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Can we define a level of protection for allergic consumers that everyone can accept?

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ABSTRACT

Substantial progress has been made in characterising the risk associated with exposure to allergens in food. However, absence of agreement on what risk is tolerable has made it difficult to set quantitative limits to manage that risk and protect allergic consumers effectively. This paper reviews scientific progress in the area and the diverse status of allergen management approaches and lack of common standards across different jurisdictions, including within the EU. This lack of regulation largely explains why allergic consumers find Precautionary Allergen Labelling confusing and cannot rely on it. We reviewed approaches to setting quantitative limits for a broad range of food safety hazards to identify the reasoning leading to their adoption. This revealed a diversity of approaches from pragmatic to risk-based, but we could not find clear evidence of the process leading to the decision on risk acceptability. We propose a framework built around the criteria suggested by Murphy and Gardoni (2008) for approaches to defining tolerable risks. Applying these criteria to food allergy, we concluded that sufficient knowledge exists to implement the framework, including sufficient expertise across the whole range of stakeholders to allow opinions to be heard and respected, and a consensus to be achieved.

1. Introduction

Significant progress has been achieved in characterizing the risk to people with food allergies from exposure to food allergens, both at an individual and at a population level. At a population level, this has facilitated the proposed use of management thresholds to guide the need for declaring the presence of unintended allergens, based on Reference Doses derived from food challenges in allergic patients. Many stakeholders across the food allergy community remain concerned that guidelines based on these Reference Doses may still not protect the occasional person with food allergy, either due to extreme sensitivity (i.e. reacting to very low doses of allergen), reactivity (responding with

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severe symptoms to exposure) or unusually high consumption levels (eating large portions of food with unintended allergen presence). As a result, acceptance of this approach has been limited, hindering the application of risk-based approaches to this aspect of food safety management. Failure to adopt risk-based approaches does not serve society well, particularly those directly affected by food allergy and their carers. In addition, the lack of uptake exposes other stakeholders to unnecessary costs and impacts such as food waste, as well as uncertainty regarding compliance with food safety measures. A critical element missing from current discussions is the absence of any transparent consideration of what level of risk is tolerable, in relation to the consequences of unintended allergen presence at an individual and public health level.

The aim of this paper is to describe the current situation in the management of unintended allergen presence. In addition, we will discuss the obstacles to defining a tolerable risk and therefore an appropriate level of protection in food allergy, and suggest a way forward.

2. The science behind the derivation of safe dose levels of allergens

For many years, it was unclear whether thresholds – a level of allergen exposure below which no symptoms occur – existed in food allergy. It seemed that the smallest amounts of allergen exposure could elicit allergic reactions. However, from a biological perspective, thresholds should be expected to exist, even if these might vary from one person to another. The idea of modelling eliciting dose data in order to estimate population threshold levels was first formally proposed in 2002 (Bindslev-Jensen et al., 2002). Although this idea was quite revolutionary at the time, it was clear that if population thresholds derived using this approach were to try and achieve zero risk in all allergic individuals, the levels would most likely be so low for most allergens that they would not be practical for most applications and result in an abundance of precautionary allergen labelling (PAL), a voluntary approach to inform allergic consumers of the unintended presence of a food allergen.

This was followed by a paper by Crevel et al. (2007) who discussed the concept of modelling such data to determine the amounts of total allergenic protein – called eliciting dose (ED) – at which a certain percentage of the allergic population would be predicted to experience allergic symptoms (ED_x at which x% is expected to respond). Since then, several papers have been published exploring this idea and reporting results of human challenge (provocation) studies and modelling the data generated (Allen et al., 2014a; Taylor et al., 2014). This forms the basis for the derivation of Reference Doses from ED_x values. While Reference Doses can be calculated for any given proportion of the allergic population, in practice the most common Reference Doses reported are for the amounts predicted to provoke objective reactions in 1% and/or 5% of the allergic population (termed ED_{01} and/or ED_{05} respectively). For an overview of terms and definitions see Table 1.

A significant advance occurred in 2014 when the results from a joint effort by TNO in the Netherlands and FARRP in the US through the VITAL Scientific Expert Panel were published. This presented ED values for 11 major allergenic foods (Allen et al., 2014a; Taylor et al., 2014), which were adopted by the Australia-New Zealand Allergen Bureau as a basis for Reference Doses in their Voluntary Incidental Trace Allergen Labelling (VITAL) programme (www.allergenbureau.net/vital/). For foods with sufficient data, the ED_{01} was used. For other allergens with less data, the lower 95% confidence interval of ED_{05} was used for the Reference Dose. Since then, many food companies and authorities have embraced the idea of using an ED modelling approach with Reference Doses for risk management purposes, including the application of PAL. However, consensus over a single harmonised approach has not yet emerged within any jurisdiction (see next section). Meanwhile, further research has generated additional data and methodologies to support and develop the use of Reference Doses. Several groups have performed studies to validate ED modelling through single-dose challenge studies. Hourihane et al. (2017) demonstrated that challenging unselected people with peanut allergy attending allergy clinics, at a dose expected to elicit an objective allergic reaction in 5% of the participants, did not result in more than 5% reactions; all reactions were of mild severity and did not require pharmacological intervention. Single dose challenges for other allergenic foods were performed in the framework of the EU project iFAAM, (http://research.bmh.manchester.ac.uk/iFAAM). These data are yet to be published, but support the safety of the Reference Doses used, although participant numbers were insufficient for the results to confirm those doses within the same confidence intervals as the peanut study by Hourihane et al. (2017). The TRACE study, funded by the UK Food Standards Agency, provided further confidence that the Reference Dose for peanut proposed by Taylor et al. (2014) remains appropriate, even in the presence of a number of co-factors (sleep deprivation, vigorous exercise) (Dua et al., 2019), indicating that there is no need for further uncertainty factors to be incorporated into the derivation of Reference Doses.

TNO and FARRP continued to collect food challenge data and expanded their joint database from ~1800 datapoints in 2014– to ~3500 datapoints in 2019. TNO and FARRP also started collaboration with external experts to develop a Model Averaging approach to allow the calculation of one single ED value based on various statistical models, rather than calculating different ED values based on the different models and deriving Reference Doses through expert judgement (arXiv:1908.11334v1 [stat.AP] Wheeler et al., 2019). Model Averaging is the preferred approach for derivation of benchmark values, such as Reference Doses, when there is no biological reason to prefer one model over another (EFSA Scientific Committee, 2017). Based on the expanded database and Model Averaging, TNO and FARRP have performed new ED value calculations for 14 different allergenic foods, the results of which largely support the original VITAL 2.0 values, notwithstanding minor changes due to the larger datasets available for most allergens (Remington et al., 2020). These new ED calculations were recently used to update the Reference Doses in the VITAL program (VITAL 3.0: http://allergenbureau.net/vital/vital-science/). Finally, TNO and FARRP are analysing data in the threshold database in more detail, to extract information on the nature of symptoms of allergic reactions elicited at dose levels in low ED ranges, to further clarify the level of protection likely conferred by Reference Doses derived from them (Blom et al., in preparation). This will also be supplemented by further analysis of the TRACE results, focusing on symptom severity.

