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Rethinking precautionary allergen labelling – Threshold doses, risk assessment approaches and analytical implications

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REVIEW PAPER

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ABSTRACT

Food allergies became a major public health and food safety interest in the past decades as their prevalence is increasing, and their only available treatment is a strict elimination diet that necessitates appropriate food labelling regulations. While such regulations are available worldwide, most of them are not taking into account inadvertent allergen cross-contamination and they usually do not define threshold doses that could support the industry in their endeavour to provide reliable food labels for allergic consumers. This resulted in the proliferation of the "may contain" type precautionary allergen labelling (PAL), which is voluntary and is intended to warn consumers for potential unintended contamination with an otherwise undeclared allergen. As this kind of labelling is hardly ever based on actual risk assessment, it puts both the industry and the consumer into a difficult position. A promising tool towards the solution of this problem could be allergen threshold doses based on clinical data, which are becoming increasingly available. This review intends to present this process, the new ways of improved risk assessment it opens, and its implications for food analysis.

KEYWORDS

food allergies, Voluntary Incidental Trace Allergen Labelling (VITAL), risk mitigation, food safety, allergen analysis

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1. INTRODUCTION

Hypersensitivity reactions triggered by certain food components have become increasingly prevalent globally. The raising occurrence (5–10%) and awareness of IgE-mediated food allergies in particular put this issue into the forefront of food safety legislation as a public health concern. To date, food allergies can only be managed by following a life-long diet eliminating the offending food (Tedner et al., 2022). To comply with their diet, food allergic patients must rely heavily on food labels. This necessity was eventually recognised by lawmakers all over the world, which resulted in the appearance of food allergen labelling regulations. The list of allergens to be declared on food labels varies across countries with the most common items being cereals containing gluten, milk, egg, soybean, fish, peanut, tree nuts, and crustaceans. (Inclusion criteria for allergens (Houben et al., 2016) and defining exemptions are critical elements of forming these regulations, although discussing these issues is out of the scope of this paper.) In most cases, regulations require displaying the listed allergens when they were deliberately added to the product as an ingredient. However, in most cases the regulations do not deal with accidental cross-contamination of undeclared allergens and they do not (with a few notable exceptions such as Japan and Switzerland (Allen et al., 2014)) define threshold levels that could be used for risk assessment purposes to fine-tune food labels. While it is fairly straightforward to indicate allergenic ingredients, due to the nature of the industry (i.e. producing foods with different allergen profiles in the same facility and/or on shared equipment), reducing the chance of inadvertent cross-contact is a very challenging task. As a consequence, the industry - having no better tool to handle this uncertainty - turned to the application of the so-called precautionary ("may contain", etc.) allergen labelling (PAL) to voluntarily indicate the potential presence of allergen cross-contact (Taylor et al., 2002; Gendel, 2013; Taylor and Baumert, 2015; Lopez, 2018; Popping and Diaz-Amigo, 2018).

Consequently, PAL has become increasingly used on the package of a wide range of products using different types of wording to advise consumers to exercise caution when consuming the product. This is very often done without performing a risk assessment of a possible allergen cross contact. As a result, some products with a PAL do not actually contain the allergen they warn about or the opposite: a product without PAL does contain undeclared allergens ranging from low levels to even thousands of mgs per kg (Do et al., 2018; Martínez-Pineda and Yagüe-Ruiz, 2022).

Studies show that consumers in general have a poor understanding of the meaning of PAL statements that leads to faulty assumptions either on the perceived risk the product represents depending on the wording, or on their personal sensitivity. This finally results confusion, distrust, an increase in risk-taking behaviour and a decrease in quality of life. This, on the one hand, indicates an urgent need for the harmonisation of the usage of PAL, while also highlights the crucial role of consumer education. The basis of this harmonisation process is appropriate risk assessment so PAL could indicate actual risk when used, thus unnecessary limitation of the products available for allergic consumers could be reduced. The missing link to achieve it is threshold doses that would indicate the level of allergenic proteins at which the consumption of the product is safe for the vast majority of allergic patients. Such threshold doses could contribute to improving PAL and to giving better advice to patients knowing their personal level of sensitivity (DunnGalvin et al., 2015, 2019a, 2019b; Yeung and Robert, 2018).

