for several of the most allergenic foods, as the most allergenic proteins in e.g. egg, milk, fish and soy have been identified. It is in principle possible to quantitate the allergenic activity of a food product and it would be possible to monitor allergen content continuously in subsequent batches of a product. Second, clinically significant threshold levels should be defined in relevant patient populations. The consensus document [9] perhaps does not go all the way in this respect. Ideally, one would test very sensitive patients, who are at risk of suffering a severe reaction if eating even small amounts of a certain food. As such patients may have a scarring history of a life-threatening reaction, some Review Boards would find it ethically questionable to recruit them into a study, which only aimed to define the threshold level and that would not offer

any real benefit to the patient. Therefore, studies may mostly have to be carried out in slightly less sensitive individuals and institutions where such procedures would be acceptable. As suitable patients are not very common, the recruitment of participants may take considerable time. This underlines the need for centres with the necessary expertise to form networks in order to collaborate closely and secure comparable data, which can be pooled. It is reasonable to suggest that the establishment of such networks of excellence is funded jointly by industry and the appropriate authorities.

A third important issue to be considered is the extreme care that has to be taken in the preparation of low-dose challenge material. Preferably, this should be carried out with access to specialized pilot plant facilities, as there would otherwise be concerns about, e.g. quality of the raw material, adequate mixing of the challenge material and possible contamination of the product.

The idea to identify threshold levels for food allergens in a representative panel of individuals who are highly sensitive to the food in question is similar to the process developed for standardizing allergen extracts for vaccination in the early 1980s. The potency of earlier allergen preparations used for immunotherapy was determined by their protein nitrogen content or merely as the extraction ratio (weight/volume). Already in 1972, it was reported that the potency of such extracts from different manufacturers and batches from the same manufacturer differed 100–1000 times in potency, as determined by RAST inhibition [11]. It was also observed that some allergen extracts usually were considerably more potent than other allergen preparations. Therefore, it was not surprising that severe reactions could occur unexpectedly during a treatment and that the clinical efficacy varied. This situation is comparable to the current regarding allergenicity of foods, where the actual allergenicity depends not only on the amount of allergenic raw material used in the manufacturing process but also on the source of the material and how it was handled during the food manufacturing process.

In order to overcome the lack of any biologically relevant standardization for allergen extracts, Aas et al. [12] in 1978 proposed that they should be standardized against biological reactivity as measured by quantitated skin prick tests in a panel of representative patients. A few years later, a line of allergen extracts with a potency determined by the results of standardized skin prick tests in panels of sensitive patients was launched [13–15]. Once the amount of allergen giving a positive skin prick test reaction in a panel of 'typical patients' was defined, this batch was used as a standard, against which future batches were compared by immunochemical methods and the potency of the extracts could be expressed in 'biological units', rather than by protein nitrogen content. 'Biological standardization' of foods would not require the use of reference batches, however, as we can today identify and accurately quantitate many of the most important food allergens that would remain in the end product [16, 17]. It is only a matter of time and priority when virtually all common food allergens could be identified. Once the threshold levels are identified, below which a food could be safely eaten by the allergic individual, analysis of the allergen content in the final food product aimed for the market can be continuously monitored in the laboratory.

The consensus document [9] would be of limited use to most clinical settings, in which food-allergic patients are diagnosed and managed, as in most cases current published procedures for food challenges are adequate [7, 8, 18]. It does, however, represent an important contribution, as it suggests a road along which we eventually may reach international agreement on labelling issues. The document adds substantially to a previous paper, in which efforts were made to define scientific criteria for the selection of allergenic foods for product labelling [6]. Statistically, it is impossible to prove 100% safety for everyone and it is not possible to conclude that the most sensitive person in the world would not react. But it would protect the vast majority and that would be a huge advance over the current situation for consumers trying to practise avoidance. This contribution [9] could be the starting point for the process and it is now up to authorities and organizations like the International Life Science Institute (ILSI) to develop the concept further.

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