Table 1
Definitions of selected terms used in the context of thresholds.

Term	Definition
Eliciting dose	The dose (mg) predicted to provoke reactions in a defined proportion of the allergic population (ED_{01}, ED_{05}, ED_{10} etc.), derived from the dose distribution of individual minimum eliciting doses (MEDs). The suffix describes the proportion e.g. ED_{01} = the dose predicted to provoke reactions in 1% of the at-risk allergic population
Reference dose	The dose (mg) derived from an acceptably low Eliciting dose (e.g. ED_{01}, ED_{05}) chosen as a health- based intake limit.
Action level	The concentration (mg/kg) in food as consumed, containing the Reference dose based on specified conditions of exposure (portion size etc).
Threshold (individual, clinical)	The lowest dose capable of eliciting an allergic reaction in an individual (also called the minimum eliciting dose - MED)
Threshold (regulatory)	The maximum concentration of an allergenic food deemed to pose a tolerable risk to the at risk population, given their susceptibility and the circumstances of exposure e.g. 20 mg gluten/kg is the threshold for gluten in gluten free food. It may or may not be a population no (adverse) effect level.

3. Diversity in management decisions from different countries

Regulation in many countries mandates that allergens present as ingredients are labelled regardless of the level of inclusion, but the use of PAL for allergens potentially present in foods due to cross-contact is not explicitly regulated in most countries, and is primarily applied on a voluntary basis and without clear guidance.

To date, only four countries (Argentina, Japan, South Africa and Switzerland) have regulations relating to PAL (Allen et al., 2014b), all taking different approaches and with only two applying a risk-based approach using a labelling threshold. For example, the use of 'may contain' statements is prohibited in Argentina, unless authorisation is sought (Lopez, 2018). The first country to define a labelling threshold is Switzerland, which requires any regulated allergen, whether ingredient or not, present at concentrations above 1000 ppm to be declared. PAL is permitted in Switzerland but only for allergens potentially present due to cross-contact and above the defined threshold. Japan has defined a threshold (10 μg per g of food (10 ppm)) above which all regulated allergens (whether deliberately added or not) must be declared, but Argentina have not. Whilst the presence of allergens below 10 ppm does not require labelling in Japan, alternative PAL statements may be used. South Africa permits the use of PAL but only where there is a documented risk assessment demonstrating potential cross-contact despite Good Manufacturing Practices (GMP). Fig. 1 illustrates graphically how the single regulatory thresholds set by Switzerland and Japan compare with the population ED distributions for various allergens for a portion size of 200 g.

In the EU, the European Commission (EC) is required to adopt an Implementing Act on PAL as part of the 2011 Food Information for Consumers (FIC) Regulation. To date, the EC have set up a working group to study PAL, organised a stakeholder workshop and published a report (June 2016). Whilst there was consensus at the workshop that PAL should be based on risk assessment combined with Reference Doses, there have been no further activities in this area. This has led to a diversity of management decisions being proposed by different EU countries, though none have been adopted into law.

Several EU countries appear to be taking a 'zero tolerance' approach, such that the mere detection of unintentionally present allergen requires PAL, no matter the amount detected. Others appear to align with the consensus from the EC workshop in taking a risk-based approach. However, a single harmonised approach has yet to emerge and the recommended threshold levels vary. This lack of consensus also has implications not only for PAL application, but also for food recalls (Bucchini et al., 2016). The approach regarding risk communication to consumers also varies among Member States.

Prior to the aforementioned workshop, in 2015, a collaborative project was undertaken by the Danish, Swedish, Finnish and Norwegian food control authorities looking into 'Undeclared allergens in food'. The report (Bolin and Lindeberg, 2016) includes a risk assessment using published ED data available at the time, indicating support for a risk-based approach to PAL using such data, though since then no further or updated guidance has been produced.

In 2016, the Dutch Bureau for Risk Assessment and Research Programming (BuRO) of The Netherlands Food and Consumer Product Safety Authority (NVWA, 2016) concluded that a quantitative risk-based approach could be applied to allergens in food and proposed the use of provisional Reference Doses. They proposed Reference Doses that correspond to the lowest ED_{01} values obtained by the Weibull model of the same studies on which Allergen Bureau VITAL® 2.0 Reference Doses are based. The VITAL® 2.0 values were derived through modelling using the Weibull, log-logistic and log-normal distributions, and the final reference dose was established dependent on the fit of the mathematical models. The BuRo-proposed temporary provisional reference doses are listed in Table 2 and were proposed in a recommendation to Dutch Ministries (NVWA, 2016), however there has been no formal follow-up to date by the Ministries regarding this recommendation.

In 2017, the Scientific Committee of the Belgian Federal Agency for the Safety of the Food Chain (SciCom, 2017) also issued an Opinion on Reference Doses, to provide information to assist with managing risks arising from the unintended presence of allergens in food, and proposed Reference Doses which they estimated would protect 95–99% of the allergic population, also based on the same studies on which Allergen Bureau VITAL® 2.0 Reference Doses are based. In contrast to the Reference Doses proposed by BuRO, these Reference Doses are generally higher than the VITAL® 2.0 equivalent: the Committee proposed to use the lower limit of the 95% confidence interval of the ED_{05}, giving

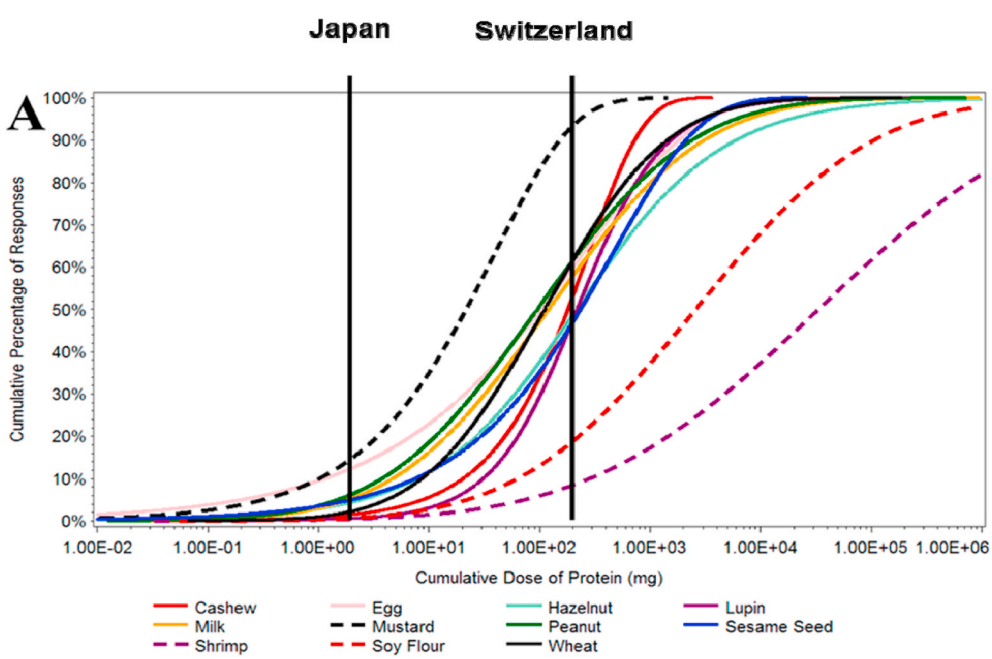

Fig. 1. Quantitative guidance for (precautionary) allergen labelling. The figure illustrates graphically how the single regulatory thresholds set by Switzerland (1000 ppm [mg/kg]) and Japan (10 ppm [mg/kg]) compare with the population ED-distributions for various allergens for a portion size of 200 g. ED-distributions based on the 2011 TNO-FARRP Threshold Database as used for the elaboration of VITAL2.0 Reference Doses (Taylor et al., 2014).