This review aims to give an overview on the history and future prospects of the establishment of threshold doses for food allergens and their place in the allergen risk assessment procedure, with a final glimpse at the related food analytical issues.

2. THE EVOLUTION OF THRESHOLD DOSES AND RISK ASSESSMENT TOOLS FOR ALLERGEN LABELLING

As allergens differ from other food safety hazards by not posing a risk to the entire population, at first it was questionable whether the tools of classic chemical toxicology can be used to assess the risk related to them. With the growing availability of data though, it became clear that the classic risk assessment procedure (hazard identification, hazard characterisation, exposure assessment, risk characterisation) can be applied for allergens taking into account their specific characteristics (Crevel et al., 2014a).

A number of approaches can be suitable to assess the risk posed by allergens. Of these, a probabilistic model proposed by Spanjersberg et al. (2007) was found to be best applicable in case of allergen risk assessment as it does not require extrapolation at the low-dose range of the allergen dose-response curve (Spanjersberg et al., 2007; Crevel et al., 2014a). The probabilistic model takes into account both variability and uncertainty of factors affecting the risk of allergic reactions by using probability distributions. The model aims to predict the number of allergic reactions by analysing the distributions of minimal eliciting doses and allergenic food intake (which is estimated by parameters such as the prevalence of an allergy, food consumption data and the likelihood and the amount of allergen contamination). The analysis results in an estimate of the ratio of the allergic population that is expected to develop an adverse reaction at a certain allergen exposure level, thus it is applicable both for recommending population threshold levels and for assessing risk for higher exposures (Spanjersberg et al., 2007). It was shown that the most sensitive parameters of the model were minimal eliciting dose distribution and food consumption data, which indicates the necessity to obtain the highest possible quality of data of these particular issues (Kruizinga et al., 2008). This must be done with particular care as study designs and other related factors may carry sources of uncertainty as reviewed by Crevel et al. (2014a).

As described above, the cornerstones of the probabilistic approach are minimal eliciting doses or threshold levels and food consumption data. Of these, the latter is out of the scope of this paper, but the interested reader is referred to the works of Birot et al. (2017) and Blom et al. (2020) to get an insight on this particular issue, while this review is focusing on the development and application of threshold doses.

The matter of establishing thresholds for allergens has been around for over 20 years. At first, the zero tolerance approach appeared (and has been in force in many countries ever since), which would most definitely protect allergic consumers if it were feasible. However, as it was discussed earlier, it cannot be granted in the industrial setting. In the meantime, it also became evident that low levels of allergens being safe for most patients do exist and can be determined using clinical data by different statistical approaches (Bindslev-Jansen et al., 2002; Taylor et al., 2002; The Threshold Working Group, 2006).

The first attempts to reach this goal were hindered by the lack of comparable high quality clinical data for most allergens, which was predominantly caused by the fact that most clinical

studies were not designed for this particular purpose and the study protocols varied greatly (Taylor et al., 2002). To solve this problem, a consensus protocol for low-dose double-blind placebo-controlled food challenges (DBPCFCs) was suggested by Taylor et al. (2004) and was later refined by the EuroPrevall project (Crevel et al., 2008). These protocols were designed particularly to obtain suitable data to determine NOAEL (no-observed adverse effect level = the highest dose not triggering a reaction) and LOAEL (lowest observed adverse effect level = the lowest dose triggering a reaction, also referred to as minimal eliciting dose) for major allergens as a basis for threshold doses. The protocols aimed to standardise crucial study elements such as patient selection, challenge material, doses to be applied, and criteria for positivity (Taylor et al., 2004; Crevel et al., 2008). The methodology to determine individual threshold doses from data obtained by such clinical studies has been recently reviewed by Westerhout et al. (2019).

Even when using data coming from standardised study protocols, it is quite hard to establish threshold doses, because the individual minimum eliciting doses show a great variability and there is a chance that people who may react to doses lower than tested are not included in the studies. While individual thresholds are also useful for best managing the condition of particular patients, population thresholds are the ones that could be used by policy makers and the industry to provide the best overall safety for the allergic population and defining such thresholds requires careful consideration. Thus, in addition to obtaining suitable data from preferably controlled low-dose DBPCFC trials, different models and statistical approaches can and must be used to determine population thresholds that might be beyond the range of tested doses (Crevel et al., 2007, 2008).

