

OPINIONS IN ALLERGY

Can we define a tolerable level of risk in food allergy? Report from a EuroPrevall/UK Food Standards Agency workshop

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Summary

Background There is an emerging consensus that, as with other risks in society, zero risk for food-allergic people is not a realistic or attainable option. Food allergy challenge data and new risk assessment methods offer the opportunity to develop quantitative limits for unintended allergenic ingredients which can be used in risk-based approaches. However, a prerequisite to their application is defining a tolerable level of risk. This requires a value judgement and is ultimately a 'societal' decision that has to involve all relevant stakeholders.

Objective The aim of the workshop was to bring together key representatives from the stakeholders (regulators, food industry, clinical researchers and patients), and for the first time ever discuss the definition of a tolerable level of risk with regard to allergic reactions to food.

Results The discussions revealed a consensus that zero risk was not a realistic option and that it is essential to address the current lack of agreed action levels for cross-contamination with allergens if food allergen management practice is to be improved. The discussions also indicated that it was difficult to define and quantify a tolerable level of risk, although both the clinical and the industry groups tried to do so. A consensus emerged that doing nothing was not a viable option, and there was a strong desire to take action to improve the current situation.

Conclusions and Clinical Relevance Two concrete actions were suggested: (1) Action levels should be derived from the data currently available. Different scenarios should be examined and further developed in an iterative process. On the basis of this work, a tolerable level of risk should be proposed. (2) 'One-dose' clinical trial with a low challenge dose should be performed in multiple centres to provide additional information about the general applicability of dose-distribution models and help validate the threshold levels derived.

Keywords EuroPrevall, food allergy, risk assessment, stakeholders, tolerable risk, UK Food Standards Agency

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Introduction

Food-allergic consumers constitute a small, but apparently growing proportion of the general population. Exposure to the offending food in individuals with IgE-

mediated food allergy (i.e. acute allergic reactions in the context of a positive serum specific IgE or skin prick test) may result in development of an acute allergic reaction that may include any of the following: itching and/or swelling of the oral cavity or pharynx,

skin rashes (urticaria, angioedema, eczema flare), gastrointestinal upset (diarrhoea, vomiting and abdominal pain), asthmatic symptoms (wheezing, breathlessness, coughing) or in extreme circumstances life-threatening anaphylaxis (a rapidly evolving multi-system allergic reaction that involves respiratory or circulatory compromise). The risk of life-threatening anaphylaxis brings with it a unique set of ethical and moral dilemmas for those discussing the public health implications of precautionary labelling.

There is significant variation in the thresholds of reaction to a food allergen between individuals. For instance, some allergic consumers are exquisitely sensitive to minute doses of an allergen and are at greater risk of anaphylaxis than others [1, 2]. Furthermore, threshold levels can vary between different exposures within one individual such that on one instance a consumer may react to a very low dose and on another occasion might tolerate a higher dose of allergen. Currently, there are neither good predictors of threshold dose for any given individual nor can the type of reaction be reliably predicted. At most, it can be said that those who have experienced anaphylaxis previously are at greater risk of a future episode of anaphylaxis [3] although in a case series 80% of those presenting with food-induced anaphylaxis had previously had a minor acute reaction on previous exposure [4].

Most important to include in these considerations is the fact that there are still rather limited data to inform those developing public health guidelines as to what proportion of allergic consumers may tolerate very low levels of allergen in food products. To add to the complexity of these considerations, there is some evidence that manufacturing processes can increase or decrease the allergenicity of certain foods. For instance, for some individuals, the allergenicity of egg appears to be lower in baked products such as cakes or biscuits, with 60–70% of egg allergic individuals tolerant of low levels of egg in baked goods [5], whereas frying or roasting peanuts appears to increase their allergenicity among those consumers reactive to peanut storage proteins [6].

Consumers at risk of acute allergic reactions have different risk profiles from those with other food associated immune-related conditions such as coeliac disease. The consequences of accidental ingestion in the former are short-lived (although potentially extreme in the form of death), whereas for the latter, long-term sequelae for those with low-level exposure to gluten provides a different risk profile and therefore public health consideration. Furthermore, new forms of therapy using specific oral tolerance induction (SOTI) are under development with the goal to protect the allergic consumer against accidental reactions after consumption of contaminated foods [7]. As new research comes to light,

views on the risk of precautionary labelling may undergo radical changes.