Table 2
Reference Doses proposed by both the Dutch Bureau for Risk Assessment and Research Programming (BuRO) and Belgian Federal Agency for the Safety of the Food Chain (FASFC) alongside the VITAL® 2.0 and 3.0 reference doses (RD).

Allergen	VITAL® 2.0 RD[a] (mg protein per portion)	Netherlands Proposed RD (mg protein per portion)	Belgium Proposed RD (mg protein per portion)	VITAL® 3.0 RD (mg protein per portion)
Peanut	0.20	0.015	1.1	0.20
Milk	0.10	0.016	1.2	0.20
Egg	0.03	0.0043	0.3	0.20
Hazelnut	0.10	0.011	0.5	0.10
Soy	1.00	0.078	2.9	0.50
Wheat	1.00	0.14	1.3	0.70
Mustard	0.05	0.022	0.1	0.05
Lupin	4.00	0.83	4.5	2.6
Sesame	0.20	0.1	0.4	0.10
Shrimp	10.00	3.7	12.1	25
Celery	N/A	N/A	N/A	0.05
Fish	N/A	N/A	N/A	1.30
Cashew	N/A	N/A	N/A	0.05
Walnut	N/A	N/A	N/A	0.03

N/A: not applicable.
[a] The Official Food Control Laboratories in Germany adopted VITAL® 2.0 RDs.

preference to the lowest value obtained by means of a log-logistic or a log-normal model on the largest dataset available. The Reference Doses proposed by the FASFC are also provided in Table 2.

In 2014 the Official Food Control Laboratories in Germany established internal action levels, based on VITAL 2.0 Reference Doses, for assessing samples (Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL), 2015; Waiblinger and Schulze, 2018). This approach converts the VITAL 2.0 Reference Doses from mg protein per portion of food, to mg foodstuff per portion and then to a reference concentration assuming a 100 g portion of food; and then, finally, to an 'Action Value' based on current analytical capability. These Action Values are not to be considered legal threshold values, but internal values used by official control laboratories to drive recommendations on the need for further investigations when allergens are found in products without them being declared. They are expected to be updated regularly as new analytical and human data become available.

In 2019, VITAL® 3.0 Reference Doses were published (Allergen Bureau, 2019) as described in Section 2, using a 'stacked' model averaging approach (arXiv:1908.11334v1 [stat.AP] Wheeler et al., 2019) applied to the extended TNO-FARRP set of challenge data. Whereas the VITAL® 2.0 Reference Doses were based on the ED_{01} or 95% lower confidence interval of ED_{05} depending on quantity and quality of available data, the VITAL® 3.0 Reference Doses, are based solely on the ED_{01} and are also listed in Table 2.

Most recently, in the Czech Republic, national recommendations for voluntary labelling of unintentional presence of allergens have been prepared 'on the basis of a consensus of representatives of the Ministry of Agriculture, the State Agriculture and Food Inspection Authority and the State Veterinary Administration' (www.eagri.cz, 2018). These recommendations appear to take a different approach to those previously mentioned, recommending (i) amounts of allergen in a food intended for final consumers, which can be regarded as "zero" and therefore not requiring PAL; and (ii) maximum amounts that can be considered as "trace amounts", stating that above this it is no longer considered as unintended contamination, thus misleading the consumer. These amounts are given as concentrations (not RDs), for some allergens the protein content is indicated and for others not, and the 'maximum values considered "zero"' are based on the 'limit of detection' of commonly used analytical methods, though what those methods are is unclear. The approach also implies that unintentionally present allergens occur at lower concentrations than allergens added as ingredients, an assumption which is not supported by experimental evidence (see Blom et al., 2018, for example).

Globalisation of the food chain and movement of people is such that the current diversity of approaches to PAL adds complexity to food production and causes further confusion among allergic consumers. A harmonised global risk-based approach would be optimal and as such, steps being taken by the Codex Alimentarius Commission to develop a Code of Practice for Allergen Management for Food Business Operators (www.fao.org/fao-who-codexalimentarius, 2018) as well as ultimately guidance on the application of PAL (www.fao.org/fao-who-codex-alimentarius/, 2019) at an international level constitute an important move in this direction.

4. The risk as it looks now with Precautionary Allergen Labelling (PAL)

The use of PAL has increased over the past decades, triggered by the mandatory labelling of common allergenic ingredients and an uncertain regulatory and risk assessment landscape. There has been a further increase in the use of PAL by catering establishments on non-prepacked foods, following the implementation of the 2011 Food Information for Consumers (FIC) Regulation in the EU. In most countries, PAL is voluntary, and there is huge variation in the way decisions regarding the use of precautionary statements are made, as well as a lack of transparency and harmonised practice (see section 3).

The indiscriminate use of PAL has important impacts on patients with food allergy, their families and healthcare providers. They significantly reduce food choices, increasing the cost of food and lead to devaluation of the warning: patients, in particular adolescents, are increasingly ignoring the warnings and using proxy markers of unintended allergen presence, such as brand, retailer, etc (Barnett et al., 2011, 2013; Ben-Shoshan et al., 2012; Cochrane et al., 2013). This is partly due to mistrust, partly because PAL appears on so many products that they feel their food choice is impaired. In addition, food-allergic individuals ignore PAL on food products which they have previously eaten without problem. The presence and extent of contamination does not correlate with the presence or absence of PAL (Allen and Taylor, 2018; Pele et al., 2007). Products with PAL often do not contain the stated allergen(s), and products without PAL may still contain clinically significant amounts of unintended allergen(s). A recent study (Blom et al., 2018) found that precautionary warnings for specific allergens did not correlate with either the presence, absence or concentration of unintentionally present allergens detected analytically. While the mandatory declaration of major allergens as ingredients aims to enable consumers with food allergies to make safe food choices, the unregulated use of PAL works against this. In light of the new results from the Dutch study, which support findings from an earlier UK study (FSA project FS241038, 2014; FSA project FS305014, 2014; Remington et al., 2015) that declaration of an allergen in the PAL statement does not necessarily imply that there is not another *unstated* unintended allergen present, allergic consumers are unable to do a risk assessment for unintended allergen presence by just referring to the label (Fig. 2).

