

What amounts of foods may trigger food allergy symptoms? And why do we need this information?

By Pia Nørhede

What is food allergy?

Some people develop symptoms when eating certain foods that cause no problems to most people. To talk about food allergy it is a requirement that the immune system is involved in the reactions leading to the symptoms. Some allergic reactions are local causing, for example, tingling of the lips, whilst other reactions may become systemic. This means that several symptoms may be triggered simultaneously in different parts of the body, for example, as a skin rash, a fall in blood pressure or difficulty in breathing. Different kinds of poisoning and enzyme deficiencies can provoke symptoms that are similar to the symptoms experienced in food allergy. In order to distinguish between a food allergy and other reactions to food the person with symptoms need to see a doctor.

Our immune system protects our bodies from infections, for example, by producing antibodies to fight germs. We do not understand why, but in some people the immune system mistakenly produces the **IgE** type of antibody against harmless things like some foods, which may lead to food allergies. Food **allergens** (the parts of food responsible for an allergic reaction) are almost always proteins, and there are usually several kinds of allergens in each food. It is not yet clear what makes some food proteins allergenic, and not others. Some people have allergic reactions where IgE is not involved. This article, however, only deals with the allergic reactions mediated by IgE since these reactions can potentially be more severe.

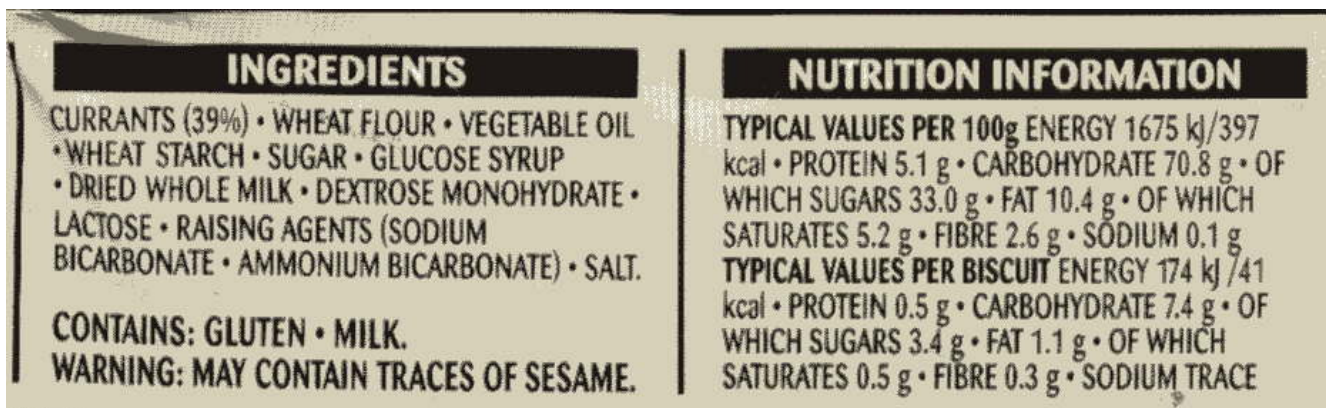
More than 120 foods have been described as causing food allergies but only a limited number of those cause most allergic reactions. The foods most commonly causing serious allergic reactions on a worldwide basis are: Milk, egg, tree nuts, peanuts, soybeans, fish, crustacea, and cereals containing gluten such as wheat. Individuals with pollen or latex allergy often experience allergic symptoms when they eat certain fruits, vegetables or nuts. This “**cross-reactivity**” occurs because the body cannot distinguish between the allergens in pollen or latex and similar related proteins in food, and may react to both.

Recent research has concluded that there exist lower limits of intake below which food allergens will cause only minor or even no apparent symptoms and that these limits vary from one allergic individual to another.

Why is knowledge on the amounts of foods that may trigger allergic reactions important?

Most of the studies in which food allergy is clinically proven report that between 1 in 100 and 1 in 20 people overall have a food allergy. Individuals with food allergy develop symptoms by eating foods that for the vast majority of the population are part of a healthy diet.