Food allergy challenge data and new risk assessment methods offer the opportunity to develop quantitative limits for the adventitious presence of allergens, which can be used in risk-based approaches. However, a prerequisite to their application is defining a tolerable level of risk. This requires a value judgement and is ultimately a 'societal' decision that has to involve all relevant stakeholders. This workshop, held in May 2009, was convened to discuss whether it was possible to define a tolerable risk for food allergy in relation to precautionary labelling for food allergens. Current European Union (EU) labelling legislation, as well as most food labelling regulations followed internationally, covers allergens as ingredients, but does not set a regulatory action level regarding their presence as cross-contaminants, as has been done for residual gluten in 'gluten free-free' labelled foods. This has resulted in proliferation of voluntary 'may contain X' type precautionary labelling. Both consumers and industry have concerns about this, as over use of 'may contain' labelling may undermine its value as a risk management measure. It also creates uncertainty; do different words mean different levels of risk? How should and can businesses decide what level of risk warrants advisory labelling? An excessive use of warnings leads to restrictions in choice for consumers if they take notice of every warning, or increases risk for consumers if such warnings are ignored. A food safety goal of minimizing the number of reactions to foods among allergic consumers therefore leads to a risk-based approach to allergen control and advisory ('may contain X') allergen labelling.

The aim of the workshop was to bring together key representatives from regulatory and industry fields, clinical research groups and patients to discuss how a tolerable level of risk with regard to allergic reactions to food could be defined.

Several papers were sent to the participants and used as background information for the workshop [8–16]. Reference 12 was at the time of the workshop (May 2009) in manuscript.

This paper presents some of the background material presented at the workshop as well as the results and conclusions from the discussions.

How do we define risk?

There is an emerging consensus that, as with other risks in society, zero risk for food-allergic people is not a realistic or attainable option. Food allergy challenge data and new risk assessment methods offer the opportunity to develop quantitative limits for the adventitious presence of allergens which can be used in

risk-based approaches. However, a prerequisite to their application is defining a tolerable level of risk on which to base the thresholds to be used for management of allergen risks. Defining a tolerable risk requires a value judgement and is ultimately a 'societal' decision that has to involve all relevant stakeholders.

A risk-based approach focuses on the probability that exposure to a food will result in an adverse effect. It should be able to provide the scientific foundation to determine agreed threshold levels for industry to use in risk-management decisions, including the use of advisory warning of possible cross-contamination. It should also be capable of being used to decide what level of cross-contamination is high enough to justify a product recall/withdrawal and what level of the allergen is sufficiently low to justify a 'free-from' claim.

How is tolerable risk defined in areas other than food allergy?

Even though chemical and microbial risk assessments have been made for many years, it is not easy to find examples where a tolerable risk is actually quantified.

When dealing with the risk from chemicals there is a traditional distinction between acceptable and tolerable risk. 'Acceptable risk' is used not only when chemicals present in food pose a risk but also deliver a benefit. These are food additives, pesticides and veterinary drugs that may occur either as ingredients or as residues in food. The term 'tolerable risk' is generally used in the context of chemical compounds that are unavoidably present, such as contaminants that have no benefit under any conditions of exposure.

For chemicals where the toxicological effect has a threshold, the acceptable or tolerable daily intake is typically used. The aim is an acceptable/tolerable intake defined as 'an estimate of the intake of a substance over a lifetime that is considered to be without appreciable risk' [17]. This procedure does not allow for quantification of the risk. The aim is to reduce the magnitude of the risk and the use of wording such as 'considered' or 'appreciable' are not defined.

The as low as reasonably achievable (ALARA) principle aims to set thresholds for the presence of the substance at levels that are meant to be as low as possible to reduce the health risk to consumers. Both 'reasonably' and 'achievable' are also open to interpretation.

Cancer from exposure to genotoxic carcinogens is a toxicological endpoint where a threshold cannot be defined. A lifetime cancer risk of one in 1 000 000 (i.e. one additional cancer case per million exposed persons per 70-year lifetime) is often used as the tolerable risk. The World Health Organisation (WHO) drinking-water quality guidelines consider that a lifetime cancer risk of <1 in 100 000 represents a tolerable risk [18], but it is

emphasized that defining a tolerable risk is a policy decision. As a threshold for the carcinogenic effect of genotoxic substances cannot be defined, the use of this concept implies acceptance of a risk of cancer.

