Executive Summary

Food allergy is now recognised as an important food safety issue. The greatest care must be taken by food manufacturers:

- to formulate foods so as to avoid, wherever possible, inclusion of unnecessary major allergens as ingredients;
- to organise and segregate raw material supplies, production, production schedules and cleaning procedures so as to prevent cross-contamination of products by "foreign" allergens;
- to train all personnel in an understanding of necessary measures and the reasons for them;
- to provide appropriate warning, to potential purchasers, of the presence or possible presence of a major allergen in a product;
- to have in place an appropriate system for recall of any product found to be contaminated but carrying no warning.

The problem of food allergens is part of a wider problem, that of all kinds of adverse reactions to foods, which can also result from microbial and chemical food poisoning, psychological aversions and specific non-allergenic responses. Dealing with at least the major serious food allergens is an essential part of Good Manufacturing Practice.

Introduction

Food allergy is now recognised as an important food safety issue to be addressed by individuals, food manufacturers, legislators and researchers.

What are food allergens? They are macromolecules (usually proteins) causing adverse reactions to food that have an immunological basis, including immunoglobulin E (IgE) mediated reactions and the gluten intolerance syndrome, coeliac disease, now thought to have a cellular immune mechanism.

On the other hand food intolerance reactions do not involve the immune system, and include reactions to histamines and other amines found in foods, and lactose intolerance, where individuals lack the enzyme necessary to break down lactose in the gut.
Food allergy is part of a wider problem – that of all kinds of adverse reactions to foods, which can also result from
• microbial and chemical food poisoning
• psychological aversions
• specific non-allergenic responses.

The immune system defence mechanism against infection produces several different types of immunoglobulins. Immunoglobulin E (IgE), is produced in response to bacterial or parasitic infections; but sometimes an IgE response to agents such as pollen, dust, and food, gives rise to allergy syndromes.

**IgE-mediated food allergies**

First there is the sensitisation stage which occurs often in childhood. An allergen triggers a sequence of events leading to a so-called Th2 immune response leading to specific IgE production. Once sensitised, repeat exposure causes full-blown allergic reaction.

Although allergy to peanut, tree nuts and seafood is likely to continue throughout the individual’s life, sensitivity to most other allergens is lost in late childhood. This explains the otherwise mystifying estimate that four per cent of adults and eight per cent of children in the EU population suffer from food allergies.

Initial sensitisation has long been the accepted principle, which, *inter alia*, has been the basis for advice to pregnant and breast-feeding women with a family history of peanut allergy to avoid consuming peanuts (advice which in practice has sometimes been mistakenly interpreted as applying to all pregnant women). The basis of this advice has been reviewed by the UK Committee on Toxicity (COT) [http://cot.food.gov.uk/pdfs/cotstatement200807peanut.pdf](http://cot.food.gov.uk/pdfs/cotstatement200807peanut.pdf) (December 2008). The shift in the balance of evidence since 1998 is such that the Committee believes that the previous precautionary advice to avoid peanut consumption during pregnancy, breast feeding and infancy, where there is atopy or atopic disease in family members, is no longer appropriate. However, the Committee considers that the basis of its more general recommendations made in 1998 is still justified and, therefore, recommends that:

(i) In common with the advice given for all children, infants with a parent or sibling with an atopic disease should be breast-fed exclusively for around 6 months;

and,

(ii) Infants and children who are allergic to peanuts or peanut products, should not consume them or foods that contain them;

and also recommends that:

(iii) those who are allergic to peanut should seek advice from medical professionals about avoidance strategies.

In consequence the UK Food Standards Agency has recommended to Government that the advice be revised in line with the COT recommendations.

Researchers are now carrying out food allergy desensitisation studies to determine whether feeding small amounts of a food allergen to children with a history of allergic reaction to that food could build up tolerance and eventually result in loss of their allergy. The technique, designated oral immunotherapy (OIT), is considered to work on a cellular level to alter the specific response of white blood cells (lymphocytes) that play a part in the immune response during allergic reactions. Studies with egg have shown preliminary promise (Buchanan et al, 2007) and a similar study is proceeding with peanuts (coFAR, 2006). Prof. Gideon Lack, of King’s College London, is currently working on novel immunomodulatory treatments for food allergies, and on developing new strategies to prevent food allergies in childhood. He has enrolled more than 200 babies under one year old with eczema or egg allergies in a trial that involves giving half the babies a peanut-containing snack; the other half
avoiding peanuts. He will then follow them all until age 5 to see if he has stopped a peanut allergy before it takes hold.