The only way for the allergic individual to manage food allergy is to avoid eating the food or any products containing the food to which they are allergic. In practice, the apparently simple advice to avoid the offending food can be very difficult to follow. To help allergic individuals avoid foods to which they are sensitive, allergen labelling rules in various countries require food manufacturers to declare specified allergens on labels whenever they are deliberately used in a product. This requirement is irrespective of whether the allergens are present in amounts that may pose a risk to people allergic to those ingredients. However, labelling rules do not generally cover the small amounts of allergens that may be present in many products due to cross-contamination during the production process. If food manufacturers consider that there is a risk of cross-contamination with allergens in their products they will often include an allergen advisory warning on the label, for example “May Contain Peanuts” or “Manufactured in the same building as foods containing soy”. However, the overuse of such labels presents allergic consumers with a dilemma. They can either accept decreased food choices or hope that, if present, the level of allergen in the food is insufficient to trigger a reaction. But they are taking a risk, as recent studies pointed out that 5 to 10 % of the “may contain” products indeed contained the allergen to which the warning referred.



Example of declaration of food allergens

Both allergic consumers and food manufacturers wish to maximise food choices and minimize risk. However, it is currently difficult to quantify the level of risk posed by trace levels of allergens because there is little knowledge about the smallest amounts of the various allergens required to trigger allergic reactions. This may appear at first glance easy to determine. However, the procedure is quite long and complicated and it is difficult to replicate in the clinic all the ways in which people can be exposed to allergen. Despite the inherent difficulties in establishing safe food allergen levels, it is of critical importance to allergic consumers and also to health professionals looking after allergic patients. They would benefit from being able to provide more useful and differentiated advice to individual allergic patients based on the overall history including individual levels of reactions to allergens. Similarly, those responsible for public health cannot formulate specific legislation or guidelines on the level of allergen below which the public impact is negligible, as they do not have the necessary information. As a consequence the food industry, which both wishes and is expected to provide safe products is unsure about what and how much needs to be done to achieve this with respect to allergens.

Knowing the lowest amount of an allergenic food, which can provoke allergic reactions, would thus benefit individual allergic consumers, health professionals, regulatory authorities, as well as the food industry.

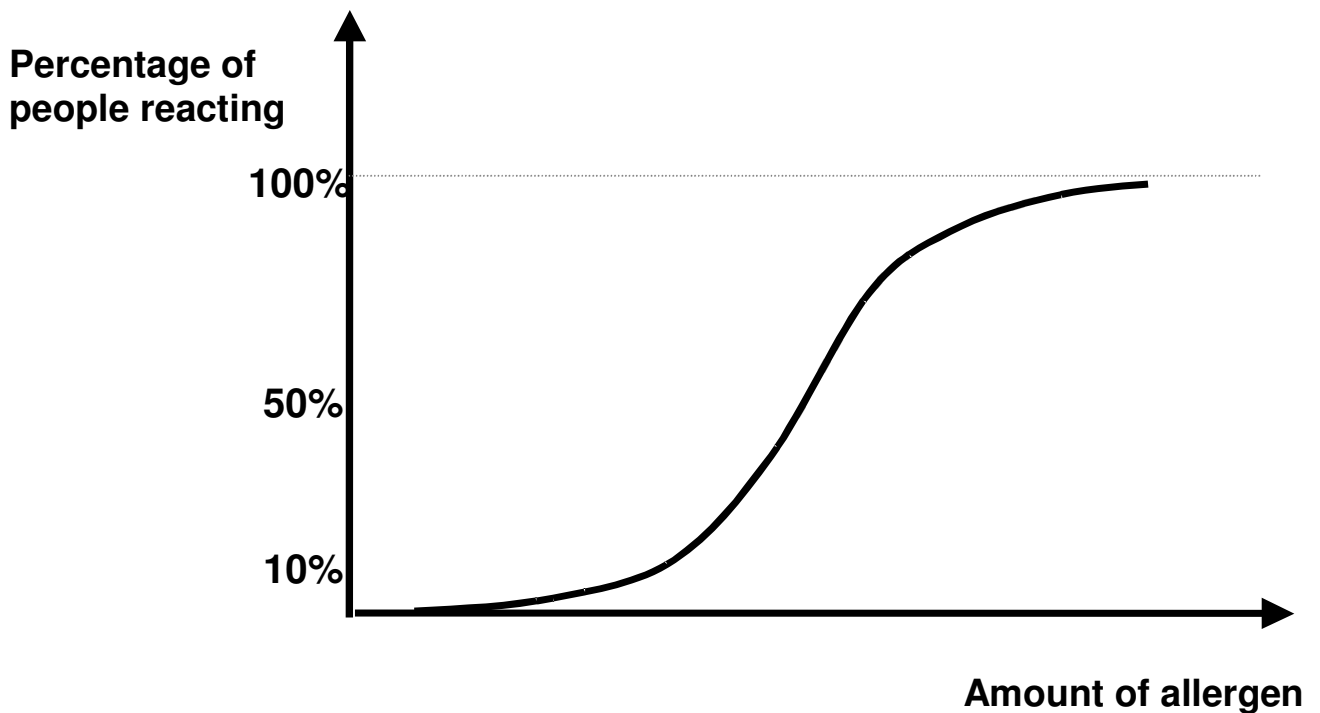
How do we obtain information on the lowest doses of food able to provoke allergic reactions?