As time went by, the body of clinical data suitable for the establishment of allergen thresholds kept growing that opened up new ways of allergen risk assessment. One of the first attempts to manage allergen cross-contact through a quantitative risk assessment approach based on threshold doses was carried out by the Allergen Bureau of Australia and New Zealand that introduced the VITAL (Voluntary Incidental Trace Allergen Labelling) program (https://vital.allergenbureau.net) in 2007 (the VITAL Program, 2023a, b). The program used action levels (i.e. allergen concentrations below which PAL is unnecessary (Crevel et al., 2014b)) for several allergens based on clinical threshold doses available at the time corrected with an uncertainty factor to assess the necessity of using PAL. With the availability of more and more clinical data and improved statistical tools, the VITAL threshold doses were revised starting in 2011 by a panel of experts. As described by Taylor et al. (2014), the panel studied every suitable data obtained from the literature or from medical centres directly using different statistical approaches and managed to determine threshold levels (referred to as reference doses) for a number of primary allergens (VITAL 2.0, Table 1). Depending on the amount and quality of data for different allergens, these reference doses are expected to protect 95–99% of the allergic population from developing any objective reactions (Taylor et al., 2014).

By 2019 data available to threshold predictions nearly doubled and new, improved statistical methods also emerged, thus the expert group created an update of the VITAL reference doses (Table 1). In this new set of thresholds (VITAL 3.0), a few new allergens could be introduced as well that had had no sufficient data at the time of the previous instalment (Remington et al., 2020).

As current results of allergen threshold dose research also indicate, due to the nature of allergens as food safety hazards and the limitations of the availability of test subjects in

Table 1. VITAL 2.0 and VITAL 3.0 reference doses (Taylor et al., 2014; Remington et al., 2020) (n.a.: data not available)

Allergen	VITAL 2.0 reference dose (2011) (mg protein)	VITAL 3.0 reference dose (2019) (mg protein)
Peanut	0.2	0.2
Milk	0.1	0.2
Egg	0.03	0.2
Hazelnut	0.1	0.1
Soy	1.0	0.5
Wheat	1.0	0.7
Cashew	2.0 (provisional)	0.05
Mustard	0.05	0.05
Lupine	4.0	2.6
Sesame	0.2	0.1
Shrimp	10	25
Celery	n.a.	0.05
Fish	n.a.	1.3
Walnut	n.a.	0.03

DBPCFCs that may hinder creating a representative sample of the allergic population, threshold doses that protect every allergic individual are not possible to be established. Thus, zero risk in allergen management is not a feasible option (Crevel et al., 2007, 2008). This leads to the crucial question of what is the level of acceptable or tolerable risk, as it may strongly affect risk assessment procedures, and subsequently risk management. Although the viewpoint of different stakeholders on this matter somewhat differs, they all agree that defining action levels based on clinical data and collecting more information on the distribution of eliciting doses and the severity of reactions are inevitable to be able to determine the level of acceptable risk. This is an issue of policymaking but it should be based on the latest scientific results in combination with communication with patient groups, the industry, and healthcare professionals (Madsen et al., 2010, 2011; Crevel et al., 2014b; Dubois et al., 2018). A framework involving all relevant stakeholders has recently been proposed by Madsen et al. (2020). They concluded that everything necessary for transparent decision-making on this issue in terms of information and expertise is readily available but is depending on the collaboration of all stakeholders including policy makers (Madsen et al., 2020). Of course, this decision-making process will always need to consider new scientific findings and adjust to them as need be (DunnGalvin et al., 2019a).