The microorganism *Giardia* has been used as a reference organism for microbial risk in drinking water and requires that the risk is <1 infection per 10 000 people per year [10]. If it is assumed that there is 50–67% frequency of clinical illness following infection with *Giardia*, this translates into an annual risk of illness of one in 20 000 if the lower boundary (50%) is used. An estimated case-fatality rate for *Giardia* is 0.1%. This results in an annual risk of death of one in 20 000 000. If this figure is converted into a 70-year lifetime risk, the result is a risk of one in 300 000. This is in the same order of magnitude as the tolerable risk from carcinogens in drinking water suggested by the WHO.

Risk assessment in food allergy

A previous workshop [11] scrutinized three possible approaches to safety assessment and risk assessment for allergenic foods based on low dose challenge data from clinical trials: safety assessment using no observable adverse effect levels/lowest observable adverse effect levels and uncertainty factors, safety assessment using Benchmark Dose and Margin of Exposure (MoE) and risk assessment using probabilistic models. Participants concluded that all three approaches to safety and risk assessment of allergenic foods could be applied, depending on the availability and quality of data. A particular strength of the MoE and probabilistic approaches is that they do not rely on low dose extrapolation with its inherent modelling issues. Probabilistic modelling is considered to be the most promising approach for use in population risk assessment (which is a particular focus for risk managers). For all approaches, further improvement of input data is desirable, particularly data on consumption patterns/food choices in food-allergic consumers, data on minimum eliciting doses and data that can be used to evaluate whether the whole population at risk has been modelled accurately. This workshop also observed that, together with new approaches, data which could be used to apply them were also becoming available. However, some of the specific characteristics of food allergens as contaminants meant that application of these new approaches depended critically on definition and acceptance of a tolerable level of risk.

Action levels

In this article, the term 'action level' is used for a level of allergenic food that may result in an 'action'. This could be used for labelling a food product as 'free-from', to apply precautionary labelling or to withdrawal

from sale. The term is used in the same manner as in the Australian Voluntary Incidental Trace Allergen Labelling (VITAL) system, which is currently the most elaborated system of action levels. Briefly, the VITAL grid consists of three action levels and two transition points. Below the lower transition point (action level 1), the risk is deemed so low as not to require precautionary labelling, whereas above the upper transition point, the concentration of unintended allergen is considered to warrant labelling it as an ingredient. Between the two points, (action level 2) the product should carry a precautionary label. The lower transition point was derived from data cited in the US FDA's Threshold Working Group publication [19] by applying a 10-fold uncertainty factor. The upper transition point was set at 10 times the lower transition point. Action level 1 ranged from <2 p.p.m. for peanut, egg, tree nuts, sesame and crustacea to <20 p.p.m. for fish and gluten, all based on the dose in a 5 g teaspoonful [20].

Method

The stakeholders invited to this workshop were people dealing with assessing and managing food allergy and food allergen risks on an individual basis, i.e. food-

allergic patients and clinicians, and on a population basis, i.e. public health and industrial risk managers.

Although there are as yet no agreed action levels for allergenic food and significant uncertainty for patients and clinicians because of 'may contain' type labelling, questions relating to food allergy risk are handled every day. This everyday management relies on a more or less well-formulated notion of what is a 'tolerable risk'. To develop a concept framework of what the participants consider to be a tolerable risk, as well as to enable discussion of new ways of managing food allergy and to shed light on how risk is currently managed, a predefined set of questions, some common to all the groups and some specifically designed for each group, were developed.

The questions were discussed in four groups (number of participants in brackets); patients (11), clinicians (10), regulators (13) and industry (18). The results of the group discussions were presented in a plenary session that also discussed common perspectives and conclusions.

Results of discussions

The outcome of the most important discussions in the stakeholder groups are presented in Tables 1 and 2. The

Table 1. Main points emerging from stakeholder breakout groups – common questions on tolerable risk

Food allergy and tolerable risk			
How does the nature of the risk or possible adverse effects affect what you would consider a tolerable risk?			
Patients	Clinicians	Industry	Public health authority
How risk is tolerated depends on the nature of the risk. The more severe the effect, the lower the tolerance			
Risk of death (anaphylaxis) is not a tolerable risk	Tolerable compared with 'every day risk', i.e. 1 in 10 000 chance of a patient having anaphylaxis in 1 year of eating foods deemed 'safe'	Different levels of tolerable risk would apply to different levels of harm 1 : 10 000 for lip tingling 1 : 10 000 000 for fatality	Tolerable risk depends on information about the risk (act based on information)
Ill defined predictability reduces tolerance		It is more important to protect from severe reactions	The list of allergens identified by regulators for mandatory declaration reflects a prioritization of risk at the population level rather than at the individual level. In effect, this is an expression of a tolerable level of risk
The perception of risk is important	What is acceptable to one patient may not be acceptable to another – therefore quantifying risk for a patient is very helpful	Risk acceptance differs by individual consumers, e.g. some ignore precautionary labelling	
	How essential is the exposure – snack foods vs. staple food		
	Ability to avoid exposure		
	Severity of previous reaction		
	Other risk factors, e.g. asthma		
	Remote living		
	We also need risk information for impact on non-allergic consumers for any public health measure that will impact the whole community (e.g. increased cost of food that has a lower risk also influences non-allergic population as cost of manufacturing is passed on to all consumers)		