Allergens are usually proteins; other macromolecules such as polysaccharides, can act as allergens, but as these usually only generate poor antibody responses they are not generally involved in IgE-mediated food allergies. Sensitisation towards many food allergens, such as egg, probably occurs via the gastro-intestinal tract. In adults the onset of food allergy may be related to inhalant allergies such as birch, grass pollen and latex. There is recent evidence to suggest that the dermal route of exposure may also be relevant. As a consequence of homologies between the allergens in, for example, pollen or latex and various fruits and vegetables, such individuals can develop cross-reactive allergies to fresh fruits and vegetables, known as pollen-fruit and latex-fruit syndromes.

Repeat exposure is because either the person is unaware of being allergic to a particular substance or is aware but unaware of the presence of that substance. IgE associates with specific IgE receptors on the surface of mast cells located in the eyes, skin, and the respiratory, intestinal and urinary systems.

The mast cells release histamine, leucotrienes and other substances into the body tissues, resulting in characteristic allergy symptoms.

![Figure 1](image.png)

**Figure 1**

The photomicrograph (Figure 1) demonstrates two mast cells. One cell is intact, the other damaged in preparation (demonstrating the individual granules). These cells express, on their cell membranes, high affinity receptors for the Fc portion of IgE antibodies, thus most of the IgE antibodies produced by plasma cells are bound to the surface of mast cells. Reaction of the bound IgE with circulating (or in the case of mast cells, localized) antigens promotes degranulation of the mast cell. In addition, cross-linking of the bound IgE or interaction of the bound IgE with antibodies to IgE will also promote degranulation of the cell.

Allergic reactions may be triggered by minute amounts of allergen and may range from relatively short-lived discomfort to anaphylactic shock and death (and not only from the well-publicised peanut).
Responsibility of the allergy sufferer

There is at present no cure for food allergies or food intolerance. So sufferers have to avoid eating problem foods. However, no warning that an allergen is present in a food can be effective for a consumer unless he or she knows what are the substances to which he/she is allergic. Only sufferers or their medical advisers can ascertain that information, by testing – whether the simpler skin test or the definitive, double-blind, placebo-controlled oral challenge test (Asero et al, 2007; Norhede, 2007).

Responsibility of food manufacturers and foodservice providers

The other half of the exercise is the responsibility of food manufacturers and foodservice providers. Dealing with the major serious food allergens is an essential part of Good Manufacturing Practice. This is an extremely complex problem to which there are no cheap or easy solutions. There are few foods or food ingredients to which someone, somewhere, is not allergic, in some cases in very small (microgramme) quantities, but the risk should be treated seriously and safeguarded against by all food manufacturers, retailers and foodservice operators. More detailed information on allergenic foods can be found in the InformAll database http://foodallergens.ifr.ac.uk/

The greatest care must be taken by food manufacturers:

1. to formulate foods so as to avoid, wherever possible, inclusion of major allergens as ingredients;

2. to organise and segregate raw material supplies, production, production schedules and cleaning procedures so as to prevent cross-contact of products by “foreign” allergens;

3. To train all personnel in an understanding of necessary measures and the reasons for them;

4. To provide appropriate warning, to potential purchasers, of the presence or possible presence of a major allergen in a product;

5. To have in place an appropriate system for recall of any product found to be contaminated but carrying no warning.

All of this is not only a duty of care and a due diligence requirement, but an essential means of minimising the risk of being subject to a product liability claim, and the risk of having to recall mislabelled or cross-contacted products. Easy to advocate, but as companies now successfully operating such a policy have found, it is far from easy to introduce and implement. The new development of such a policy requires nothing less than a change in the company “culture”, an allocation of very substantial funds and resources and a concentrated and sustained effort by everyone led by the Board; and its application and maintenance thereafter requires ongoing effort. Part of the work of implementing the plan, however, is the difficult and ongoing task of training all concerned – general managers, buyers, production managers, quality managers, engineers, supervisors, operators, cleaners, to understand the importance of the plan and the need to carry out conscientiously the measures that it contains. Increasingly, from the mid-1990s onwards, major responsible companies in the US and Europe were adopting these policies voluntarily, but now it is a legal requirement in both places.

