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Risk assessment for food allergy – the industry viewpoint

A safe food supply is a legitimate expectation of consumers, which the food industry must meet. Allergic reactions to food are recognised as a significant public health problem. Protecting allergic consumers against such reactions, while minimising the impact of food allergy on their quality of life, poses a challenge to the industry. Risk assessment is the process whereby the likelihood of an adverse event is related to exposure. Allergic reactions to foods can arise in one of three ways, which are not mutually exclusive. Firstly, a known allergen may be present in a food at a level above that at which the allergic individual reacts, secondly, an individual may react to a known or novel allergen because of sensitisation to another, cross-reactive, allergen and finally sensitisation may occur to a novel allergen, followed by reaction on subsequent exposure. A total absence of risk of reaction to an allergen implies no exposure, a situation which in most food manufacturing environments is unrealistic, and in any event would not help in the context of novel allergens. Possible approaches to risk assessment for food allergy in each of the contexts described above are examined, together with their limitations.

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Consumers expect, and the food industry must ensure, that its products will be safe for all consumers. If the products pose risks to specific groups of consumers (e.g. certain disease states, metabolic idiosyncrasies), these consumers should be protected against possible adverse effects by appropriate information being included on the food label or specific ingredients being excluded . Sufferers from food allergy, defined for the purposes of this paper as immunological reactions to foods mediated by IgE antibodies, is one consumer group that presents a major challenge to these objectives.

Food allergy affects about 1–2% of the total population in industrialised societies, and up to 8% of children, particularly young ones. In the European Union these numbers equate to about 8 million sufferers in total. For most allergic people, adverse reactions to foods limit their quality of life because of the symptoms they evoke (1). However, for a small minority, namely those who experience anaphylactic shock, food allergy is potentially lethal. There is also evidence that the number of people experiencing severe reactions, although still small, is increasing. For instance, in England, hospital admissions for which the primary diagnosis was anaphylactic shock due to food rose from 312 in 1996–7 to 406 in 1998–9 (2, 3). If this incidence of reactions is extrapolated to the whole EU population, this produces a figure of about 3000.

Risk assessment

The relationship between hazard, the intrinsic capacity to produce an adverse effect, and risk, the likelihood of an adverse outcome following exposure to the hazard, can be represented as:

$$\text{Risk} = f(\text{exposure}, \text{hazard})$$

When performed for a particular hazard (e.g. allergenicity), risk assessment is an evaluation of the probability of a specific adverse event given the nature of the hazard in question and the exposure to that hazard (4). Formal risk assessment consists of several well-defined steps:

- Hazard identification
- Hazard characterisation.
- Exposure assessment
- Calculation of probability (frequency) of adverse event (Risk characterisation)

Risk assessment: what do we want to achieve?

Living is a risky business; part of this risk derives from the consumption of food. An activity is considered to be safe when the risk is acceptable. A safe food will not be risk free. The aim of risk assessment in food allergy is not, and cannot be to reduce the risk of reactions to zero, but to make it as low as reasonably achievable, and thereby acceptable. What is considered as low as reasonably achievable is not a fixed number, but is largely dependent on society's perceptions of the issue. The level of risk accepted will, for example, be lower for severe reactions than for mild ones, and may also be

lower for foods that are not commonly consumed in a society than for those that are. In food allergy, adverse reactions may occur through three different scenarios:

1) Presence of a known allergen in a food at a level above that at which the allergic individual reacts
2) Reaction to a known or novel allergen because of sensitisation to another, cross-reactive, allergen.
3) Sensitisation to a novel allergen, followed by reaction on subsequent exposure

Clearly, scenarios 1 and 2, and 2 and 3 can co-exist.

For known allergens, industry's responsibility can only extend to those who know they are allergic. However, in the case of newly introduced foods and food ingredients, industry has a responsibility to assess the allergenic potential of those foods or ingredients and to protect consumers against possible allergy to them.

Risk assessment for food allergy: the problem

Food allergy, compared to other potential risks from foods, possesses certain unique features.