As for the practical application of threshold doses, the VITAL system mentioned earlier was one of the first approaches that not only determined reference doses but also used them in a systematic risk assessment process to create a credible and reliable way of PAL usage. VITAL is supposed to be used as a supplementary tool for a company's food safety system that includes a detailed allergen management plan. The VITAL risk assessment tool allows food manufacturers to analyse their products and processes in order to determine a quantified risk of allergen cross-contact. This analysis includes determination of relevant allergens, both as ingredients or as cross-contaminants from either raw materials or the production process. These pieces of information serve as a basis for calculating potential allergen contamination in the final product. Then, this estimated level of contamination is compared with reference doses turned into action

level concentrations based on the reference amount (the amount normally consumed at a single eating occasion, e.g. serving size) of the particular food item. The VITAL system operates a two-tiered action level grid. If the analysis shows that the expected allergen contamination is below the determined action level of that particular allergen, the use of PAL can be safely omitted. Otherwise, the term "may be present" is to be used, without any variation in language to indicate that the PAL statement is a result of the VITAL risk assessment process. Implementation of the program in the industry is supported by a set of so-called VITAL tools including guidelines and a calculator software (Taylor et al., 2018).

As a response to the growing interest and as a mean to encourage wider implementation, a VITAL Standard is now available as a supplementary certification scheme for companies running GFSI (Global Food Safety Initiative) certified food safety management standards (Taylor et al., 2018; https://vital.allergenbureau.net/vital-standard/).

The VITAL approach is gaining ground outside of its region of origin as well (Taylor et al., 2018). VITAL thresholds are used by German official food control laboratories as a basis for internal action levels to make decisions about products testing positive for an undeclared allergen. If the level of contamination is below their determined threshold levels, further investigation of the issue on site may be deemed unnecessary. Although, in this particular case, action levels are not used primarily to control labelling issues, they can be useful to level the playing field for decision-making in official food control cases (Waiblinger et al., 2018).

In addition to the German example, in the Netherlands and Belgium threshold doses based on VITAL are also recommended to be used for allergen risk assessment (Madsen et al., 2020). The US is also aiming for a risk assessment approach similar to the VITAL system as a way to improve the application of PAL (Yeung and Robert, 2018).

As an alternative approach, Zuberbier et al. (2022) recently proposed a uniform threshold of 0.5 mg protein/100 g processed food for all major allergens based on the results of a systematic literature review finding that no fatal allergic reactions were reported below this particular allergen concentration. The proposed system received serious criticism both in terms of methodology and applicability as described by Turner et al. (2022).

3. ANALYTICAL PERSPECTIVES OF FOOD ALLERGEN RISK ASSESSMENT

The development of allergen risk assessment based on threshold doses is a very promising approach to improve food allergen labelling issues, in particular for PAL. However, compliance with determined threshold and action levels require reliable analytical methodologies. There are a number of analytical methods available for the detection and quantification of allergens, including immunoanalytical methods such as ELISA (enzyme-linked immunosorbent assay), molecular biological methods such as PCR (polymerase chain reaction), and chromatographic methods coupled to mass spectrometry. As the capabilities of analytical methods are a very important aspect of our ability to control compliance, an ILSI (International Life Sciences Institute) expert group was established to analyse the performance characteristics of the currently available methods of food allergen analysis. The expert group performed a thorough assessment of commercially available or otherwise published existing ELISA, PCR, and mass spectrometry methods for major allergens in terms of their ability to detect and quantify allergens at the VITAL threshold doses and action levels derived thereof in serving sizes ranging

from 5 to 500 g. They concluded that methods for the analysis of peanut, soy, hazelnut, and wheat were applicable at such levels of allergen presence. As for milk and egg, they found that matrix effects could influence analytical results considerably and so do the variability of particular target proteins and applied conversion factors to calculate total protein content (Holzhauser et al., 2020).

The report of the ILSI expert group also highlighted some shortcomings generally applicable for the entirety of food allergen analysis, namely the problem of method validation and data comparability, the lack of reference materials, and the question of varying reporting units (Hozhauser et al., 2020). These issues can be demonstrated by assessing the advantages and challenges of ELISA, which is the method-of-choice for routine allergen analysis due to its specificity, sensitivity, and relative ease-of-use. However, ELISA methods have long been known to provide varying results depending on the applied antibody, extraction procedure, and calibrating materials. With no reference methods and certified reference materials available, ELISA results must be handled with appropriate care. The problem is exacerbated by the potential variability of the analyte (genetic and/or environmental), the effects of accompanying matrix components, and the applied processing technologies on the properties of the allergenic protein in terms of extractability and detectability (Cucu et al., 2013; Török et al., 2015; Yeung and Robert, 2018).