Foodservice responsibilities and problems

Reference has already been made to the responsibility of individuals with an allergy to find out to what substance(s) they are allergic. Only then can they make use of warning information. This also applies when eating food prepared by others.
In this context foodservice may be viewed as a particular kind of manufacture with added complications. In general, the principles referred to for product formulation and avoidance of cross-contact by manufacturers apply equally to foodservice providers; and similar warnings should be given adjacent to appropriate items on menus or self-service display notices.

In some large restaurant chains, the expertise exist to do this, and their buying power enables them to lay down specifications and monitor performance of ingredient suppliers; but many small foodservice outlets have neither that expertise nor buying power. Label warnings on bulk packs supplied by manufacturers for foodservice use may be of some help.

An additional problem arises, however, in an establishment where a chef has a free hand in creating dishes. It is important, therefore, that chefs are given training in recognition of the major allergens, the principles of minimising risk in respect of them and the need to notify any use of allergens, including their use in ways that might go unnoticed by others, for example use of an egg glaze on pastry.

Throughout foodservice, the main cross-contact problem is that due to common use of equipment such as ladles, which inevitably happens in busy kitchens despite admonitions to the contrary.

In parts of the foodservice field, such as aircraft in-flight meals in economy (coach) class (where there is normally neither printed menu nor display) the problem of giving adequate warnings is far more difficult to solve. The same applies to the multiplicity of small foodservice outlets, where, in addition, many proprietors would not have sufficient knowledge to know what warnings to give.

With in-flight meals, the problem is compounded by having to deal with a tray containing several components (starter, main course, dessert, roll/bun and butter, cheese). Moreover, it is not like a situation where someone who is, for example, allergic to soya can look at the label of a food product before purchase, find a soya warning and decide not to purchase.

Aircraft meals are prepared in so-called "central kitchens" which are really factories manufacturing short-life high risk ready meals under stringent conditions of hygiene, and have technical managers with the expertise to deal with the minimisation of unnecessary allergens in recipes, monitoring of their suppliers, prevention of cross-contact and provision of warning information. One solution would be for the central kitchen to provide a menu (which could be just a sheet of paper), with each item carrying a warning of any major allergens present, and cabin staff distributing this to passengers in advance of meal selection. Another solution could depend on cabin staff being provided with such an annotated menu list and passengers being asked on the address system "If you have a food allergy, please tell the cabin staff what you are allergic to and they will be able tell you if that is present in any part of the meals available".

The situation is very different in small foodservice outlets (or in many larger restaurants), and street vendors. For the allergy sufferer to say "I am allergic to X. Is there any X in dish Y?" may or may not produce an accurate answer where the allergen is very obvious as a direct component of the dish, but is most unlikely to do so where X is a sub-component in, say, a sauce or a soup. Furthermore the question may well be put to a transient low-paid employee whose first language may, anyway, not be the language in which the question is put.

Foods sold loose, or from foodservice outlets represent a considerable risk to allergic consumers. The UK Food Standards Agency has developed some guidance for the catering (foodservice) industry (UK FSA, 2005). In USA, the Hospitality Institute of Technology and Management has produced guidance for caterers and retailers (Snyder OP, 2005).

**What are the “major allergens”?**

It has been estimated that around 95% of food allergic reactions are caused by several major groups of food allergens. However such estimates are imprecise, and debate about which allergens should be the subject of mandatory label warnings accounts for the fact that it took until 2003 (EU) and 2004 (USA) to determine regulatory lists.
In the EU member countries, under Directive 2003/89/EC amending Directive 2000/13/EC, as from 1 January 2006 food labels must declare any of a specified list of allergens present, or (with certain specified exemptions) products derived from such allergens (EU, 2000, 2003).