Table 2. Main points emerging from the different stakeholder breakout groups – impact on your group

What do you think would be the impact on <i>your</i> group of not dealing with 'undeclared allergenic food' properly?			
Patients	Clinicians	Industry	Public health authority
Diminished trust in food labels	Ongoing uncertainties about information to give to patients	Consumer confusion, i.e. loss of confidence and brand damage, mistrust	Subjectivity from risk managers when dealing with the risk from allergenic food
Negative impact on quality of life	Possible over-management, e.g. defensive medicine due to lack of reliable information	Precautionary labelling proliferates	A high level of uncertainty of the potential risk of cross-contamination
Risk of reactions		Inconsistent use of risk communication across industry – devaluing precautionary warning statements	Lack of predictability of the level of contamination in foods with 'may contain' labelling
Restricted food choice	Possible under-management, e.g. physicians recommending patients can ignore precautionary labels because they are so wide spread	Risk assessment by individuals rather than public health authorities	The current situation contributes to 'risk taking behaviour' such as ignoring labelling information
	Lack of trust in allergy experts due to variation in recommendations from different physicians	Quality of life for consumers decreases	Undermine use of food labelling
	Cost to public and society – fear, lack of education, increased cost of food	Ignoring 'may contain' leading to increased risk taking and fatalities	There is a need for a harmonized approach: amongst all stakeholders and between regulators on an international level
	More reliable thresholds may drive more food challenges to reassure patients that they can tolerate that particular threshold. This would impact on patient waiting lists for challenges	Lack of dietary choice for allergic consumers – only niche foods.	
		The majority of processed foods have precautionary labelling	
		Lack of dietary choice for all consumers, e.g. no nuts in schools, reluctance to use allergenic foods in processed foods (fish, tree nuts, nuts)	
		Lack of capability to make economic food	
		Litigation	
		Legal fees	
		Compensation	
		False or uninformed claims	
		Enforcement	
		Increased costs	
		Inconsistency between enforcement jurisdictions	

following is a summary of the most important points under the main headings.

Tolerable risk

In the discussion on what is a 'tolerable risk', there was acceptance among all groups that zero risk was not a practicable proposition in food safety in general or in food allergy management in particular. Different stakeholders differed in their description of 'tolerable risk'. Industry and regulators visualized a very quantitative conception, reflective of their public health approach. Thus, industrial stakeholders referred to an expectation that food should be safe for the vast majority of consumers, with concepts such as the US Food and Drug Administration's (US FDA) 'reasonable certainty of no harm' representing an upper boundary. They also considered factors modulating tolerability, such as severity, duration and reversibility of any potential adverse effects. In addition to these concepts, regulators also emphasized the role of cost benefit assessments (pro-

portionality between harm to be prevented and resources required for prevention) in determining tolerability. In relation to food allergy, all four groups agreed that risk tolerance depends on the nature of the effect. The more severe and wide spread the effect, the lower the tolerance. It was also recognized that at an individual level, perception of risk is important, and that if uncertainty is high, then the tolerability of the risk decreases.

Not dealing with undeclared allergenic food

When discussing the impact of not dealing with the adventitious presence of allergens in food, all groups stated that not dealing with this issue would have negative implications for their group. The patient group emphasized diminished trust in food labels, negative impact on quality of life and risk of reactions. The clinicians found that ongoing uncertainties about information to give to their patients would lead to the inappropriate level of management by physicians with

regard to allergen avoidance recommendations. The regulators acknowledged that the current situation leads to ad hoc management and practices including a degree of subjectivity from risk managers when dealing with the risk from undeclared allergens found in food. If the current situation continues, then we are accepting a high level of uncertainty about the potential risk of cross-contamination. Industry found that consumer confusion would lead to mistrust and lowered confidence. The proliferation of precautionary labelling and the inconsistent use of risk communication devalue their importance and impact. Industry also worried about the economic and cost implications. Without defined standards, enforcement would be inconsistent and subject to local interpretation. This could lead to increased costs without any concomitant gain in terms of food safety.