The many uncertainties around labelling can increase the risk of accidental reactions in patients (Versluis et al., 2015). In a recent prospective study, the number of unexpected reactions was around 1 per person per year (Michelsen-Huisman et al., 2018). Strikingly the majority of these events were at least moderately severe and at least 28% included anaphylaxis; despite most patients not seeking medical attention, there were still 6 emergency hospital visits among the 108 patients. Further analyses by Blom et al. (2018) found that in products causing an accidental reaction, levels of undeclared allergenic constituents (cow's milk, hen's egg, peanut, hazelnut, walnut) varied from 4 ppm to 5000 ppm (protein). When actual amounts consumed were calculated by including the food intake of the patient, the estimated level of allergen exposure varied from 0.4 to 170 mg (protein) for peanut, 0.01–3.5 mg for hazelnut, 0.1–42 mg for sesame, 0.09–9 mg for egg, and 0.13–123 mg for milk. For all cases where culprit allergens were detected, the intake

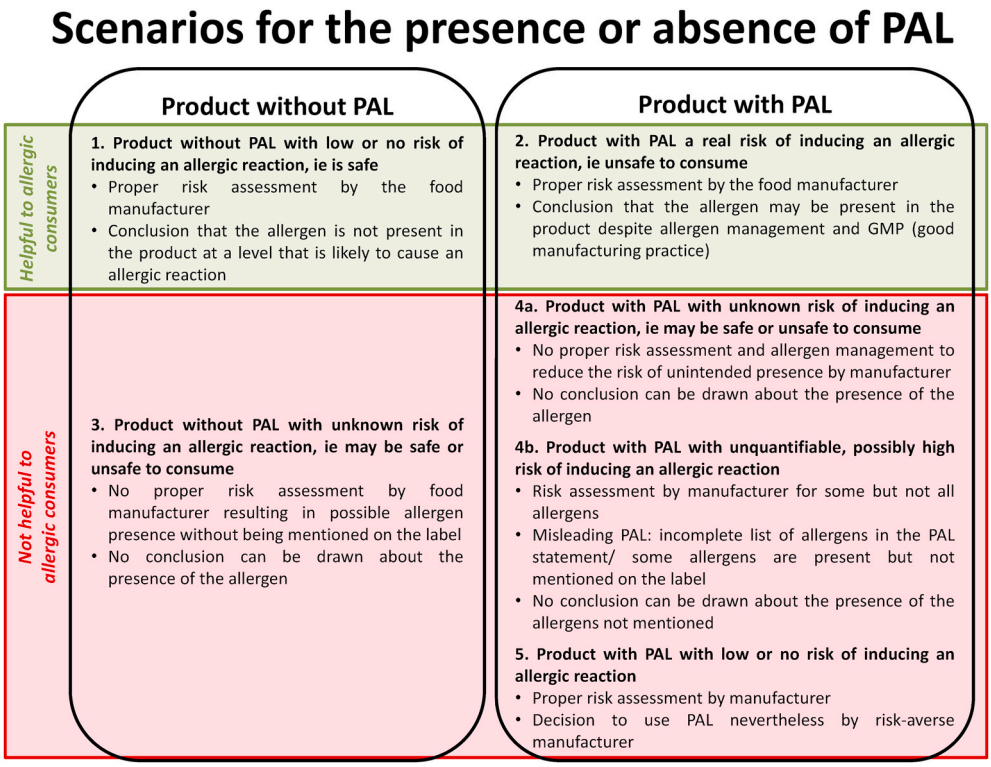

Fig. 2. Scenarios for the presence or absence of precautionary allergen labelling (PAL). Modified from DunnGalvin et al. (2015).

of at least one unintended allergen exceeded the Reference Dose or a culprit allergen with a yet unknown Reference Dose was present (on the basis of Taylor et al. (2014)). This implies that the Reference Doses as proposed by Taylor et al. (2014), might be highly protective in practice. The study also showed that a large variety of products was responsible for unexpected reactions, with just over half (53%) attributable to a relatively small number of foods such as bread (rolls), cookies, chocolates, meat and meat products. Important to note, while eating out of home is often thought to be the main risk factor for unexpected allergic reactions, prepacked foods were the main cause of unexpected reactions in this prospective study in the Netherlands.

Together these data indicate that PAL currently

1. Is not related to the actual risk
2. Does not always cover the right allergens
3. Limits food choices unnecessarily
4. Is misinterpreted
5. Is increasingly ignored
6. Is of limited value for patients due to the inconsistencies in its application.

5. How have similar problems been handled in other areas?

It is clear that PAL is a tool which is often used injudiciously, and its power as part of risk management has therefore been seriously eroded. It can be argued that one of the reasons for this is the apparent lack of agreement on an appropriate level of protection for the various regulated allergens in potential scenarios of unintended presence. This translates to a question of which level of residual risk society is prepared to accept, considering that for several food safety risks, an absolute zero risk probably does not exist nor is achievable. It is therefore interesting to explore how other food safety risks are being managed. Table 3 summarises the criteria that have been used in deciding limits to protect public health in the case of other food safety risks, as detailed below.

5.1. Acrylamide

In 2002 food industry and authorities were surprised by the presence in many heated foods of acrylamide at levels significantly greater than those predicted to cause more than the generally accepted one additional case of cancer per million people exposed. Industry started an approach to lower the acrylamide levels in food, not aimed necessarily at achieving safe levels but to result in lower levels compared to those detected at the time. The Codex Alimentarius Commission recommended that industry takes mitigation measures (FAO/WHO Codex Alimentarius, 2009). FoodDrinkEurope developed an Acrylamide Toolbox, based on the ALARA (As Low As Reasonably Achievable) principle (FoodDrinkEurope, 2019). Off the back of this, other industry organisations supported the management of acrylamide levels in food by issuing foodstuff specific guidance, e.g. a pantone chart was developed by Good Fries EU (2019). In 2018 (effective date) benchmark dose levels were implemented in the EU (European Commission, 2017b), not with the aim of achieving 'safe' levels but rather, gradually reducing future exposure in line with the ALARA principle.

Acrylamide is a genotoxic carcinogen, so it is not considered to have a threshold below which no risk exists i.e. it is not possible to establish a safe level of exposure. The European Food Safety Authority (EFSA) therefore uses a 'margin of exposure' (MOE) approach. For substances that are both genotoxic and carcinogenic, a MOE of 10,000 or higher (based on the BMDL10[1] (EFSA, 2009; EFSA Scientific Committee, 2017) derived from benchmark dose modelling of animal studies as the Point of Departure and taking into account overall uncertainties in the interpretation) would be of low concern from a public health perspective. The MOE values for acrylamide range from 50 to 425: since these are all substantially lower than the value of 10,000, the Commission's Standing

[1] The BMDL10 is the lower confidence limit of the Benchmark Dose. The Benchmark Dose (BMD) approach estimates the dose that causes a low but measurable target organ effect (e.g. a 5% reduction in body or organ weight or a 10% increase in the incidence of kidney toxicity) (EFSA (2009) (EFSA, 2017)).