The variability of ELISA methods also manifests in the way different assays report their results. While the VITAL reference doses are expressed as mg total protein of the allergen in question, ELISA kits very often provide results in different units (e.g. concentration of a particular protein type or a commodity instead of total protein). This requires the application of conversion factors to recalculate results to become comparable (Holzhauser et al., 2020). In certain cases, such as e.g. gluten, the generally applied conversion factors may not be the best approach for every sample due to the genetic and environmental variability of the source (Wieser and Koehler, 2009). This issue was also recognised as a major one by a FAO/WHO expert consultation that recommended that the reporting unit of analytical methods should be standardised to mg total protein of the allergenic food per kg food product (FAO/WHO, 2021).

Another aspect that comes up as critical regularly in food allergen analysis is sampling. While in some cases the allergen contamination is distributed in the food product evenly, allergens are very often present in a particulate form, which makes proper sampling paramount in order to detect and quantify allergenic proteins reliably (Allen et al., 2014).

To conclude, methods of food allergen analysis, ELISA or other, need to be harmonised, validated as per determined performance criteria in all kinds of relevant matrices, with special attention to sampling (FAO/WHO, 2021).

A promising tool to overcome the inherent problems of immunoanalytical methods are mass spectrometry based proteomics methods. While these methods require costly equipment and specialised expertise, thus they cannot be applied routinely (at least for now), they also offer a chance to increase the accuracy of allergen quantification and to obtain information on a sample even at the epitope level. This could help to develop methods targeting clinically relevant proteins or epitopes, even in the presence of multiple analytes in complex matrices (Nitride et al., 2018; Mills et al., 2019; Fiocchi et al., 2021).

Regardless of the type of method, reference materials for all major allergens will be necessary that is a challenge on its own (Lacorn and Immer, 2011). There have been a number of research efforts to find the most suitable reference materials for a range of allergens. Giving an overview of all of them is out of the scope of this paper, but a few notable examples are provided.

Reference materials for certain allergens are commercially available, including a milk reference material created by the MoniQA Association (https://www.moniqa.org/node/910). An example for a workflow aiming at the development of a gluten reference material has been recently published by Xhaferaj et al. (2023) as the latest instalment of a series of studies also stemmed from the activity of the MoniQA Association.

It can be concluded that analytical methods that are able to detect and quantify allergens at or below the VITAL thresholds are available for at least some of the major allergens, and analytical methodologies should be continuously improved in parallel with reference doses to provide quantification as reliable as possible.

4. CONCLUSIONS

In recent decades, food allergies have grown into a public health issue globally, and consequently the management of food allergens has become a major food safety issue. An integral part of this is allergen labelling, the problems of which, particularly of the voluntary precautionary allergen labelling is now very well-known and serious efforts are underway to improve the situation.

Risk assessment of food allergens as inadvertent contaminants in food is essential to optimise the usage of precautionary allergen labelling. This activity offers the basis of effective risk management of the particular problem of unintended allergen cross-contact. Although this is a very important aspect, one must keep in mind that allergen risk management includes a range of other issues as well (e.g. mislabelling, mispackaging, etc.) and these are all should be taken care of systematically, integrated into the food safety system (a Codex Alimentarius code of practice on this matter was published recently (Codex Alimentarius, 2020)). Finally, not even the best approach can be effective without proper communication of the risk of allergen cross-contamination to all relevant stakeholders that is necessary to encourage implementation of new risk assessment and management tools and to restore the trust of consumers in product labelling (Crevel et al., 2014b; Hattersley et al., 2014).

A globally harmonised approach of food allergen labelling and PAL usage is the desired outcome of the research efforts highlighted in this paper. The road towards this goal is not an easy one: it requires collaboration from a number of fields from medicine through food manufacturing to food analysis, each carrying uncertainties of their own (Allen et al., 2014; Reese et al., 2015; Crevel et al., 2018). It makes creating effective voluntary or legislative frameworks a challenge, but as a growing body of high quality data and evidence suggests, not an impossibility if the challenge is met with a will and strong collaboration of all stakeholders to make food safer for allergic consumers.

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