

The threshold concept in food safety and its applicability to food allergy

Down the years there have been many clinical reports of exquisite sensitivity to low doses of food allergens. There are many factors that may contribute to a variation of threshold in an individual exposed to an allergen during the course of his or her daily life. Some of these factors are intrinsic and unavoidable. Other factors may be predictable but not easily controllable, such as asthma, exposure to allergens during the pollen season and predicting situations that may be risky. Other factors may be out of the control of the individual. The most important one of these is the adequate training and awareness of manufacturers and caterers who aim to provide safe and nutritious meals to their allergic and non-allergic customers alike. Clinical histories of reactions in the community and the use of labial exposure during food challenge show that most non-ingestion exposures to peanut usually result in easily treated minor reactions. Formal, oral food challenges have shown that low dose reactivity is relatively common but studies have not yet had the power to investigate whether peanut allergy is more commonly associated with very low dose reactivity than other foods. This means that industry must not concentrate only on peanut and tree nuts when looking at issues of contamination just because they are associated with the majority of severe reactions. There are more milk and egg allergic children in the general population and they deserve the same protection from allergen exposure as sufferers of peanut or tree nut allergies.

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Peanut allergic subjects and their families often state that they do not feel in control of their allergy. In the psychology literature this is termed an external health locus of control (1). This external health locus of control of peanut allergy is due to two depressingly accurate perceptions that families have, which are supported by the medical literature. Firstly, a potentially serious exposure to peanut can occur at any time despite vigilance (2, 3). Secondly, there is the perception that treatment options are limited to crisis response such as epinephrine rescue therapy. Diabetics are a comparable disease group that has an internal health locus of control, though they, too, must make daily decisions about food intake and injections, because they are able to influence the health impact of their disease. Once trained in the use of insulin and responses to hypoglycaemic attacks (low blood sugar levels) an internal health locus of control is achieved by a diabetic as food servings and doses of insulin can be controlled by the patient and his family. Comparisons have also been made between the anxiety burden borne by peanut allergics and sufferers of chronic musculoskeletal disease as both have daily issues of socialisation and freedom from stress (4).

The current clinical situation is that there are no

meaningful treatments for peanut allergy. Such treatments remain some way off. Exposures to peanut are frequent and often unpredictable. This means families and the people and corporations with whom these people must interact as part of normal family life (and who may be liable for errors of omission or commission), must all try and minimise the risks of exposure and reaction that these families must endure. If therapies rather than avoidance strategies and response plans are not achievable for peanut allergic subjects in the short term, then medical and dietetic information and training of families must be of the highest standards achievable (5). Family support networks such as the Anaphylaxis Campaign in Britain and the Food Allergy Network in the United States are a key facet of the integrated care of allergic families. Their major short-term goal is to increase the confidence of families in their own ability to minimise or prevent allergen exposure crises and to react appropriately to them.

It has been suggested that one of the reasons peanut allergics are so vulnerable to accidental exposures is that they react to smaller doses of peanut than people with other food allergies do to the relevant foods. This hypothesis remains to be tested. Anecdotally, the four most severe reactions to challenges that we have seen in

our unit recently have all been to egg rather than peanut. The selection bias of subjects for food challenges may have an effect.

Contamination of prepared foods and the issue of labelling

Many families are frustrated by the proliferation of “may contain” labels. In many cases these labels are appearing on products that the food allergic subjects have eaten safely for many years. Manufacturing processes may change, leading to a change in risk. The perception among food allergic subjects and many clinical allergists is that this labelling is over-inclusive and defensive to cover liability for contamination when the risk is probably very small. Many families make empirical judgements from day to day. On the basis of their safe previous consumption of the product they may consider the risk acceptable and continue to eat the product. If they are aware of two varieties of the product, one with and one without the allergen, they often consider the risk not acceptable and avoid both products.