Table 3
Criteria used in setting regulatory thresholds.

	Threshold in food	Criteria for setting threshold based on					Comments	Ref.
		Protecting general population	Protecting sensitive sub-population	Threshold aimed at protecting from	Level of protection	Limitation of analytical methods		
Gluten (gluten free food)	20 ppm	n.r.	+	Clinical disease and histological changes in the gut	The majority of persons with coeliac disease	(+)		1
Histamine (fish)	**EU**: Fish and Fish products with high histidine content: Mean value is < 100 ppm and no value > 200 ppm. Higher values for fermented fish products. **US**: Decomposition action level is 50 ppm. Hazard level is 500 ppm	+	–	Acute histamine poisoning with symptoms such as headache and urticaria	?		No EU or US limits for histamine in other products high in histamine e.g. cheese. No limits for other biogenic amines	2, 3
Sulphite	10 ppm	n.r.	+	Acute symptoms such as asthma and urticaria	LOAEL not known, but probably the majority of sulphite sensitive	+	10 ppm threshold for declaration	4, 5
Acrylamide	No regulatory limits. Appropriate mitigation measures should be laid down to reduce levels	Aim is risk reduction MOE values: 50-425		Cancer	Unknown MOE for low concern level in relation to cancer is > 10,000 (ALARA)			6, 7
Campylobacter	20/50 samples may exceed 1000 cfu/g for broiler meat carcasses	+		GI infection from campylobacter contaminated food	The suggested threshold is expected to result in a calculated risk reduction of >50% compared to previous levels		The threshold will be reduced gradually down to 10/50 samples that may exceed 1000 cfu/g by 2025	8

n.r.: not relevant; **LOAEL**: Lowest Observed Adverse Effect Level; **MOE**: Margin Of Exposure; **ALARA**: As Low As Reasonably Achievable; **cfu**: colony forming units; **GI**: Gastro-intestinal.
1 (Joint FAO/WHO Food Standards Programme CODEX ALIMENTARIUS Commission, 2008):
2 (European Commission, 2005):
3 (FDA, 2005):
4 (EFSA, 2014):
5 (Federal Register, 1986):
6 (European Commission, 2017b):
7 (EFSA Panel on Contaminants in the Food Chain (CONTAM), 2015):
8 (European Commission, 2017a):

Committee on Plants, Animals, Food and Feed concluded that although the available human studies have not demonstrated acrylamide to be a human carcinogen, the MOEs across surveys and age groups indicate a concern with respect to neoplastic effects at current levels of exposure (EFSA Panel on Contaminants in the Food Chain (CONTAM), 2015; European Commission, 2017b). Thus, **there is a principle that (i) zero risk is not possible, and (ii), the most effective strategy is one of risk minimisation rather than risk elimination**.

5.2. Histamine

EFSA assessed the incidents of histamine intoxication during 2010–2015 in some EU countries and found 191 outbreaks linked to 1060 cases, resulting in 107 hospitalizations but no deaths (EFSA, 2017). Fish and fish products were reported as the major cause, but also shellfish/crustacea and dairy products (and specifically cheese) were involved (EFSA, 2017). These findings are consistent with the EFSA Opinion on risk-based control of biogenic amine formation in fermented foods, that established dried anchovies, fish sauce, fermented vegetables, cheese, other fish/fish products and fermented sausages as the major causes of concern (EFSA Panel on Biological Hazards (BIOHAZ), 2011b). While doses of 50 mg histamine for healthy individuals were reported to cause no adverse health effects, this did not apply to people with histamine intolerance, for whom only a below-detectability level was considered protective (EFSA Panel on Biological Hazards (BIOHAZ), 2011b).

The Dutch Food Safety Authorities assessment of the risk of biogenic amines in cheese refers to 36 mg histamine as the smallest amount that can lead to symptoms in healthy people (Recommendations on risks of biogenic amines in cheese, 2010). Like EFSA, they state that a lower value is appropriate for ~1% of the population who suffer from histamine intolerance. Considering a portion size of 50 g, they derived a preliminary risk-based limit for the healthy population of 720 mg histamine/kg cheese. Of note, **since this limit is based on human observations, no safety margins/uncertainty factors were applied**.

The USA Food and Drug Administration (FDA) Policy Guide (FDA, 2005) considers 500 ppm histamine in fish such as tuna as a health hazard, but FDA can act based on the decomposition action level of 50 ppm rather than on the hazard action level. While the 500 ppm hazard action level has been established in the US for tuna, it was highlighted that similar data need to be gathered for other fish species and other foods. Fermented fish and cheese products were highlighted to be of importance in that respect (Taylor, 1985).

The available information on histamine clearly demonstrates areas of residual risk that have not been regulated so far:

- While products such as fermented vegetables, shellfish/crustacea, fermented sausages and dairy products (specifically cheese) can contain histamine, only fish products have been regulated in the EU (European Commission, 2005).

- The Dutch food safety authorities have set a provisional limit of 720 mg histamine/kg cheese. This limit is provisional, until EFSA sets a limit.
- In the legislation, the higher sensitivity of consumers with histamine intolerance has not been considered.

Although actual risk management rationales are not always traceable, risk management levels have been set for histamine in the presence of residual risks. At some stage, the residual risk inherent in the set levels must have been considered and deemed acceptable by public risk managers – including the concept that **for some individuals** (in this case, those with histamine intolerance), **the proposed risk management levels may not confer complete protection**.

5.3. Sulphites

Sulphites are an interesting case study to consider in the context of tolerable risk and food ingredients, because they cause similar symptoms to food allergy in a subset of sensitive individuals (Corder and Buckley, 1995; Vally and Misso, 2012). The mechanisms remain unclear by which sulphites can cause symptoms such as bronchoconstriction, and whilst people with asthma are the primary population that appears to be particularly at risk, there are some reports of reactions in non-asthmatics too.

The US FDA acted in 1986 to implement labelling of foods containing levels of sulphites ≥10 ppm (10 mg/kg). The aim was to quickly reduce the risk from 'hidden' sulphites to sulphite-sensitive individuals, despite a lack of data to support this action level: the FDA stated "that the available information is inconclusive regarding whether there is a biological threshold level for sulfiting agents below which sensitive individuals will not experience adverse reactions". Accordingly, the FDA did not use a biological criterion for determining what constitutes a significant level of sulphites, but rather based its level on analytical capability, and considered "that the regulatory threshold of 10 ppm sulphite will adequately protect consumers of large servings as well as those who consume several servings of different foods containing sulfiting agents".

