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## Industrial dimensions of food allergy

R. Crevel<sup>1</sup>

SEAC, Unilever, Sharnbrook, Beds. MK44 1LQ, U.K.

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### Abstract

Serious attempts to estimate the impact of allergic reactions to foods on public health did not begin until the 1980s. Until about 15 years ago, food allergy was considered a minor aspect of food safety. Two developments probably prompted a radical re-appraisal of that situation. The first was the apparently inexorable rise in the prevalence of atopic diseases, of which food allergy forms a part, with its possible consequences highlighted by some well publicised severe reactions. The second was the growth of genetic modification technology, manifested by the commercialization of transgenic crops. Each of these developments impacted on the food industry in distinct ways. On the one hand, food-allergic consumers had to be enabled to avoid specific allergens in products formulated with existing ingredients. Food manufacturers therefore had to identify those specific allergens down to trace amounts in all the ingredients forming the product, and label or remove them. On the other hand, the introduction of products using ingredients from novel sources required an assessment of the allergenicity of these ingredients as an integral part of safety assurance. The approaches used by the food industry to protect existing allergic consumers and those at potential risk of sensitization by novel proteins will be illustrated, emphasizing how they need to be built into every stage of the life cycle of a product.

### Introduction

Food allergy has been long recognized as a clinical phenomenon, with numerous reports in the 20th Century medical literature [1–3]. However, while it was known that patients could suffer extremely severe and sometimes fatal reactions following ingestion of minute amounts of the offending food, food allergy was perceived as a problem for the sufferers as individuals. Over the last two decades, however, food allergy has become recognized as a public health problem. A major factor in this

increased concern is probably the rise in the prevalence of atopic disease [4], which can be considered a manifestation of food allergy. The prevalence and incidence of food allergy and the number of severe reactions [5] may be increasing, although the lack of sound baseline epidemiological data precludes firm conclusions. The increasing interest has driven action by food manufacturers, retailers and regulatory bodies to ensure that the risk to food-allergic individuals is minimized. It has also helped to shape the regulatory requirements for the introduction of new proteins to the market, particularly, but not exclusively, those produced by modern biotechnology. This paper reviews the ways in which food allergy has affected the food industry and how it has met the challenges posed.

### Dimensions of food allergy

The term 'dimension' refers to two different concepts: size (i.e. how big is the problem and how many people does it affect?) and scope (i.e. what are the limits of the problem?). Both concepts are relevant to the current discussion.

The size of the food allergy problem relates to the prevalence of the condition and to the extent to which it affects quality of life. A consensus exists around a prevalence of 1–2% of the overall population, increasing to 5–8% in children [6,7], in whom food allergy is in part a phase of the development of an allergic condition [8]. In the European Union, this represents about 5–10 million people. However, the number actually affected will be several-fold larger, including, for instance, members of the immediate family or household. The prevalence of self-reported food allergy is many times greater than the true prevalence estimated from clinical measures [7]. The potential direct impact on the food industry through loss of sales, for instance, is therefore greater than suggested by true prevalence figures, although it would be difficult to quantify. A different way to look at the size of the food allergy problem is to consider the resources deployed to address it or the impact of compliance activities by different authorities. Thus the U.S. Food and Drug Administration recorded over 100 allergen-related recalls per year in the period 1996–

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Abbreviation used: HACCP, Hazard Analysis Critical Control Point.

<sup>1</sup>E-mail rene.crevel@unilever.com

2000. A large-scale recall, such as occurred in the context of Starlink corn, can cost a company several hundred million dollars.

The scope of the problem of food allergy refers to where the limits of responsibility lie for the different stakeholders. In some cases this is easy to define: diagnosis and treatment belong with the patient (consumer) and clinicians, with industry's role being limited to providing information on product formulations. Similarly, the food allergy sufferer is responsible for checking product labels. One of the prime responsibilities of the industry is to provide safe foods for all intended consumers. Preventing sensitization to existing common allergens would imply the removal of many wholesome foods from the food supply, and is not generally an option. However, food manufacturers can help people who know they suffer from a food allergy by informing them when the specific allergen is present in a product (labelling) or by ensuring that it is not present. While labelling or removing specific allergens from foods fully discharges the food manufacturers' responsibility in respect of commonly allergenic foods, society demands a more stringent test where novel proteins or foods are concerned. Specifically, the novel protein or food should not only not provoke reactions in individuals allergic to a specific allergen, but should be shown also to have little or no potential to produce IgE-mediated immune responses.

