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INVITED EDITORIAL

"Too high, too low": the complexities of using thresholds in isolation to inform precautionary allergen ("may contain") labels

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The disclosure of "priority" allergens when present as an (intended) ingredient in foods is, in most countries, enshrined in legislation. However, the disclosure of unintended allergen presence (UAP) due to cross-contact or cross-contamination (for example, through the use of shared production facilities) is not.[1] Many food businesses use precautionary allergen ("may contain") labels (PAL) to advise consumers as to the possibility of UAP, however use of PAL is voluntary and not specifically regulated, and the presence/absence of PAL does not inform as to the actual level of risk that a particular food product might pose.[2] The use of PAL has significantly increased over the last decade,[3] but because of the perception that they are used by food businesses to limit their own legal liability rather than convey useful information to consumers with food allergies and their caregivers, they are frequently ignored.[4] Similarly, there is similar variation in interpretation of PAL by healthcare professionals, including allergy specialists.[5,6] Most foods with a PAL statement do not contain detectable levels of the identified allergen, while some products without a PAL do have UAP which can pose a significant risk of allergic reaction.[3,7] A recent research prioritisation exercise, undertaken by the UK Food Standards Agency and involving all relevant stakeholders (including consumers with food allergy, members of the general public, clinicians and researchers, representatives from the food industry and regulatory organisations) highlighted the need to improve use of PAL as a key priority, to allow consumers with food allergy to make informed decisions as to whether a food is 'safe' for purchase/consumption.[8]

In theory, the need for PAL could be informed by "action levels". When the level of potential UAP is above a certain concentration, this would trigger the use of PAL; no PAL would be needed if levels were equal to or lower than this cut-off. While some very dose-sensitive people might react to levels of allergen below the action level if a large amount of food containing UAP is consumed, risk could be mitigated in these individuals through risk communication (e.g. patient-specific advice to those who react to smaller amounts of allergen).[9] Action levels have been developed based on *Eliciting dose* (ED), the dose (mg) of total protein from the allergenic source predicted to provoke reactions in a defined proportion of the allergic population (e.g. ED_{05} is the dose predicted to provoke reactions in 5% of the at-risk allergic population). Notably, single-dose

challenges at an ED_{05} level of exposure have been used to validate ED_{05} values for peanut[10] and cow's milk.[11]

There have been attempts to improve the use of PAL through formal allergen risk assessment,[12] for example the Voluntary Incidental Trace Allergen Labelling (VITAL®) scheme established by the Allergen Bureau of Australia & New Zealand.[13] However, the current lack of international consensus over use of PAL has led to a variety of regulatory approaches and increasing inconsistency in how food businesses use PAL, even between different member states of the European Union (EU).[2] To address this concern the Codex Committee on Food Labelling, a committee of the Food and Agriculture Organization of the United Nations and World Health Organization (FAO/WHO), is currently evaluating the evidence over improving the use of PAL.

In this issue of Allergy, Zuberbier et al report a systematic review in which they sought to assess the number of fatal cases of anaphylaxis to exposures below 5mg protein for food allergens. They found only 8 cases of fatal anaphylaxis reported in which the level of exposure could be estimated; there were no reported fatalities to levels of exposure below 5mg protein.[14] On the basis of these data, and a reasonable assumption that a portion size of 100g is more typical than 1000g, the authors propose a cut-off of 0.5mg food protein due to UAP per 100g food (5ppm) to inform whether PAL is needed.

The finding that no deaths have been reported to exposures under 5mg protein is useful; however the number of anaphylaxis fatalities is not a good indicator to define policy with respect to UAP and food safety, to prevent allergic reactions due to UAP. This is partly because more developed healthcare systems may be more effective at managing anaphylaxis, limiting morbidity and mortality. Using a very rare outcome (fatal anaphylaxis, in this case) to a common scenario (unintended allergen exposure) to define public health policy is not good practice. We therefore have significant reservations over some of the proposed suggestions put forward by Zuberbier et al.