The use of action levels

The patients found that having different action levels with different labelling for allergenic foods would not be a benefit to patients. On the other hand, they agreed that high level of unavoidable contamination should lead to having the contaminating allergenic food labelled as an ingredient. A prerequisite for having different action levels is that food-allergic patients may be stratified into more and less reactive groups. The clinicians found that this is currently an inexact science although some clinicians attempt to do it, for instance in deciding on prescription of epinephrine auto-injectors. In contrast, it is possible to categorize those at highest risk of *anaphylaxis* [3, 21].

If stratification of patients is not possible, 'free-from' foods may be a way forward to protect the most reactive food-allergic individuals, while maintaining some choice. The patient group emphasized that if 'free-from' foods are to be of value, then rules regulating precisely what is meant by 'free-from' are needed and such rules need to be enforced. The clinicians found that 'free-from' foods could shortcut the requirement for allergist/dietician education and therefore circumvent the variation in educational practices of various health professions and dietitians. The availability of a sufficient range of defined 'free-from' foods would simplify advice for the most sensitive patients.

When asked about how industry handles the unintended presence of residues of allergenic foods when there are no agreed action levels, industry answered that management levels are used both for cleaning and for risk assessment during incidents. Qualitative standards are used across the board, e.g. visibly clean, but not always quantitative levels. A small number of large food companies do use in house action levels, but the great majority of companies do not. When a company decides to use 'may contain' labelling, many of the rea-

sons for doing so are because of lack of information to do scientific risk assessment.

Industry and food regulators need action levels to manage the risk from food allergens. When asked what the consequences are to society if action levels are not agreed, the regulators answered that this would lead to continued confusion over allergen warnings, leading to potential risk behaviour by allergic consumers. In addition, this would lead to inconsistent approaches to allergen management between different businesses and different regulators, potentially compromising safety.

The suggestion for an action level of 1–10 mg allergenic food per kg [22] was not well received by any of the groups. The regulators found that this question could not be answered during the course of this workshop, and decisions on where to strike the balance between choice and safety would need to be made. Any suggested action level would require agreement from all stakeholders, as part of the risk management process. The industry group was sceptical about the science behind the action levels suggested in that paper and noted that there is a need to use the data now becoming available to set scientifically robust limits. There was some acceptance in the group that a best guess approach may be applicable in the shorter-term to meet the urgent need for agreed levels. The discussion in the clinical group also reflected that it is not possible to give a definitive answer to this question, as there are several aspects to consider. The clinicians would want to see more data to assess what proportion of patients react to 1 mg/kg for each allergen and importantly whether any develop anaphylaxis. If there was a suggested action level, the risk could be calculated. Whilst 1 mg/kg is better than 10 mg/kg, this may be different for different foods. The allergic community would be likely to tolerate some adverse reactions provided they are not severe, and so a higher threshold could be chosen to ensure that precautionary allergen labels are really only used at levels which pose a clinical risk to patients. In line with this, the regulators suggested that some of the levels reported from the risk assessments are very low and perhaps too low for practical management and analytical detection, with the result that they would amount in practice to a zero tolerance policy.

Conclusions and actions

The discussions revealed a consensus that zero risk was not a practicable or realistic option and that it is essential to address the current lack of agreed action levels for cross-contamination of allergens if food allergy and food allergen management are to be improved. The discussions also indicated that it was difficult to define and quantify a tolerable level of risk, although both the clinical and the industry groups tried to quantify that risk,

and proposed that a higher number of reactions could be tolerated for mild symptoms than for severe symptoms.

A consensus emerged from the final plenary session that not doing anything was not a viable option and there was a strong desire to take action to improve the current situation.

Two concrete actions were suggested.

Action 1

1 Review available food challenge data and derive provisional action levels. Develop different scenarios and implications for each level and ask stakeholders to comment.

2 Propose a value for the tolerable level of risk (e.g. as a level of protection).

The above will form part of an iterative process. All stakeholders, including non-allergic consumers, should be invited to participate in this process.

Action 2

Conduct a 'one-dose' clinical trial in multiple centres across the world using a standardized food challenge protocol with a low dose. The ED₅, the dose estimated

by statistical modelling to elicit a reaction in 5% of allergic patients (ED₅), based on challenge studies, is proposed for this trial as a good compromise between the need to assure patient safety and the number of patients who would need to be challenged to obtain a statistically significant result. It is not suggested that the ED₅ value as such would provide the desired level of protection. However, the trial will help to validate the dose-distribution models in the wider food-allergic population and additionally provide information about the severity profile of reactions that might be expected at that level. This information will contribute to defining the tolerable level of risk in relation to allergic reactions to foods.