### **Challenges for the food industry**

Several obstacles lie in the way of achieving the objectives outlined in the preceding section. The most significant in relation to existing allergens is that total absence of a specific allergen from foods where it is not intended to be present is often very difficult to achieve, because of manufacturing practices. For instance, few production lines are used to manufacture a single product. To produce a safe product, the manufacturer therefore has to ensure that any residual allergen is below the level at which it might provoke reactions, even in highly sensitive individuals. However, individuals allergic to a food protein vary greatly in their sensitivity, with very low amounts documented as causing reactions [9,10]. The lowest eliciting dose (threshold) is therefore very difficult to define, although it is at least accepted that such thresholds exist [10]. This affects the decision to label, which must be driven by the need to protect consumers, rather than by the continuous refinement of analytical techniques and hence the ability to

detect ever more minute traces of allergen. It also influences the measures that must be taken to reduce or avoid cross-contact, the stringency (and therefore the cost) of which will depend, other factors being equal, on the level of allergen that must be reached. Such measures can reach a point of diminishing returns, whereby additional resources bring little additional protection. An interesting and unresolved issue about thresholds is whether repeated stimulation of some exceptionally sensitive allergic individuals through ingestion of residual allergens in sub-threshold amounts could result in such individuals becoming ultimately primed to react to those levels. Although the physiology of IgE-mediated reactions gives biological plausibility to such a scenario [11,12], there is currently no clinical evidence to support this hypothesis. However, should evidence emerge to support it, current risk assessment paradigms for food allergens would need to be revised. Another issue that is unclear at present is the relationship between sensitivity and severity of reaction. It is usually implicit in discussions that the most sensitive individuals are also those who experience the most severe reactions, but this is by no means formally proven.

The phenomenon of cross-reactivity between allergens, sometimes from unrelated sources, also challenges the aim to make foods safe for allergic individuals. While many instances have been documented experimentally, their clinical significance has not been studied to the same extent, and data are therefore lacking with which to assess potential risks from this type of exposure.

Another obstacle relates to demonstrating that a novel protein is not a potential allergen. Currently no single predictive test exists to identify and rank protein allergens, nor is knowledge about the relationship between protein structure and allergenicity adequate for the prediction of protein allergenicity [13]. Knowledge of the functional family to which a protein belongs can help us to form a judgement on the probability of it being allergenic, but is not sufficiently predictive on its own. The current paradigm is, therefore, that any novel protein is considered a potential allergen and must be assessed.

### **Food industry approach to allergen risk management**

#### **Management of known allergens**

Current approaches to the management of the allergen risk in the food industry recognize that it has to be integrated into the whole product life

cycle from its design right through to the point at which the consumer eats it. Major food manufacturers have devised specific corporate policies for the handling of allergens, supplemented by guidelines which provide practical advice to individual manufacturing units. These methods ensure that a high minimum standard exists for the handling of allergens throughout the company. For instance, Unilever has a policy for dealing with allergens which states that it shall declare the presence in its products of any allergen that is a common cause of allergic reactions. At a minimum, any allergen required by local regulations will be declared. However, beyond that, the allergenic risk from foods not commonly known to be allergenic may be assessed if clinical or epidemiological data indicate the need. If then classed as a common cause of allergic reactions, this food component would then be declared on labels and included in Hazard Analysis Critical Control Point (HACCP) plans. Unilever also undertakes to inform any consumer who asks about the presence of uncommon allergens in specific products.

As mentioned above, there are basically two ways of protecting allergic consumers: the first is to inform them, and the second is to ensure that the allergen is not present in products at levels sufficient to cause harm. Information is provided by appropriate labelling and should therefore be readily understood by the consumer. This means using generally understood terms, not technical ones, to name allergenic components. For instance, the term 'milk proteins' is preferable to 'whey powder' or 'casein', even though the latter are more technically accurate.