These are – and subject to certain exemptions for derivatives thereof --
- Cereals containing gluten, (i.e. wheat, rye, barley, oats, spelt or their hybridised strains) and products thereof
- Crustaceans and products thereof
- Eggs and products thereof
- Fish and products thereof
- Peanuts and products thereof
- Soybeans and products thereof
- Milk and products thereof (including lactose)
- Nuts i.e. Almond, Hazelnut, Walnut, Cashew, Pecan nut, Brazil nut, Pistachio nut, Macadamia nut and Queensland nut and products thereof
- Celery and products thereof
- Mustard and products thereof
- Sesame seeds and products thereof
- Sulphur dioxide and sulphites at concentrations of more than 10mg/kg or 10 mg/litre, expressed as SO$_2$.

As from 2007, molluscs and lupin were added to the above list.

The derivatives for which exemptions are listed are those which are deemed no longer to retain the allergenic DNA (EU, 2005).

The Directive does not specify the format in which allergen declaration must appear other than that in general it must be included in the (usually small print) list of ingredients. Since 1997 the Institute of Food Science & Technology has advocated that in addition, they should be more prominently drawn to attention of intended purchasers, for example by naming the allergen(s) present in a separate box headed “Allergy Information” and some manufacturers and retailers are doing that. It is also important that they be named in a way that conveys their meaning to the public, for example “milk protein” rather than “casein” or “whey”.

The UK Food Standards Agency has product a useful on-line Guide to implementing the EU Regulations (UK FSA, 2006).

In USA, regulation is by the Food Allergen Labeling and Consumer Protection Act of 2004 (FALCPA) (US FDA, 2004). All packaged foods regulated under the Act that are labelled on or after January 1 2006, must comply with its food allergen labeling requirements

FDA’s list of allergens that must be indicated in labelling is

- Milk, egg, fish, crustacean shellfish, tree nuts, wheat, peanuts, soybeans (or protein derived from any of them).

Not to be outdone, on 7 July 2005, the US Department of Agriculture (USDA) Food Safety and Inspection Service issued a Notice to inspectors, giving instructions for verifying that establishments have the appropriate process controls in place for meat and poultry materials that can trigger food allergies and intolerances). The Notice was prompted by the number of recalls because of undeclared presence of ingredients that are capable of causing adverse reactions.

**Cross-contact**

Cross-contact allergens are allergens that enter foods accidentally. There are three types of cause:

1. cross-contact of an ingredient before or after receipt;
2. accidental mis-formulation;
3. cross-contact by an allergen from a different product.

Both in USA and in Europe there are numerous product recalls of products containing major allergens not mentioned on the label. Prevention requires a HACCP-style analysis of the operations.

**Precautionary Labelling**

Where, despite all efforts to prevent it there remains a risk of cross-contact, possible label wordings are “May contain...” or “Made in a factory where.. is used”.

Such labelling should NEVER be used to justify less than thorough implementation of the preventive measures outlined.

**Novel foods and GM foods**

As no single criterion is sufficiently predictive of allergenicity, the Codex Alimentarius Commission Ad Hoc Intergovernmental Task Force on Foods Derived from Biotechnology (ALINORM 03/34) recommended that the risk assessment process should adopt an integrated step-wise case-by-case approach which takes account of information of several types. Such an integrative approach would be likely to include information on

- relationships between novel proteins and known allergens, defined using bioinformatics tools,
- cross-reactivity defined using patient allergic sera,
- *in vitro* measures of protein digestibility
- *in vivo* sensitisation using animal models.

Evidence to date is that allergenic risks posed by genetically-modified foods are no greater than those posed by crops and foods developed by traditional methods. The allergenic risk assessment process used to assess the safety of candidate transgenes (Metcalf et al,1996; Wall & Pascall, 1998) makes it highly unlikely that an allergenic GM food would be introduced into the market. It was this procedure that famously proved its worth back in 1995 when a research attempt to increase the methionine content of soya by inserting a Brazil nut gene was shown to have introduced the Brazil nut allergen into the soya. The findings were published and the research was terminated (Nordlee et al, 1995).