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References

- Wainstein BK, Studdert J, Ziegler M, Ziegler JB. Prediction of anaphylaxis during peanut food challenge: usefulness of the peanut skin prick test (SPT) and specific IgE level. *Pediatr Allergy Immunol* 2010; 21:603–11.
- Rolinck-Werninghaus C *et al.* Outcome of oral food challenges in children in relation to allergen threshold dose and allergen-specific IgE. *Allergy* 2011; accepted for publication.
- Mullins RJ. Anaphylaxis: risk factors for recurrence. *Clin Exp Allergy* 2003; 33:1033–40.
- Ewan P, Clark A. Management of peanut and nut allergy. *Lancet* 2001; 357:1127–8.
- Tey D, Heine RG. Egg allergy in childhood: an update. *Curr Opin Allergy Clin Immunol* 2009; 9:244–50.
- Beyer K, Morrow E, Li X-M *et al.* Effects of cooking methods on peanut allergenicity. *J Allergy Clin Immunol* 2001; 107:1077–81.
- Blumchen K, Ulbricht H, Staden U *et al.* Oral peanut immunotherapy in children with peanut anaphylaxis. *J Allergy Clin Immunol* 2010; 126:83–91.
- Crevel RWR, Ballmer-Weber BK, Holzhauser T *et al.* Thresholds for food allergens and their value to different stakeholders. *Allergy* 2008; 63:597–609.
- Hourihane JO'B, Grimshaw KEC, Lewis SA *et al.* Does severity of low-dose, double-blind, placebo-controlled food challenges reflect severity of allergic reactions to peanut in the community? *Clin Exp Allergy* 2005; 35:1227–33.
- Hunter PR, Fewtrell L. Acceptable risk in water quality. In: Fewtrell L, Bartram J, eds. *WHO guidelines, standards and health: assessment of risk and risk management for water related infectious disease*. London: IWA Publishing, 2001:207–27.
- Madsen CB, Hattersley S, Buck J *et al.* Approaches to risk assessment in food allergy: report from a workshop "Developing a framework for assessing the risk from allergenic foods". *Food Chem Toxicol*, 2009; 47:480–9.
- Madsen CB, Crevel RWR, Chan C-H *et al.* Food allergy: stakeholder perspectives on acceptable risk. *Regul Toxicol Pharmacol* 2010; 57: 256–65.
- Pumphrey SH, Gowland MH. Further fatal allergic reactions to food in the United Kingdom, 1999–2006. *J Allergy Clin Immunol* 2007; 119:1018–9.
- Sampson MA, Munoz-Furlong A, Sicherer SH. Risk-taking and coping strategies of adolescents and young adults with food allergy. *J Allergy Clin Immunol* 2006; 117:1440–5.
- Shah E, Pongracic J. Food-induced anaphylaxis: who, what, why, and where? *Pediatr Ann* 2008; 37:536–41.
- Taylor SL, Crevel RWR, Sheffield D, Kabourek J, Baumert J. Threshold dose for peanut: risk characterization based upon published results from challenges of peanut-allergic individuals. *Food Chem Toxicol* 2009; 47:1198–204.
- OECD. *Description of selected key generic terms used in general hazard/risk assessment*. OECD series on testing and assessment no. 44. ENV/JM/MONO (2003)15. Paris: OECD, 2003.
- WHO. *Guidelines for drinking water quality*. 2nd Edn. Vol. 2: Health Criteria and other Supporting Information. Geneva: WHO, 1996.
- Threshold Working Group. Approaches to establish thresholds for major food

- allergens and for gluten in foods. *J Food Prot.* 2008; 71:1043–88.
- 20 Australian Food and Grocery Council Food industry guide to allergen management and labelling. 2007. Available at <http://www.allergenbureau.net/vital> (accessed 15 January 2011).
- 21 Järvinen KM. Food-induced anaphylaxis. *Curr Opin Allergy Clin Immunol* 2011; 11:255–61.
- 22 Vieths S, Holzhauser T, Erdman S *et al.* Stellungnahme der Arbeitsgruppe Nahrungsmittelallergie der Deutschen Gesellschaft für Allergologie und klinische Immunologie und des Ärzteverbandes Deutscher Allergologen, *Allergologie* 2006; 15:114–23.