First, we recognize the allure of a straightforward approach, with a single analytical value applied across all food allergens and for all food product categories. The first iteration of the VITAL® scheme (VITAL-1) attempted a similar approach: a "trigger" cut-off or action level (expressed in terms of a single concentration of allergen protein (ppm), independent of the serving size of a food), above or below which PAL was or was not recommended.[13] The ppm cut-offs were derived from using a food portion of 5 grams (equivalent to one Australian teaspoonful) as the reference quantity. The rationale was that the resulting action level would reflect the lowest amount of allergen in a small mouthful of food, which might cause a more dose-sensitive allergic individual to experience subjective symptoms. However, the use of a fixed food portion size (and hence a preset concentration) encountered significant criticism from consumers with food allergy, industry and government, for reasons including:

1. the data used to establish the trigger amounts of allergen protein were not – at the time – considered sufficiently robust, and
2. the use of a single concentration, based on a single portion size, meant that the system did not provide a consistent level of protection across different foods and food groups, and thus the resulting PAL recommendation did not protect consumers of foods typically eaten in larger quantities. For example, serving sizes of 50g or 250g could contain 10 or 50 times the trigger amount of allergen per serving, respectively, before PAL was recommended.

These criticisms were then acted upon in subsequent iterations of VITAL (VITAL-2 and -3): the development of reference doses based on statistical dose-distribution modelling using a more extensive dataset of reaction thresholds reported in further clinical studies; and the introduction of Reference Amounts (amount of food eaten in a typical eating occasion) to inform the potential exposure level.[13] Therefore, the proposal by Zuberbier et al to return to a preset 5ppm cut-off would seem to ignore the real-world experience obtained in VITAL-1, and represent a potential step backwards in providing meaningful PAL communication which can be trusted by consumers.

Second, it can be very difficult to attribute cause and estimate consumption amounts in tragic cases of fatal anaphylaxis. Most of the literature identified by Zuberbier et al describes reactions

at food challenges, when the level of allergen exposure is known and patients are clinically well and without the presence of co-factors which might increase reaction severity.[15] This is in stark contrast to allergic reactions occurring in the community. Unfortunately, Zuberbier et al do not provide the overall number of fatal or life-threatening reactions included in their review, nor the number of participants included in studies, so it is difficult to estimate the degree of uncertainty in their estimate. Indeed, they report only 8 cases of fatal anaphylaxis, a number which is less than the number of food-related fatal anaphylaxis cases in the United Kingdom in any one year,[16] and probably less than the number occurring globally in any one month. So there is a very significant risk of under-reporting in the literature – which is a major limitation of their review. Whilst we truly hope no deaths have occurred to exposure amounts ≤5mg, there has been at least one death reported in the literature where there might have been potential oral exposure below 5mg.[17] The risk of the approach of Zuberbier et al is that it runs contrary to the accepted consensus that zero risk for food-allergic people is not a realistic or attainable option.[18]

Zuberbier et al propose a PAL statement of "this product contains the named allergens in the list of ingredients, it may contain traces of other contaminations (to be named, e.g. nut) at concentrations less than 0.5mg per 100g of this product" as a voluntary declaration on prepacked foods.[14] This implies 5ppm for the allergenic food, rather than total protein from that food (as stated in the review's title), and highlights the need for consistent communication across all stakeholders: consumers, risk assessors, risk managers and healthcare professionals. The Food and Agriculture Organisation of the United Nations/World Health Organisation (FAO/WHO) recommend expressing analytical results as "mg total protein of the allergenic food per kg food product;" we are concerned the similar but different wording proposed here will lead to confusion. Consumer surveys explicitly concur that a major limitation of PAL is the lack of a clear and short statement which can be understood by consumers of all literary abilities. The phraseology proposed by Zuberbier et al is certainly not clear or short, nor does it accommodate the varying levels of literacy on the part of consumers.