This practice may not be safe for every food allergic subject. Foucard et al. reported that four fatal reactions in peanut allergic subjects with no known history of reactivity to soy were to foods containing up to 7% soy but not obviously containing any peanut (6). Niemann & Hefle have also sounded a cautionary note (7). This report, from the University of Nebraska’s Food Allergy Research and Resource Programme, reported testing for contamination by peanut in 144 products displayed under three different warning labels. Peanut protein was found to have contaminated 8 out of 37 (21.6%) products labelled “may contain peanut”; 4/23 products (17%) labelled “manufactured on shared equipment” and in 3/22 products (13.6%) labelled “manufactured in a facility that also processes peanut”. Contamination ranged from the limit of detection of the assay (1 part per million – ppm) equivalent to 1 mg/kg to 4300 ppm (4.3 g/kg) (7).

Keating et al. noted in 1990 that it was cheaper for industry to deffavour and reffavour peanuts than to use the original more expensive tree nuts (8). Keating also noted that the literature at the time stated that the amount of protein needed to cause a reaction in mild or moderate reactors (severe reactors are not challenged often) was felt to be between 100 and 350 mg of protein. This level has since achieved significant industrial importance due to the application of immunological methods to determine safety and quality control mechanisms in the industry.

Manufacturers must also be aware of the potential impact of labelling on non-allergic shoppers. Restrictions or bans of snacks containing peanut are common hazard control responses of schools to the identification of a peanut allergic child in a class. The

average class size in state schools in Britain is 30 pupils. Hypothetically, each child in the class could be considered to be from a “normal” family of four members. Most families practise uniform shopping for the whole family rather than selective shopping for individuals. It is conceivable (but has yet to be measured) that for each peanut allergic child there are 120 unaffected members of the public who may be dissuaded from buying a snack or other food because of a “may contain” label.

Route of exposure

It appears that most severe reactions to foods are, not surprisingly, to ingested allergens rather than to inhaled or transcutaneously absorbed allergens. There are many case reports and series of significant reactions to very low dose oral exposure.

The amount of peanut protein involved in eliciting “non-ingestion” reactions must be very small. In our survey of 622 peanut allergic subjects in Britain, 17% reported reactions to the smell of peanut and 66% to non-ingestion contact with peanut (3). Many subjects whom we see in clinics report reactions to exposure to peanut through intact skin. Most reactions elicited in this way are minor and usually consist of localised urticaria or angioedema.

Allergic reactions in the community

Food allergy is the most common cause of anaphylaxis in the community, causing more than a third of reactions in a population-based study (9) and up to half of reported cases of anaphylaxis (10). A large series of fatal cases of anaphylaxis suggests that fatal reactions to food are more commonly due to inadvertent ingestion of a food that is high risk rather than to low dose contamination of a food thought to be low risk (11). This British series is consistent with the landmark findings of Sampson et al. in the early 1990s (12), in that there were also failures of response by sufferers and even health professionals that contributed to the deaths. It is easy to be wise after the fact but preparedness to “treat and review” known allergies who may or may not be having a severe reaction rather than “wait and see” is a more appropriate response by patients, members of the public, paramedics and doctors.

In support of the finding of low dose reactivity in the community is the paper by Sicherer, reporting a telephone survey of peanut allergic subjects who had experienced reactions during aeroplane flights (11). Of 42 reactions 20 were due to ingestion, 8 to skin contact and 14 to inhalation, with a correlation between route of exposure and severity of reaction (13). Anxiety, claustrophobia and the distance from medical care may

contribute to symptoms experienced. The relatively low partial pressure of oxygen in the cabin of aeroplanes, compared to the normal partial pressure of oxygen on the flight deck, may render passengers more vulnerable to experiencing airway symptoms.

Other intrinsic and extrinsic factors that may exacerbate reactions to food allergens or cause reactions to lower doses of peanut are listed in Tables 1 and 2. Asthma, particularly if poorly controlled, has been shown to be an indicator of risk of severe allergic reactions. The St Mary's group in London has suggested that poor control of both seasonal allergic asthma and seasonal allergic rhinitis may have contributed to their finding that, over an 18-month period, six of seven ICU admissions for life-threatening allergic symptoms occurred during the summer months (14). Pollen sensitive sufferers of oral allergy syndrome can tolerate the implicated fruits if their pollen allergy is successfully treated with immunotherapy (15). Subjects who suffer from exercise-induced, food-related anaphylaxis can also decrease their symptoms if they limit their exercise during the pollen season (16).