- Allergens in food are usually normal constitutents of the food, often making up a significant proportion of a product, and present no hazard to the large majority of consumers. At the outset, therefore, there are two distinct groups in any population, those who are sensitised and will react to the allergen and those who will not, however much or little allergen they are exposed to.
- Food allergy is an immune response and consists therefore of two phases: sensitisation (induction) and elicitation. During sensitisation, even susceptible individuals will not experience any symptoms as a result of exposure to the allergen. Also the amounts of allergen required to sensitise and elicit reactions are thought to differ considerably, although there is little, if any, information available about this for the human population.
- The range of minimum doses of allergen required to trigger a reaction in sensitised individuals has not been defined accurately for any allergen, but is known to vary considerably from one person to another. For example, in a study on peanut-allergic individuals, some patients reacted (subjectively) to as little as 100 μg of peanut protein, whereas others required up to 50 mg to have the same effect (4). Similar observations have been made with other allergens.
- The relationship between dose of allergen ingested and the reaction experienced has not been well defined.
- There are no accepted and validated animal models which can be used to estimate the potency of the hazard from any particular allergen. In conventional toxicology, safety/uncertainty factors are applied to a No Observable Adverse Effect level determined in a toxicological study, to ensure safe use of a substance. This approach is impracticable in food allergy because the NOAEL is usually not known and the conventional safety factor (100) is not appropriate. This approach also ignores the fact that allergens present no risk to a large majority of the population, who may benefit from the nutrition offered by the foodstuff to which they are not sensitive.
- Cross-reactivity between food allergens, and between food allergens and inhalant allergens complicates any risk assessment, as well as subsequent risk management.

The practice of risk assessment with respect to food allergens

The practice of risk assessment can be examined in several different ways. One of these is to consider each of the individual steps in turn and relate them to the scenarios previously described:

Scenario 1: evaluating the risk from the presence of a known allergen in a product

- Hazard is known to be an allergic reaction
- Hazard characterisation will include information on the allergen in question, its potency estimated from clinical data and by comparison with other allergens, any data on minimum eliciting doses (thresholds). Since the allergen will usually be present as part of an ingredient, not as pure protein preparation, knowledge about the abundance of the component responsible for allergenicity, if known, can also be taken into account. Hazard characterisation also includes consideration of the frequency with which reactions, and particularly severe reactions, are reported. However, it should be noted that there is at present no sound scientific basis for classifying allergens solely on the basis of the severity of the reactions they can provoke.
- Exposure assessment: the relevant variable for individual exposure is the amount of allergen present in a portion of the food. Additional factors which will influence the probability of a reaction include the known prevalence of reactions to the allergen in the market in which the food is sold, the population who will eat the food (e.g. children or adults) and the extent of distribution (total number of units available for sale). Exposure is one of the factors that can be altered through the food processing procedures in order to reduce risk.
- Calculation of the probability of an allergic reaction is the final step which uses all the information gathered in the earlier parts of the process. Given the

data available, it is not an exact mathematical operation, but rather the formation of a judgement. The outcome could typically be:

1) The allergen content is significantly lower than the lowest amount reported to provoke reactions (or if that is not known, the lowest amount of the most potent food allergen (e.g. peanut) reported to provoke reactions) and consequently the risk of reaction is very remote.
2) The allergen is present in sufficient amount in the product to produce reactions in a significant proportion of allergic individuals.
3) The allergen may be present in sufficient amount in the product to produce reactions in some sensitised individuals.
4) The following simple example illustrates the above considerations for a case of cross-contact. Milk protein has been added to a 200-tonne batch of a product mix which does not normally contain milk protein, such that it now contains 100 ppm. This product is normally made into 50 g portions and is eaten mostly by children.

The following can be calculated:

- 200 tonnes makes 4 000 000 portions
- Each portion contains 5 mg of milk proteins

Assumptions are:

- 4% of children are milk-allergic
- 50% of the product is consumed by children (i.e. 2 000 000 portions) and only one portion per child
- 1% of milk-allergic consumers react to 5 mg or less of milk proteins.

Applying those simple assumptions to the data shows that about 800 children might be at risk, if the product were marketed without any warning about the presence of milk proteins.