Fourth, the assertion that a 5ppm threshold "can be readily detectable for all [14 EU priority] food allergens with the currently existing technology" is not uniformly true in practice.[19] It should

also be noted that detectable and quantifiable are not the same, and quantification will be needed for any risk-based regulatory/enforcement framework. Furthermore, the assertion does not even begin to take into consideration the impact of (1) particulate contamination (where the allergen (e.g. a nut fragment) is not equally distributed throughout the food, but restricted to just one particular area of the food product, which may or may not be the part selected for analysis); and (2) food processing and matrix effects which significantly reduce allergen detectability in some instances.[20,21] Indeed, both the literature[19] and a recent FAO/WHO expert panel concluded that while levels of allergen presence around a concentration of 5ppm total protein of the allergenic food "can be implemented and monitored to some degree with current analytical capabilities, [there remain] significant limitations in method performance".[22] It is for this reason that most experts recommend a quantitative risk assessment which does not exclusively rely on analytical capabilities.

A 5ppm cut-off unfairly restricts some allergens and food categories, resulting in a very over-conservative action level, while for others it leaves a higher-than-intended residual risk. Table 1 describes the proportion of individuals with food allergy who would be predicted to experience any/objective/anaphylaxis symptoms to a 5ppm cut-off applied to a 100g and 250g serving portion, compared to using ED_{05} reference doses.[23-26] For some food groups, particularly seafood and spices, a 5ppm cut-off would be overly restrictive, leading to a higher number of products with PAL than is necessary. For others, a significant proportion (greater than 10% for most allergens) would still have an objective allergic reaction, particularly at a 250g serving portion – which is not unrealistic – and some would have anaphylaxis. Given these data, while at first glance a 5ppm seems beneficial, in reality such an approach could inadvertently lead to more PAL, as many food businesses might conclude that the risks to health posed by a 5ppm cut-off are too great, or the mitigation measures to comply with a 5ppm cut-off are too difficult to achieve consistently in practice, and therefore default to using PAL.

Finally – and most importantly – consumers with food allergy want more than just "not to die". Rather, they don't want to experience *any* allergic reaction. A 5ppm cut-off would still mean that for some allergens, consumers would still experience symptoms (including anaphylaxis) (Table 1).

These data demonstrate the hierarchy of symptoms that individuals with food allergy might experience to 5ppm concentrations (Figure 1).[26] Given that zero risk is not a realistic or attainable option,[18] there is a need to properly engage with food-allergic consumers as to the appropriate use and messaging over PAL.

We look forward to learning how the recent recommendations of the Ad hoc Joint FAO/WHO Expert Consultation on Risk Assessment of Food Allergens are implemented at a global level, to better protect the consumers with food allergy.[22] In the meantime, however well-intentioned, there is a risk that less-informed approaches may be counter-productive.

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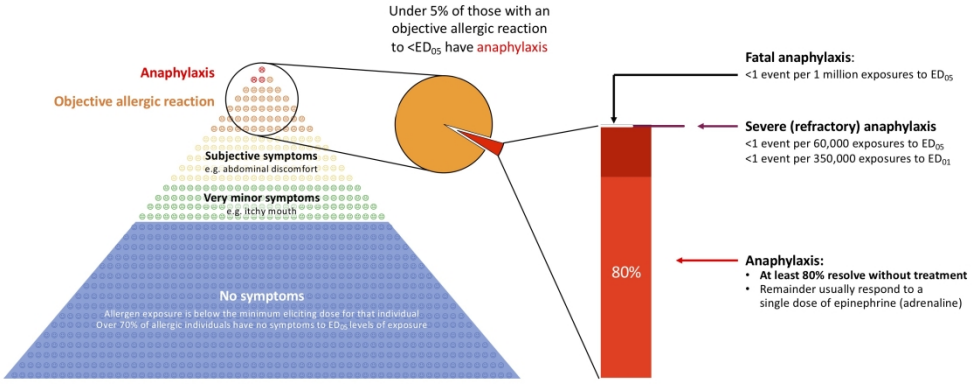
FIGURE LEGENDS

Figure 1: Hierarchy of risks faced by people susceptible to IgE-mediated food allergy. Estimates refer to occurrence of allergic symptoms at ED_{05} levels of exposure in food-allergic individuals, using peanut as a reference allergy. Reproduced from Turner et al[26] under a Creative Commons CC-BY license.