Allergic reactions in formal food challenges

The concept of mild to moderate reactivity to low-dose "non-ingestion" exposures to allergen has been the basis of the early steps of a food challenge, negating the need for ingestion of capsulated allergens, which do not give the desirable early warning reactions that can be easily elicited by labial challenges (17, 18). Labial challenges with peanut and peanut oils have elicited positive reactions (19, 20). The conflicting evidence regarding the allergenicity of refined peanut oils used in the British and French studies is likely to be due to differences in protein content of the oils. Consistent with this interpretation is our finding of reactivity to unrefined peanut oil in subjects with positive peanut challenges but negative challenges with refined oil reactions (19).

The gold standard investigation to diagnose or refute food allergy is a double-blind placebo-controlled food challenge (17, 18). The following paragraphs deal with a selection of the most important papers that have relied

Table 2. Extrinsic human and non-human factors that contribute to reaction severity

Exposure	Location: "home" or "non-home" (1) Dose of allergen
Response of others	Accuracy of information given to subject about ingredients (29) Recognition of reaction Using rescue medication (11) Seeking additional help (11)

upon this gold standard. Other equally worthy papers have not been cited for reasons of space. Table 3 summarises the findings of the papers discussed.

Maximum doses ingested were explicitly stated in the early series of food challenges from Denver by May & Bock. The emphasis of most studies thereafter was on making or refuting the diagnosis of food allergy. To do that, it is important to "capture" high-dose reactors by ensuring an adequate dose of allergen is consumed. Though these high-dose reactors are relatively rare in a food allergic population it is a clinical imperative that a false negative challenge is avoided. A negative challenge, which results from that subject's (high) threshold not being reached, would be false reassurance to the subject challenged. A false negative challenge may have significant liability implications if a positive reaction occurred on a later exposure to allergen away from medical help.

In the seminal papers on the diagnosis of food allergy by May and colleagues the issue of *eliciting* dose is mentioned but not emphasised. There is also clear evidence of subjects reacting to the first dose, implying that they might have been sensitive to a lower starting dose. In 1976, May reported that only 11 out of 38 children who reported symptoms in response to foods had a positive double-blind placebo-controlled food challenge and that only 14 of the total of 70 challenges were positive (21). One challenge, with peanut, was positive after the first dose of 100 mg of peanut. The same group reported a positive reaction to 20 mg of whole egg in a 12-year-old child (22).

The same group reported further in 1988 that seven subjects had presented with allergic symptoms after consuming a new food supplement. Six of the seven had positive SPTs with cottonseed, an ingredient of the supplement. The first two scheduled double-blind, placebo-controlled food challenges with cottonseed were both positive. The reactions were so impressive

Table 1. Intrinsic human factors that contribute to reaction severity

Medical features	Age Asthma (3, 12) Cardiovascular disease Medication
Allergic history	Target organ Severity of previous reaction (12)
Decision making	Awareness of friends and colleagues Carrying rescue medication (11) Using rescue medication (11) Exercise Alcohol consumed with meal containing allergen (29)

Table 3. Minimum doses of allergen in double-blind, placebo-controlled food challenges

Food	Dose	Paper	Comment
Egg	<100 mg	Moneret-Vautrin (20) Sicherer (26)	100 mg was lowest dose tested
Codfish	55.6	Hansen (24)	
Milk	<100 mg	Sicherer (26)	100 mg was lowest dose tested
Peanut	1 mg	Rancé (28)	Diagnostic challenges in children
	2 mg	Hourihane (27)	Adults with previous positive challenges
Soy	88 mg	Magnolfi (25)	Capsules

that the remaining subjects were not challenged. One subject reacted after the last dose (500 mg), having had no difficulties with the preceding doses of 100 mg and 350 mg. The second subject reacted after the first dose of 100 mg. This comparison of two challenge subjects is the first clear illustration of a threshold effect: two subjects with broadly similar histories of reactions to similar doses of a food in the community reacted to substantially different doses in the setting of a formal food challenge (23).

Hansen & Bindslev-Jensen reported a series of double-blind, placebo-controlled food challenges of adults with reported codfish allergy. Challenge confirmed the diagnosis in seven of the 10 subjects with the "lowest dose eliciting objective signs" being 55.6 mg of codfish (24).

