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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

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125 challenges at an ED_{05} level of exposure have been used to validate ED_{05} values for peanut[10] and
126 cow's milk.[11]
127
128 There have been attempts to improve the use of PAL through formal allergen risk assessment,[12]
129 for example the Voluntary Incidental Trace Allergen Labelling (VITAL®) scheme established by the
130 Allergen Bureau of Australia & New Zealand.[13] However, the current lack of international
131 consensus over use of PAL has led to a variety of regulatory approaches and increasing
132 inconsistency in how food businesses use PAL, even between different member states of the
133 European Union (EU).[2] To address this concern the Codex Committee on Food Labelling, a
134 committee of the Food and Agriculture Organization of the United Nations and World Health
135 Organization (FAO/WHO), is currently evaluating the evidence over improving the use of PAL.
136
137 In this issue of Allergy, Zuberbier et al report a systematic review in which they sought to assess
138 the number of fatal cases of anaphylaxis to exposures below 5mg protein for food allergens. They
139 found only 8 cases of fatal anaphylaxis reported in which the level of exposure could be
140 estimated; there were no reported fatalities to levels of exposure below 5mg protein.[14] On the
141 basis of these data, and a reasonable assumption that a portion size of 100g is more typical than
142 1000g, the authors propose a cut-off of 0.5mg food protein due to UAP per 100g food (5ppm) to
143 inform whether PAL is needed.
144
145 The finding that no deaths have been reported to exposures under 5mg protein is useful;
146 however the number of anaphylaxis fatalities is not a good indicator to define policy with respect
147 to UAP and food safety, to prevent allergic reactions due to UAP. This is partly because more
148 developed healthcare systems may be more effective at managing anaphylaxis, limiting
149 morbidity and mortality. Using a very rare outcome (fatal anaphylaxis, in this case) to a common
150 scenario (unintended allergen exposure) to define public health policy is not good practice. We
151 therefore have significant reservations over some of the proposed suggestions put forward by
152 Zuberbier et al.
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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

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184 at food challenges, when the level of allergen exposure is known and patients are clinically well
185 and without the presence of co-factors which might increase reaction severity.[15] This is in stark
186 contrast to allergic reactions occurring in the community. Unfortunately, Zuberbier et al do not
187 provide the overall number of fatal or life-threatening reactions included in their review, nor the
188 number of participants included in studies, so it is difficult to estimate the degree of uncertainty
189 in their estimate. Indeed, they report only 8 cases of fatal anaphylaxis, a number which is less
190 than the number of food-related fatal anaphylaxis cases in the United Kingdom in any one year,[16]
191 and probably less than the number occurring globally in any one month. So there is a very
192 significant risk of under-reporting in the literature – which is a major limitation of their review.
193 Whilst we truly hope no deaths have occurred to exposure amounts ≤5mg, there has been at
194 least one death reported in the literature where there might have been potential oral exposure
195 below 5mg.[17] The risk of the approach of Zuberbier et al is that it runs contrary to the accepted
196 consensus that zero risk for food-allergic people is not a realistic or attainable option.[18]
197
198 Zuberbier et al propose a PAL statement of "this product contains the named allergens in the list
199 of ingredients, it may contain traces of other contaminations (to be named, e.g. nut) at
200 concentrations less than 0.5mg per 100g of this product" as a voluntary declaration on
201 prepacked foods.[14] This implies 5ppm for the allergenic food, rather than total protein from that
202 food (as stated in the review's title), and highlights the need for consistent communication across
203 all stakeholders: consumers, risk assessors, risk managers and healthcare professionals. The Food
204 and Agriculture Organisation of the United Nations/World Health Organisation (FAO/WHO)
205 recommend expressing analytical results as "mg total protein of the allergenic food per kg food
206 product;" we are concerned the similar but different wording proposed here will lead to
207 confusion. Consumer surveys explicitly concur that a major limitation of PAL is the lack of a clear
208 and short statement which can be understood by consumers of all literary abilities. The
209 phraseology proposed by Zuberbier et al is certainly not clear or short, nor does it accommodate
210 the varying levels of literacy on the part of consumers.
211
212 Fourth, the assertion that a 5ppm threshold "can be readily detectable for all [14 EU priority]
213 food allergens with the currently existing technology" is not uniformly true in practice.[19] It should