The methods referred to above may be used for novel foods but because one may be dealing with protein(s) not previously encountered, the situation is more problematic

**Food allergy research**
Such an assessment process will be even more effective once our understanding of the molecular basis of allergic disease has improved. Information resulting from research into what makes an individual become allergic and what makes some proteins, and not others, become allergens, will provide even more effective assessment of the allergenic potential of novel foods. While there are plenty of anecdotal accounts, particular regarding peanut, where extremely small amounts have caused serious reactions, the most difficult research area, and one with ethical considerations, is that of determining threshold levels of different allergens causing allergic reactions in individuals very sensitive to those allergens (US FDA 2005).

EuroPrevall is an EU-funded multidisciplinary integrated project (IP) involving 16 European member-states, Bulgaria (a candidate country), Switzerland and Iceland, plus Ghana and now New Zealand and Australia. Of the 55 partners, there are 15 clinical organisations, three major manufacturers and six small-medium sized enterprises (SMEs) as well as the leading allergy research organisations in Europe.

EuroPREVALL research will:
- Characterise the patterns and prevalence of food allergies across Europe in infants, children and adults
- Develop methods to improve the quality of food allergy diagnosis, reducing the need for food challenge tests
- Determine the impact of food allergies on the quality of life and its economic cost for food allergic people and their families, workplace and employers, and healthcare

An obvious route for research would be to use genetic modification to produce non-allergenic versions of allergenic foods. Examples are research to produce a non-allergenic GM peanut (University of Arkansas); to produce a non-allergenic GM prawn (Tulane University); and in Japan, to produce a GM non-allergenic rice.

A new line of research which might reap huge benefits some years down the line, stems from the discovery that nanoparticles of 60-carbon-atom buckminster-fullerenes, so-called “bucky balls”, which are powerful antioxidants, when incubated with human cell cultures and subjected to an immune system challenge, resulted in a significant reduction of mast cell histamine formation and inhibition of inflammation. The human cell cultures grow normally in the presence of these nanoparticles. Trials in mice showed significant reduction in anaphylaxis (Kepley C, 2007).

References


Anaphylaxis Searchable Database.
http://www.anaphylaxis.org.uk/db/TACstart.php

http://www.aaaai.org/media/jaci/2007/02/buchanan.stm

http://www.fao.org/DOCREP/005/Y2770E/y2770e02.htm#bm02

http://europa.eu.int/comm/food/food/labellingnutrition/labelling/comm_legisl_en.htm


EU "Informall" Food Allergens Database.  
http://foodallergens.ifr.ac.uk/


http://content.nejm.org/cgi/content/full/334/11/726


http://admin.ga2len.net/files_new/filesPublic/Educ_FoodAllDiagnosis_paper_Final.pdf


http://www.food.gov.uk/multimedia/pdfs/allergyleaflet.pdf

http://www.food.gov.uk/safereating/allergyintol/caterers/

UK Food Standards Agency. Providing allergen information for non pre-packed foods.
http://www.food.gov.uk/foodindustry/guidancenotes/labelregsguidance/nonprepacked


http://www.cfsan.fda.gov/~acrobat/alrgact.pdf

http://www.cfsan.fda.gov/~Dms/Alrgn.Html

http://www.cfsan.fda.gov/~dms/alrguid.html

http://www.cfsan.fda.gov/~dms/medfguid.html

Other selected Related Websites

Anaphylaxis Campaign (UK)  
http://www.anaphylaxis.org.uk/

Australasian Society of Clinical Immunology and Allergy_ www.allergy.org.au

Consortium of Food Allergy Research (coFAR)  
https://web.emmes.com/study/cofar/

European Federation of Asthma and Allergy Associations_ www.efanet.org

EU “EuroPrevall” multi-disciplinary allergy research project.  
http://www.europrevall.org/

Food Allergy and Anaphylaxis Network (FA AN) (USA) _ www.foodallergy.org

Global Allergy and Asthma European Network (GA_LEN) _www.ga2len.net/hp/homepage2.cfm_  
International Union of Immunological Societies (IUIS.)_ http://www.allergen.org/Allergen.aspx

World Allergy Organisation  
http://www.worldallergy.org/links.php

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