In a report of challenges of children of mixed ages with positive SPT to soy, Magnolfi et al. also showed reactivity to the first dose of a challenge series (25). Only eight of the 131 (6%) subjects with positive SPT to soy had a double-blind, placebo-controlled food challenge with soy. Younger children consumed soy powder in fruit juice and older subjects consumed up to 40 capsules each containing 88 mg of soy protein. Two subjects, one with and one without a history of soy reactivity, reacted after one capsule (88 mg) and another subject reacted after two capsules (176 mg) (25).

In 1998, Moneret-Vautrin and colleagues reported their review of 142 peanut allergic children and adults in France (20). Eighty-two subjects had positive labial food challenges; 31 subjects had negative labial challenge followed by positive oral challenge; 11 subjects had positive oral challenge only and eight subjects had positive labial and oral challenge. Fourteen subjects (10%) had positive oral challenges with peanut oil.

The authors noted that oral reactivity was more common at low doses of peanut than egg: 44 of 50 positive oral peanut challenges were to cumulative doses below 1 g, compared to 24 of 40 egg challenges. This difference was due to differences in the 100 mg–1 g range rather than in the very low dose range, below 100 mg, where 25% and 30% of subjects, respectively, reacted to peanut and egg.

Sicherer reported a review of 13 years (1980–1993) of diagnostic food challenges in children with atopic dermatitis (26). (There was selection bias of subjects for challenges after that date, depending more on SPT and specific IgE measurements). The starting dose was occasionally lower than the conventional 400–500 mg dose, at the discretion of the attending doctor. Overall, 196 children had 513 positive challenges. Forty four per cent of the positive challenges were to cumulative doses at or below 500 mg, with percentages varying for each food (egg 49%, milk 55%, peanut 26% and fish 17%).

Twenty five per cent of the positive milk challenges and 11% of the egg challenges were positive at a starting dose of 100 mg, but it is not stated how many challenges were started at this lower dose. The authors conclude that routine challenges should start at 100 mg, though even lower doses may be necessary occasionally.

The above studies started with low doses but were not designed to test for a threshold, but to make a diagnosis. As far as I am aware, our study of peanut allergics, in collaboration with Steve Taylor in Lincoln, Nebraska, was the first deliberate attempt to determine a threshold dose (27). The subjects we tested all had clear histories of reactivity to peanut and had all experienced positive reactions to open challenges during a previous study (19). The positive challenges had been: to a labial challenge with peanut (eight subjects), implying low dose sensitivity to peanut; to unrefined peanut oil (four subjects) or to both unrefined peanut oil and, in a separate challenge, to labial challenge with peanut (two subjects).

The doses tested were 10 µg, 20 µg, 50 µg, 100 µg, 250 µg, 500 µg, 1 mg, 2 mg, 5 mg, 10 mg, 20 mg and 50 mg. The top dose of peanut, 50 mg, was well below previous published levels of reactivity. The other innovation was the interspersing of placebo doses between the active doses so that in total 12 active and 12 placebo doses were given in random sequence. This contrasts with routine challenge practice, which consists of two separate challenge series, one of all active doses and one of all placebo doses.

We expected that the six subjects who had reacted to the unrefined peanut oil would be most likely to show low dose reactivity. This was borne out by the low dose challenge series in which all six unrefined oil reactors reacted to one of the low doses, two of them to just 5 mg of protein. In contrast, six of the seven subjects who had not reacted to unrefined oil did not react to the low dose challenges.

The most instructive case was the remaining subject who had not reacted to the unrefined oil but had the most severe reaction in the low dose challenge. Her reaction in the low dose challenge was also to the lowest dose, 2 mg. She had suffered subjective symptoms to doses as low as 100 µg. This case is the first evidence of a varying threshold within an individual as opposed to between individuals, as had been shown by Atkins & Bock with cottonseed (23).

A recent conference report from Rancé and colleagues in France has confirmed the usefulness of starting challenges at very low doses (28). The challenge series was also continued to include doses up to 5 g. A total of 125 subjects had a positive double-blind, placebo-controlled food challenge with peanut. Six subjects (4.8%) reacted to the lowest dose tested, 1 mg, and 45 (36.2%) to a cumulative dose below 100 mg.

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