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214 also be noted that detectable and quantifiable are not the same, and quantification will be
215 needed for any risk-based regulatory/enforcement framework. Furthermore, the assertion does
216 not even begin to take into consideration the impact of (1) particulate contamination (where the
217 allergen (e.g. a nut fragment) is not equally distributed throughout the food, but restricted to just
218 one particular area of the food product, which may or may not be the part selected for analysis);
219 and (2) food processing and matrix effects which significantly reduce allergen detectability in
220 some instances.[20,21] Indeed, both the literature[19] and a recent FAO/WHO expert panel concluded
221 that while levels of allergen presence around a concentration of 5ppm total protein of the
222 allergenic food "can be implemented and monitored to some degree with current analytical
223 capabilities, [there remain] significant limitations in method performance".[22] It is for this reason
224 that most experts recommend a quantitative risk assessment which does not exclusively rely on
225 analytical capabilities.
226
227 A 5ppm cut-off unfairly restricts some allergens and food categories, resulting in a very over-
228 conservative action level, while for others it leaves a higher-than-intended residual risk. Table 1
229 describes the proportion of individuals with food allergy who would be predicted to experience
230 any/objective/anaphylaxis symptoms to a 5ppm cut-off applied to a 100g and 250g serving
231 portion, compared to using ED_{05} reference doses.[23-26] For some food groups, particularly seafood
232 and spices, a 5ppm cut-off would be overly restrictive, leading to a higher number of products
233 with PAL than is necessary. For others, a significant proportion (greater than 10% for most
234 allergens) would still have an objective allergic reaction, particularly at a 250g serving portion –
235 which is not unrealistic – and some would have anaphylaxis. Given these data, while at first
236 glance a 5ppm seems beneficial, in reality such an approach could inadvertently lead to more
237 PAL, as many food businesses might conclude that the risks to health posed by a 5ppm cut-off
238 are too great, or the mitigation measures to comply with a 5ppm cut-off are too difficult to
239 achieve consistently in practice, and therefore default to using PAL.
240
241 Finally – and most importantly – consumers with food allergy want more than just "not to die".
242 Rather, they don't want to experience *any* allergic reaction. A 5ppm cut-off would still mean that
243 for some allergens, consumers would still experience symptoms (including anaphylaxis) (Table 1).

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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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396 **FIGURE LEGENDS**

397

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

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									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 $\leq ED_{05}$ exposures derived from Turner et al.[26]

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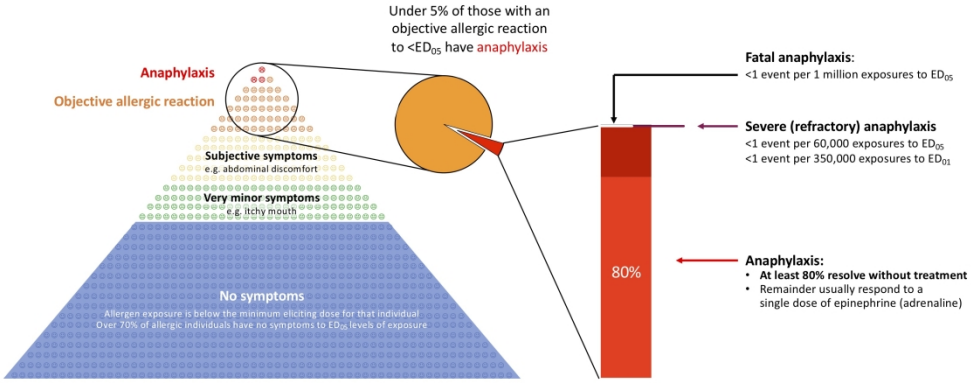

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