Allergen	Expected rate of symptoms to a level of allergen exposure at 5ppm (100g serving)			Expected rate of symptoms to a level of allergen exposure at 5ppm (250g serving)			Expected rate of symptoms to an ED_{05} level of allergen exposure			Published cumulative ED_{05} (mg protein)
	Any symptoms	Objective symptoms	Anaphylaxis	Any symptoms	Objective symptoms	Anaphylaxis	Any symptoms	Objective symptoms	Anaphylaxis	
Peanut	~20%	Up to 1%	0.3 per 1000 (95%CI: 0.1 to 0.7)	15-25%	Up to 3%	5.6 per 1000 (95%CI: 2.4 to 13)	~25%	5%	2.3 per 1000 (95%CI: 1.0 to 5.1)	3.9
Cashew	5-10%	Up to 5%	1.2 per 1000 (95%CI: 0.6 to 2.6)	~30%	Up to 9%	2.2 per 1000 (95%CI: 1.0 to 4.7)	~30%	5%	2.5 per 1000 (95%CI: 1.1 to 5.3)	1.6
Hazelnut	~30%	Up to 3%	0.4 per 1000 (95%CI: 0.1 to 2.4)	~40%	Up to 5%	0.6 per 1000 (95%CI: 0.1 to 4)	~50%	5%	1.2 per 1000 (95%CI: 0.2 to 7.9)	4.7
Walnut	Insufficient data	Up to 8%	1.9 per 1000 (95%CI: 0.7 to 4.6)	~10%	Up to 12%	2.7 per 1000 (95%CI: 1.0 to 6.5)	~10%	5%	2.7 per 1000 (95%CI: 1.0 to 6.7)	1.2
Cow's Milk	10%	Up to 3%	0.7 per 1000 (95%CI: 0.3 to 1.7)	10-15%	Up to 5%	1.5 per 1000 (95%CI: 0.6 to 3.3)	~20%	5%	2.5 per 1000 (95%CI: 1.1 to 5.5)	3.1
Egg	~5%	Up to 3%	0.3 per 1000 (95%CI: 0 to 11)	~10%	Up to 5%	0.5 per 1000 (95%CI: 0 to 17)	~12%	5%	0.8 per 1000 (95%CI: 0 to 27)	2.4
Wheat	Not reported	Up to 1%	0.1 per 1000 (95%CI: 0 to 3.8)	Not reported	Up to 3%	0.2 per 1000 (95%CI: 0 to 7.5)	Not reported	5%	1.1 per 1000 (95%CI: 0 to 38)	9.3
Fish	~10%	Up to 1%	Insufficient data	~20%	Up to 3%	Insufficient data	~50%	5%	Insufficient data	15.6
Shrimp	<1%	Up to 0.2%	Insufficient data	~5%	Up to 0.5%	Insufficient data	~50%	5%	Insufficient	429

									data	

Table 1: Estimated frequency of subjective and objective symptoms (including anaphylaxis) in allergic individuals with exposure to 5ppm concentrations for different allergens, and using estimated ED_{05}.[23] Maximum predicted rates for objective symptoms following exposure to 5ppm allergen per 100g and 250g portion size estimated from Houben et al.[23] Data relating to frequency of any symptoms estimated from the literature.[10,11,23-26] Rates of anaphylaxis to ≤ED_{05} exposures derived from Turner et al.[26]



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