Allergy specialists use food challenge tests to find out whether someone is allergic to a food and have adapted these tests to find out the lowest amount that can provoke a reaction. A challenge test involves giving a patient increasing doses of the suspected allergenic food, allowing ample time (usually 15 to 30 minutes) between doses for a response to occur. For older children and adults, challenges are normally conducted in a double-blind manner with a placebo control. Clinicians refer to this diagnostic method as a double blind, placebo-controlled food challenge (**DBPCFC**). This is when neither the patient, nor the investigator knows whether or not the food preparation being given contains the specific allergen under investigation hidden in it. The suspected allergenic food will be hidden in a food **matrix** (recipe) consisting of foods normally tolerated by the patient. Pancakes, meat recipes or cookies are examples of suitable food matrices because they can disguise the allergen being tested.



Increasing doses of peanut for use in a challenge test

When a DBPCFC is used to diagnose food allergy, the focus is to confirm whether a patient has an allergy or not. In practice, many of the patients who had a DBPCFC got an allergic reaction when they ate the first dose of the suspected allergenic food. In those cases, the minimum amount able to trigger a reaction was clearly not found. In the last few years, doctors have started challenge tests with tiny amounts of allergen (as low as a few millionths of a gram) and they have therefore been able to detect in almost all cases the lowest amounts to which patients might react. They have also been able to see how many people just reacted to different amounts of allergen and so build up a picture of the number of people in the tested population who react to various amounts of allergen.



Picture of the percentage of people in a tested population who react to various amounts of allergen.

The data obtained can also be analysed statistically to predict how many allergic people might be expected to react if they eat a food containing a particular amount of allergen. This is the kind of information that is useful to guide the food industry and those responsible for public health.

Threshold and minimum eliciting dose

Researchers use the word **threshold** for the lower limit under which a food allergen will not cause any symptoms. Some researches have suggested using the term **minimum eliciting dose** to refer to the amount of allergen predicted to be safe for the majority of allergic individuals to eat. This is to distinguish it from the individual thresholds determined in DBPCFC studies.

What is known today on the lowest doses of food able to provoke allergic reactions?

Currently available data makes it very difficult to estimate safe levels of food allergens. The amount that may trigger allergic reactions observable by others ranges from a tenth of milligram in rare cases, up to grams and sometimes tens of grams, with considerable differences between individuals as well as between allergens. Current knowledge seems to indicate that, across the allergic population as a whole, as the dose of food is decreased so does the severity of symptoms and the proportion of allergic people who react. However, patients who in diagnostic challenges with milk, egg, peanut, soy and wheat experienced more severe reactions tended to react to a lower dose than those experiencing milder reactions. A review of diagnostic challenges conducted since the 1970s reveals that the majority of food-allergic individuals tested need to eat more than 500 mg of the offending food to experience allergic reactions, but a significant minority reacts to lower amounts.