This level found its way into Codex and EU regulation. In 2014 EFSA published a systematic review concluding that 'Minimal eliciting doses have not been systematically assessed and the smallest concentration of sulphites able to trigger a reaction in a sensitive person is unknown' (EFSA, 2014). Despite this, many countries (EFSA, 2014; Federal Register, 1986) have regulations requiring sulphites to be declared at concentrations of 10 ppm (10 mg/kg) or higher in foods. Whilst this limit is stated to be based on the LOD of analytical methods at the time (1980), the level of protection provided across serving sizes does appear to have been considered and deemed acceptable based on the limited human data that was available (Federal Register, 1986). Thus, **there is precedent for the application of a Reference Dose based on available (but not necessarily completely comprehensive) data in the protection of the public from what is considered in legislation to be an allergen**.

5.4. Microbiology

Another example of how a prevalent food safety risk is being managed is the manner in which EU authorities have regulated the presence of *Campylobacter* in broiler meat carcasses. A joint European Centre for Disease Prevention and Control (ECDC)/EFSA review in 2017 reported the occurrence of 246,158 cases of campylobacteriosis (EFSA and ECDC, 2018). In terms of root cause analysis, EFSA reported in 2008 an average contamination rate of broiler carcasses with *Campylobacter* of 75.8%, with significant variations between Member States and slaughterhouses (EFSA, 2010). Moreover, EFSA established that "the handling, preparation and consumption of broiler meat accounted for 20–30% of human cases of campylobacteriosis, while 50–80% could be attributed to the chicken reservoir as a whole" (EFSA Panel on Biological Hazards (BIOHAZ), 2010). In an additional Opinion in 2011, EFSA concluded that "*a public health risk reduction of > 50% or > 90% could be achieved if all batches complied with microbiological criteria with a critical limit of 1000 or 500 Colony Forming Units* per *gram (CFU/g) of neck and breast skin respectively, while 15% and 45% of all tested batches failed to comply with these criteria*" (EFSA Panel on Biological Hazards (BIOHAZ), 2011a).

ADAS UK Ltd carried out a report for DG SANCO of the European Commission (Elliott et al., 2012) on the cost/benefit analysis of setting certain control measures for reduction of *Campylobacter* in broiler meat at different stages of the food chain. Its main conclusion was that "setting a process hygiene criterion for *Campylobacter* in broiler carcasses would best balance reducing human campylobacteriosis attributed to the consumption of poultry meat, and adverse economic consequences from the application of the criterion." (recital 8, EU Reg 2017/1495).

Finally, with the publication of EU Commission Regulation 2017/1495 (European Commission, 2017b), a process hygiene criterion was adopted in EU law of 1000 CFU/g for broiler meat carcasses, with a maximum of 20/50 samples allowed to exceed this value. Over time, this ratio will gradually reduce to 10/50 samples by 2025.

The campylobacter case study can therefore be considered as an example where, after thorough risk assessment and considering additional factors such as the economic consequences of the proposed measures, **a practical risk management approach is taken to benefit the health of EU consumers, whilst not insisting on zero risk**.

5.5. Coeliac disease and definition of the standard for gluten-free foods

5.5.1. Coeliac disease

Coeliac disease is an immune-mediated disease triggered by ingestion of gluten, which is found in cereals such as wheat, barley and rye. There is international agreement on a threshold for gluten in gluten-free foods of 20 ppm. This was based on observations that the Lowest Observed Adverse Effect Level (LOAEL) for gluten in consumers with coeliac disease was about 50 mg/day and, taking dietary consumption patterns into account, this would ensure that gluten exposure would remain well below this amount (Codex Alimentarius Commission, 2005).

An important factor in selecting this level was the ability to verify it analytically. The US-FDA also adopted 20 ppm as the gluten threshold, but conducted a health risk assessment to establish an amount below which no adverse effects could be observed. This derived a No Observed Adverse Effect Level (NOAEL) of 0.015 mg gluten per day. However, in formulating their conclusion to adopt 20 ppm, the FDA explicitly noted (Federal Register, 2013) that (i) concentrations as low as the NOAEL could not be verified analytically and (ii) such a low level risked depriving people with coeliac disease of products which would be safe for most of them. Moreover, they considered that a lack of such products could increase the risk to people with coeliac disease by limiting their choice of suitable products. The 20 ppm threshold thus **aims to protect the majority of persons** with coeliac disease. It is **based both on clinical data and on the ability to measure gluten at the suggested level**. In the case of the US FDA, it also recognises that **the most effective level of protection may not be that associated with a theoretical zero risk, with consumer choice an important factor**.

Together, these examples show that current problems are handled:

- In a pragmatic rather than risk-based manner: e.g. acrylamide, focusing on lowering levels without necessarily aiming for safe levels
- In a pragmatic, risk-based way: e.g. *Campylobacter*, focusing on lowering levels and taking into account additional factors such as the economic impact
- By setting acceptable intake levels for the general population only, excluding the most sensitive individuals e.g. for histamine

- By setting a threshold aiming to protect the majority of a sensitive population, e.g. threshold for gluten (majority of people with coeliac disease are protected), remaining mindful of the possibility that a more stringent criterion could paradoxically increase risk
- By setting a threshold based on the detection limit, e.g. for sulphites, but a risk-based approach indicates this level likely protects the population.

6. A framework to move forwards

6.1. A framework for defining tolerable risk: outline

Hunter and Fewtrell (2001) discussed acceptable and tolerable risk in the context of drinking water quality standards, sketching the outline of a framework in which acceptable and tolerable risk could be derived (Hunter and Fewtrell, 2001). More recently, Murphy and Gardoni (2008) proposed several criteria for approaches to defining tolerable and acceptable risks. These include that

- All relevant factors are taken into account in an appropriate way.
- Required data inputs are accurate, available and accessible
- An approach should provide concrete practicable and theoretically justified information and conclusions on what types of action to take (or not)
- Value judgements and method of approach should be transparent
- The approach should describe the societal distribution of the risks.

Fig. 3 attempts to depict the relationship between the Murphy and Gardoni (2008) criteria listed above and how a proposed framework for defining tolerable risk could operate in terms of **what** needs to be taken into account, **how** and **by whom** as discussed in detail in this section.