The second component involved in protecting the allergic consumer is to avoid the inadvertent presence of allergen in a product. Like most food manufacturers, Unilever has prepared guidelines to help avoid the inadvertent presence of specific allergens in food products. These illustrate well how this process requires consideration at all stages of the product life cycle, from its design, through the sourcing of ingredients to manufacture, labelling and distribution. Specifically, it needs to deal with the following points.

#### Innovation

Is the use of the allergenic ingredient necessary for the functionality of the product, or could an equivalent non-allergenic ingredient serve as well?

#### Supply chain

Control of allergens in the supply chain requires a close relationship with suppliers, so that they

understand our needs and can meet our requirements. Typically, the basis of the supplier assessment will be a questionnaire about allergens handled and precautions in place to avoid cross-contact, including the existence of a HACCP plan. This is backed up by periodic audits of the suppliers' facilities. Additionally, suppliers are required to seek agreement to any change in the formulation of the ingredient they supply.

#### Manufacturing protocols

These are another critical element. The main considerations are the inclusion of common allergens in HACCP plans, production scheduling to minimize cross-contact, validated cleaning procedures, and clear labelling and separation of specific allergenic ingredients within the factory. Procedures need to cover rework, where sound product is not packaged but 'recycled'. Staff training to understand the importance of allergen control procedures is vital, and improves support for what can be additional procedures in the production process. Finally, the same degree of attention is needed whether the company's own manufacturing facility or that of co-packers is concerned.

#### Packaging, promotion and advertising

Packaging carries the label and therefore the allergen information. Care is required to ensure that information remains with the product until it reaches the consumer. Other considerations include warnings if the formulation has changed to include an allergenic ingredient not present previously.

#### Retailers

Generally, the manufacturer's allergen information will be sufficient. However, situations such as in-store promotions require care to ensure that the consumer is fully informed. Sound product that fails to meet all standards for general sale may be repackaged and sold on in specialized outlets or even in a different market. The manufacturer needs to ensure that appropriate allergen information is retained and available to the ultimate consumer.

#### Food professionals

Most allergic reactions to foods occur outside the home, in conditions where the product is often not labelled and, even when asked, food professionals fail to provide correct information. Where prepared food is provided to that sector, the

manufacturer has a responsibility to ensure that accurate allergen information is provided and conveyed to the consumer.

### Assessment of the potential allergenicity of novel proteins and foods

The introduction of novel proteins requires an assessment of their potential allergenicity. Current strategies consist of systematically building up a body of evidence in order to form a judgement on the allergenicity of the protein (or food) of interest. One of the first such schemes was that proposed by International Life Sciences Institute/International Food Biotechnology Council [14], which was revised and updated by a consultation organized by the Food and Drug Administration/World Health Organisation in 2001 [15]. Those recommendations have since been revised by the Codex Alimentarius commission [16]. All schemes contain common elements. These include sequence analysis, investigation of IgE binding and measurement of resistance to proteolysis in the presence of gastric enzymes. Analysis of the primary sequence of the proteins serves to identify global similarity with known allergenic proteins or the presence of short matching sequences which would be possible epitopes. Investigation of IgE binding can look at both reactivity with other proteins from the same source and reactivity with potentially cross-reactive proteins, based on structural or functional similarities. Resistance to pepsin digestion is based on the observation that several well known allergens are hydrolysed relatively slowly in the stomach, and hence will reach the immune tissues of the gastrointestinal tract largely intact. All the schemes also allow for the possibility of human testing (e.g. skin prick testing) to confirm a lack of reactivity. The schemes differ mainly in the way that they allow for interpretation of findings. The two earlier ones were proposed as decision trees, which ineluctably led to a specific conclusion, but the current Codex Alimentarius proposals specifically endorse a weight-of-evidence approach.

### Conclusions

Food allergy is recognized as a significant public health problem. It can have severe and sometimes fatal consequences for a minority of sufferers, and

impairs the quality of life of other sufferers and their families. In addressing the issue, the food industry has faced many challenges. Meeting these challenges has required a systematic consideration of all the elements that contribute to a product, from the initial concept to the point at which it reaches the consumer. In particular, much closer links have been developed with suppliers, and manufacturing processes have been re-thought to reduce the risk arising from allergens. Nevertheless, gaps remain which place limits on the assessment of allergenic risks, including a lack of information about thresholds of reactivity and of good predictive tools to assess the allergenicity of novel proteins.

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