To date, the most reliable data on individual threshold levels come from studies performed in peanut allergic patients. Enough challenge data probably exist worldwide now for cows' milk, eggs and peanuts to allow statistical analyses to predict doses of those foods safe to eat for the majority of allergic individuals. However, scientists and regulatory authorities have only recently started to discuss how to make statistical evaluations of the data. There is therefore still much work to be done before we can use individual threshold data to predict reliably the amount of food safe to eat for most allergic patients.

What are the challenges of using data from DBPCFCs to predict the amount of allergen safe for the majority of allergic individuals to eat?

So far very few DBPCFC studies have been conducted using the same methods. In order to compare and combine individual data in a statistical model to predict safe dose limits for an allergic population, researchers need data from DBPCFC studies performed in a standardised manner. The challenge materials, the selection of patients, and the challenge procedure are the major variables, which may affect the results.

a. Materials for challenge tests

The key to success in the DBPCFC is the accurate delivery of a range of doses of the allergenic food under test in a form that is unrecognisable to the patient. The allergenic food and matrix combination must therefore be blinded for taste, smell, colour and texture. The simplest way to achieve this is to deliver the food in capsules. With capsules it is, however, difficult to deliver relatively high doses. In addition the use of capsules may result in more severe symptoms as the allergens will not be in contact with the mucous membranes in the mouth and will not give early warning signs, leading the patient to consume more allergen before reacting. For these reasons, European allergy experts discourage the use of capsules.

The only alternative to capsules is to hide the allergenic food in a matrix that is a “real” food. Taste and smell can be masked by a stronger taste and smell. For example, cows’ milk can be masked in a non-dairy (soya) dessert containing fruit syrup. Clearly, this approach presents challenges when the allergenic food itself has a strong smell or flavour. Adding material of a granular nature such as oatmeal will often mask texture. The addition of relatively small amounts of highly coloured ingredients can be sufficient to mask colour. Before the matrices are used for DBPCFCs people trained in sensory testing should verify the effectiveness of the blinding.

In real life, foods are consumed in various prepared forms, e.g. raw, boiled, baked or roasted and often in complex meals. Ideally, DBPCFCs should use the most allergenic form of the food provided it can be given safely to the patient. However, knowledge of the most allergenic form of different foods is limited. In pollen-related food allergy, cooked food is often better tolerated than raw food since heating will destroy the allergens. In peanut allergy most of the allergenic proteins are heat-stable and roasting may even increase allergenicity.

In different studies clinicians have used many different forms of food in DBPCFCs. For example, they have given peanuts as peanut flour, partially defatted peanut flour and peanut butter, all of which contain very different amounts of fat. This can affect the result. For peanut allergy it has recently been shown that a higher content of fat in the matrix resulted in a higher consumption of peanuts before a reaction occurred and more severe symptoms in some patients. Some varieties of the same food (apples and peanuts) may also be more allergenic than others, which is an added complication. So clinicians have used a variety of materials to mask and deliver food allergens in challenges, but they have never systematically investigated to what extent differences in the form of the food or the matrix influence the measured threshold doses.

In practice this means that results obtained in one study, using one food variety in one state of preparation and in one matrix may not give the real threshold.

b. Selection of patients

If we want to use the results to predict a amount of a specific allergenic food that will be safe for the majority of allergic individuals to eat, the measured individual thresholds need to reflect the “real” range of thresholds found among allergic people. In practice patients are not generally selected at random from the allergic population, which is what would be needed to get a true overall picture. Instead, most studies have used groups of food-allergic patients referred to specialist allergy clinics. These clinics will tend to see patients whose care requires the greatest expertise available. On the other hand patients with lower thresholds than those tested to date might exist, given that some clinicians exclude from challenge those they consider very likely to react severely.