- ***All relevant factors taken into account***: Two key factors underlie the tolerability of the risk posed by food allergens: the proportion of the food-allergic population who are affected, and the health consequences for these individuals. Reference doses encapsulate the first part, as they are directly based on the proportion of the allergic population predicted to react. They also provide some information about the second element – the likely *severity* of the reaction – although the ability to predict severity is hampered by the multiplicity of influencing factors (Dubois et al., 2018). New knowledge on the impact of exercise and sleep deprivation have also recently emerged to improve our understanding of some of these variables (Dua et al., 2019). However, assessment of the value of Reference Doses should not only be based on a simplistic interpretation of the proportion predicted to react, but attempt to form a judgement about the likelihood that any reactions would be "harmful to human health", to borrow a term used in the USA's allergen labelling legislation. The possible harm done by *not* implementing Reference Doses should also receive consideration, including, for instance, the uncertainty and anxiety experienced by people with food allergies as a result of an inconsistent and excessive use of PAL
- In managing the risk from allergens, Reference Doses (derived from human provocation studies) can be used, but these need to be translated into action levels (defined in Table 1), which reflect tolerable concentrations after taking into consideration the amount of food consumed by an individual. In this case additional relevant factors come into play, such as assumptions about portion size eaten. Although not directly relevant for defining an appropriate level of protection, the capability of analytical methods also enters into play in the practical application of action levels.
- Beyond the biology, selection of appropriate Reference Doses may also need to consider behavioural factors, such as understanding and adherence to PAL, as well as unintended consequences, such as impact on consumer choice and also cost to the consumer (products which are labelled as suitable following a risk-assessment could cost more, impinging on consumer choice) (Remington et al., 2015).
- ***Required data inputs are accurate, available and accessible***: common standards are developed for inclusion and exclusion of data used for dose-distribution modelling, and appropriate steps are taken to enable these data to be shared or be accessible for review while protecting the rights and obligations of the owners of the data including privacy protection requirements. A significant step towards common standards has been achieved with the recent publication of Westerhout et al. (2019). This could form the basis of quality standards for data in a common curated database, allowing sharing of data as mathematical formulas or full population ED-distribution details, making true availability and accessibility possible.
- ***An approach should provide concrete practicable and theoretically justified information and conclusions on what types of action to take (or not)***:
  - o Implementation of Reference Doses or action levels would meet this criterion, supported by further studies such as single dose

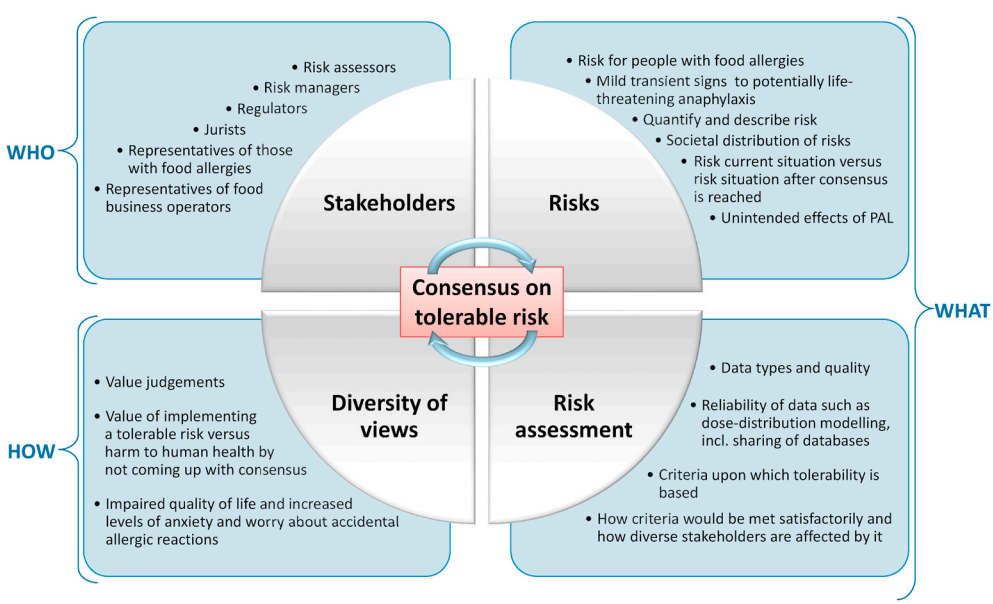

Fig. 3. Outline of a framework to help define an appropriate level of protection for consumers with food allergies. This framework is based on the criteria developed by Murphy and Gardoni (2008). Our proposed framework aims, in a transparent way, to take into account all relevant factors and diversity of views needed to reach a consensus for establishing a tolerable risk and subsequently management thresholds for an appropriate level of protection in food-allergic consumers arising through the unintended presence of allergen(s) in food products. This should lead to an improved and fair decision-making that is better accepted by society.

challenge studies (Hourihane et al., 2017) to validate predicted values and the health consequences of exposure.

  - o PAL is currently, and is likely to remain, an important approach for managing and mitigating the risk from unintended allergen presence. Reference doses guide risk managers on the level of risk beyond which PAL is required; if no other mitigation is possible. Reference doses are, however, the starting point, and clear guidance on the application of PAL, including its verification, is needed to support their introduction. At a minimum, this should include guidance on allergen risk assessment, as well as the application of analytical methods and meaningful sampling.

- ***Value judgements and method of approach should be transparent***: A value judgement is a judgment of the rightness or wrongness of something or someone, or of the usefulness of something or someone. A value judgment can refer to a judgment based upon a particular set of values or on a particular value system. We do not make value-free judgements, therefore in risk assessment we need to think about how we make value judgements responsibly and how we communicate those value judgements. In order to do this, we need to be aware of our own biases when developing and communicating a framework. Identification of value judgements can be aided by conducting peer review, interdisciplinary working and engaging consumer involvement. Applying this to Reference Doses, their theoretical basis and potential utility should be clear to all stakeholders within the food allergy community. The latter should be invited to share their views on them, also understanding that they can influence the outcomes.
- ***The approach should describe the societal distribution of the risks***: only people with food allergies are at risk of experiencing the health consequences of exposure to the allergen(s) to which they are reactive, but the consequences of living with someone with a food allergy extend to their family and beyond. The fact that food allergy risks can be mitigated – but not necessarily eliminated – needs to be acknowledged; appropriate efforts must be made to quantify the risks as accurately as possible in order for allergic consumers and their families to take informed decisions about possible exposure below the Reference Dose. Of note, allergic consumers are already at risk from the current situation, something which would be reduced if Reference Doses were implemented as discussed above. Beyond that, other stakeholders currently face risks which need to be considered, for example for food businesses which may be required to undertake product recalls because of an enforcement decision which is not currently supported by the scientific evidence. This also could be reduced if Reference Doses were implemented.

The purpose of the framework is to ensure, in a systematic manner, that any criteria deemed to be necessary for the equitable definition of tolerable risk are formally applied. This should ensure that the Reference Doses and/or action levels defined enjoy wide support. In practice, this would mean that all relevant stakeholders are involved, that all relevant points are taken into account, and that any decisions are taken systematically and in a transparent manner. This approach will help to ensure in particular that the conclusions reached earn the trust of those affected, as well as wider society.

6.2. Who should or needs to be involved?

Defining tolerable risk is a societal activity. Most, if not all discussions of tolerable risk, irrespective of the field under consideration, recognize that failure to involve all relevant stakeholders in defining tolerable risk will most likely result in sub-optimal decisions (Hunter and Fewtrell, 2001; Murphy and Gardoni, 2008). Unsurprisingly, such outcomes carry a strong likelihood that they are distrusted by those who have to bear that risk, who are often the least likely to be included in discussions, creating a barrier to adoption. This aspect is also reflected in the Murphy and Gardoni (2008) criteria mentioned above. One challenge is to identify all relevant stakeholders, including those belonging to subpopulations. At a minimum, a framework pertaining to food allergy demands the involvement of risk assessors and managers, regulators, jurists, representatives of those with food allergies (including any vulnerable subpopulations) and food business operators.