If data are available on the distribution of minimum eliciting doses (thresholds) in the population, they can be used in statistical models to determine the likelihood of a defined level of allergen being present. This information can be combined with data on allergen removal from machinery etc, e.g. by particular cleaning regimens, to give the desired assurance that residual allergen could not provoke a reaction in more than a specified proportion of consumers (e.g. 1:10 000 000).

Scenario 2: evaluating the risk of reaction to a known or novel allergen because of sensitisation to another, cross-reactive, allergen.

Most of the elements of scenario 1 will apply to scenario 2, but the hazard characterisation element will be expanded to include evaluation of the extent of cross-reactivity. This can be done by considering, for a particular food, the amounts of the cross-reactive components, together with a detailed immunochemical analysis of those components to determine how effectively they can trigger reactions, compared with the sensitising allergen. The aim here is to arrive at a quantitative assessment of cross-reactivity, if possible.

The calculation of the probability of a reaction would also be modified to take into account the proportion of individuals allergic to the cross-reactive allergen who respond to the allergen in the food.

Scenario 3: Sensitisation to a novel protein allergen, followed by reaction on subsequent exposure.

- Hazard: in this scenario, allergenicity is assumed, but needs to be confirmed.
- Hazard characterisation will initially involve comparisons with known proteins (e.g. sequence comparison), immunochemical studies to identify possible cross-reactivities with existing allergens, *in vitro* digestion and consideration of the function of the protein. Animal studies may be performed, but the necessity for them will also depend on exposure assessment. At present, such studies may be able to provide information about the hazard (i.e. the potential to generate IgE-mediated sensitisation), but will have little, if any, predictive value regarding the risk. Even in the pharmaceutical field, where such reactions are more frequent, animal tests have not proved useful in predicting the likelihood of IgE-mediated allergic reactions to drugs. All this information will permit a judgement to be formed on the likelihood that a novel protein could manifest allergenic characteristics
- Exposure assessment will be on the same basis as previously described.
- Calculation of the probability that the novel protein could sensitise and therefore result in allergic reactions will result in the following conclusions:

1) The novel protein content is no greater than the lowest amount of the most potent food allergen (e.g. peanut) reported to provoke reactions and consequently the risk of sensitisation and subsequent allergic reactions is very remote (This might typically be the case with insecticidal proteins inserted into crops).
2) The novel protein is present in such amounts in the product that it could produce reactions in a significant number of individuals if it has allergenic potential in man. In addition, it possesses characteristics associated with food allergens and is able to produce IgE-mediated sensitisation in animals (under those circumstances, it would probably not be developed further, if it were a GM product).
3) The novel protein is present in significant amounts in the product, but shows none of the characteristics of food allergens, nor does it generate IgE responses in animals (under those circumstances, it could be regarded as safe).

With novel proteins, the risk assessment can also be

further refined by gathering data on reactions, if any, after it has been marketed (post-launch monitoring). Allergy patient organisations may also be alerted about launch of new products.

Conclusions

Food allergy is at best a life-limiting and, at worst, a potentially fatal condition for sufferers.

Knowing the probability of the risk, which it is the purpose of risk assessment to calculate, is an essential prerequisite to managing that risk. Risk management will often include informing the consumer of the presence of the allergen, particularly where it forms a significant part of the product. However, labelling a product as containing a specific allergen when the content is so low as to pose an infinitesimal risk of reaction, is onerous to the food industry and unhelpful to the allergic consumer. Risk assessment helps to quantify such risk and, if necessary, identify appropriate measures to reduce it. However, the conclusions that can be drawn from the risk assessment process and, in particular, the precision of the risk estimate, can only be as good as the data that are used to derive them. For the scenarios examined in this paper, data available to undertake the risk assessments are inadequate. For known allergens, information is needed on the distribution of minimal eliciting doses in defined populations, as well as how they vary in individuals over time. For novel allergens, the most pressing requirements are an understanding of the sensitisation process in food allergy to permit development of predictive models, together with knowledge of how protein structure relates to the development of IgE responses.

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