Not enough studies have been performed to know if threshold doses are similar for different groups of people (e.g. adults, children, people with asthma). A few published challenge studies have evaluated both infants and adults for peanuts, but more often such studies have covered only certain populations for specific allergenic foods. For instance milk and eggs have been investigated largely in children because these allergies occur most frequently among them.

For statistical evaluation of data it is necessary to include enough patients. The current recommendation is that a minimum of 29 patients with documented food allergy should be included in challenge studies, which may be used to predict the amount of allergen to be safe to eat for more than 9 out of 10 allergic individuals. Many of the published challenge studies have included far less than 29 patients.

c. Challenge procedure

In different challenge studies different symptoms have been used as criteria for stopping the challenge. Doctors have placed different weight on symptoms reported by the patient (e.g. itching or pain) or observed by study personnel (e.g. redness, swelling, vomiting or asthma).

In addition, different challenge tests may differ in what doses are used (including the starting dose) and the time interval between doses. Differences also exist in at what time in the study the patients get food preparations with or without allergens.

Challenge tests are performed by giving a patient increasing doses of the suspected allergenic food at intervals of usually 15 to 30 minutes. No agreement currently exists on whether the threshold is the dose at which a reaction occurs or the dose of all the allergenic food that has been consumed from the start of the test.

Research in EuroPrevall on the amount of food that may trigger symptoms of food allergy

EuroPrevall is a large European research project aimed at improving the quality of life for food allergic individuals. As part of meeting that objective, clinical partners across Europe will conduct low dose challenge studies in well-defined populations for a range of allergenic foods of importance in Europe. The clinical partners will use the guidelines below for the challenge studies. EuroPrevall strongly recommend that other clinicians follow the same procedures, so that it is easy to compare and combine the results of different studies.

Key features of the recommended protocol are:

1. The people participating in the study will be carefully selected to represent the allergic population, so that meaningful conclusions can be drawn about that population.
2. The tests have two purposes, namely to reveal individual thresholds and to obtain a picture of how these thresholds vary across the allergic population, so that the results can be analysed statistically. Enough patients will therefore be challenged to have at least 29 patients with allergic symptoms in the challenge.
3. The allergenic food will be masked in a real food matrix, specially designed as part of the project and the meals will be tested by tasting experts to check that they cannot tell which meal contains the allergenic food.
4. Patients will be tested with up to 13 doses of allergenic protein ranging from 3 millionths of a gram up to 3 grams (equivalent to a normal serving of the food).
5. Clinicians will record all reactions in detail, whether reported by the patient (subjective) or observed by study personnel (objective).

The knowledge that the DBPCFC studies generate will help determine what amounts of foods may trigger food allergy symptoms. In addition to determining individual patient thresholds, EuroPrevall has in May 2007 conducted a workshop in cooperation with the UK Food Standards Agency to discuss the best way to make statistical evaluations from individual threshold data. A statistical evaluation of the data is necessary in order to predict a dose of a specific allergenic food that will be safe for the majority of allergic individuals. This is the kind of information that is useful to guide the food industry and those responsible for public health.

The above writing is based on the paper:

R. W. R. Crevel, B. K. Ballmer-Weber, T. Holzhauser, J. O'B. Hourihane, A. C. Knulst, A. R. Mackie, F. Timmermans, S. L. Taylor (2008). Thresholds for food allergens and their value to different stakeholders. *Allergy* 63, 597-609.

See the InformAll database at <http://foodallergens.ifr.ac.uk> for detailed information on the foods, which may cause allergic reactions. The database e.g. contains data from DBPCFC studies.

EuroPrevall is an EU-funded project about food allergy. The primary objective of EuroPrevall is to improve the quality of life for all food allergic consumers. To meet that objective EuroPrevall will conduct research to obtain information that we currently lack. EuroPrevall will also develop the tools necessary to manage food allergies more effectively. The 63 partners from 25 different countries include some of the leading allergy research organisations in Europe as well as clinical, patient, and industrial organisations. Visit www.euoprevall.org for more information on the project.