Risk assessors will characterize the risk in terms of how it relates to variables which can be controlled, such as amount of allergen and frequency of reaction, any factors which may aggravate or mitigate the risks, and associated uncertainties.

Risk managers will use the risk assessment as a basis for their decisions, effectively representing the societal input. A good understanding of what risk is tolerable, the output which the framework is meant to develop, should result in better-founded decisions, more accurately reflecting societal views on the risk and its tolerability, with appropriate weight given to the views of different stakeholders.

Jurists and regulators help to develop and implement the legal framework that delivers the intentions of society as elucidated through the framework.

Representatives of those with food allergies are a critical stakeholder to both educate other stakeholders about what it means to live with the risk, and how that could be improved. They will understand what works in practice for the allergic consumer, and what does not, and be able to convey the views of other stakeholders to their constituency. Patient Representative Organisations will thus contribute a synthesis of an overall patient view, if necessary soliciting input beyond their members alone, informed by their interactions with allergic consumers and their carers. In discharging their role, they may also need to call on other expertise, such as that of clinicians, scientific experts, etc.

Representatives of food business operators will contribute knowledge about practicalities of managing operations. Similar to patient organisations, they will need to ensure contributions from the diversity of businesses in the sector, with attention to the constraints on different types and sizes of business.

6.3. What does the framework need to include?

The risk posed by food allergens ranges from mild, transient signs and symptoms to systemic reactions and anaphylaxis, which are in general treatable but can occasionally be fatal (Turner et al., 2019). What may be judged tolerable will sit within two dimensions, namely (i) numbers at risk of reacting, as measured through epidemiological and clinical studies and (ii) the characteristics (severity) of any resulting reaction. Other ILSI expert groups have also identified these two factors as critical and proposed ways in which they could be addressed, albeit in a different context (Houben et al., 2016). The impact of food allergy extends beyond the experience of an allergic reaction, and the adverse effect on health-related quality of life due to high levels of anxiety is well-documented in both food-allergic individuals and their carers (Howe et al., 2014; Walkner et al., 2015). All these aspects could be evaluated in the context of a capabilities-based derivation of tolerable risk proposed by Murphy and Gardoni (2008), specifically the extent to which a risk degrades the ability of individuals to lead the kind of life they have reason to value. For food-allergic consumers and those purchasing food for them, this includes an ability to make informed (food) choices which are safe for them, allowing them to enjoy a good quality of life and minimise the worry and anxiety associated with the risk of accidental allergic reactions.

The framework therefore needs to define carefully what is required of the risk assessment in terms of data types and quality. Beyond this, it will also need to consider the criteria upon which tolerability is based, and how they would be met satisfactorily in the context of food allergy and the diverse nature of stakeholders affected by it. These will vary across different stakeholders, and users of the framework will need to reach a consensus on prioritising them, appropriately balancing the needs of those stakeholders.

6.4. How should the framework operate?

Those involved in the determination of tolerable risk within the proposed framework will start with a diversity of views, possibly even contradictory and antagonistic. The framework must facilitate the expression of these opinions, allowing meaningful contributions from all stakeholders. Approaches such as a Delphi process may be helpful in this regard, helping to assemble the evidence required and analyse it to identify implications. Our proposed framework does not aim to circumscribe those who will use it, but rather to describe the elements which need to be included. Those operating the framework will therefore need to decide at the outset on the desired outputs. This could range from scrutinising the basis of Reference Doses to gathering data on health-related quality of life. Ultimately, defining a tolerable risk, which is accepted beyond the group itself, will depend on the degree of consensus achieved.

7. Conclusion

Defining an appropriate level of protection from the risks to food-allergic consumers due to the unintended presence of allergen(s) in food products remains a pressing priority. Lack of regulation has resulted in proliferation of different risk mitigation strategies, leaving food-allergic individuals uncertain and confused about the safety of food products. This impairs their ability to make safe food choices – one of the aims of the Food Information for Consumers Regulation (European Parliament and Council, 2011), a pivotal piece of consumer safety legislation.

In contrast the science behind setting safe Reference Doses and action levels, an essential foundation to defining tolerable risk in the context of food allergy, grows ever more robust. Advances in modelling utilising the ever more abundant data from human provocation studies, including single dose challenges, are helping to validate inferences about exposure to low doses of allergen and better understand the impact of co-factors. However, Reference Doses and approaches to allergen risk assessment are not yet harmonised in any jurisdiction, even in the European Union where a legislative framework exists. Abundance of data of sufficient quality is clearly insufficient by itself to allow decisions on tolerable risk, highlighting the urgent need to understand and integrate into the process other, perhaps less obvious factors, such as how risk is perceived by different stakeholders.

We have reviewed the factors contributing to tolerable risk decisions and how they were made for a diverse range of other foodborne hazards. We found that neither the actual target level of protection, nor the process used to derive it, are commonly described sufficiently for the underlying rationale to be transparent to all stakeholders. Of note, we were unable to find evidence of the process leading to the decision on acceptable risks in the examples investigated nor have we always been able to identify all the stakeholders contributing to the risk decision. These observations illustrate the lack of transparency behind these processes. We noted that notwithstanding the presence of residual risks, risk management measures were always instituted to mitigate those food safety risks. The examples demonstrate that decisions on risk level can be taken despite residual uncertainty, illustrating the need to progress from the risk assessment stage to risk management measures, even if risk is *minimised* rather than *eliminated.* Furthermore a diversity of rationales led to the conclusions, ranging from analytical capability to health-based criteria, but also in one case integrating wider socio-economic considerations affecting the ultimate risk (the FDA's assessment for coeliac disease).

Lack of agreement on a tolerable level of residual risk in food allergy has hindered the development of effective risk management approaches and has rendered one measure – precautionary allergen labelling – almost meaningless, to the serious detriment of people with food allergies and other stakeholders. To address this issue we proposed a framework for the definition of tolerable risk based on the criteria developed by Murphy and Gardoni (2008). Reviewing these criteria with respect to food allergy, we concluded that sufficient knowledge exists to implement the framework, including sufficient expertise across the whole range of stakeholders with an interest in the outcome to allow opinions to be heard and respected, and a consensus to be achieved. A strength of our proposal is that it advocates a fully transparent process which should lead to better and more equitable decisions which are better accepted by society. The framework is also equally applicable to allergens that are not currently regulated.

As highlighted by Hunter and Fewtrell (2001), as well as Murphy and Gardoni (2008), failure to involve all relevant stakeholders in defining tolerable risk will most likely result in sub-optimal risk management decisions, or decisions that are not supported by those bearing the risk. We therefore hope that this publication will trigger the much-needed cross-stakeholder engagement and collaboration to finally define appropriate levels of protection for food-allergic consumers. We hope Competent Authorities will understand the urgent need, and see that – of all the stakeholders – their role provides an ideal opportunity to champion and lead this activity.

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