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RISK ASSESSMENT OF FOOD ALLERGENS

PART 3: REVIEW AND ESTABLISH PRECAUTIONARY LABELLING IN FOODS OF THE PRIORITY ALLERGENS

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ABBREVIATIONS AND ACRONYMS

AL	action level
CAC	Codex Alimentarius Commission
CCFH	Codex Committee on Food Hygiene
CCFL	Codex Committee on Food Labelling
CD	coeliac disease
CI	confidence interval
ED_p	the eliciting dose predicted to provoke reactions in a specified percentage (p) of the allergic population
ED₀₁	the eliciting dose predicted to provoke reactions in 1% of the allergic population
ED₀₅	the eliciting dose predicted to provoke reactions in 5% of the allergic population
ED₁₀	the eliciting dose predicted to provoke reactions in 10% of the allergic population
ED₅₀	the eliciting dose predicted to provoke reactions in 50% of the allergic population
ELISA	enzyme-linked immunosorbent assay
FAO	Food and Agriculture Organization of the United Nations
FBO	food business operators
FSANZ	Food Standards Australia and New Zealand
GPFH	General Principles of Food Hygiene
GSLPF	General Standard for the Labelling of Packaged Foods
HBGV	health-based guidance value
HACCP	hazard analysis and critical control points
IgE	immunoglobulin E
LoQ	limit of quantification
MED	minimum eliciting dose
NOAEL	no observed adverse effect level
PAL	precautionary allergen labelling; may also be referred to as allergen advisory labelling or statements in certain jurisdictions
p₅₀	50th percentile value from the general population distribution of the single-eating occasion intake of a food (used to estimate RfA)

RA	risk assessment
RfA	reference amounts of food intake (based on percentile of consumption appropriate to risk management objective)
RfD	reference dose
1D- or 2D-SDS PAGE	1-dimensional or 2-dimensional sodium dodecyl sulphate-polyacrylamide gel electrophoresis
TNO	Netherlands Organisation for Applied Scientific Research
SF	safety factor
UAP	unintended allergen presence
UF	uncertainty factor
VITAL®	Voluntary Incidental Trace Allergen Labelling
WHO	World Health Organization

DECLARATIONS OF INTERESTS

All participants completed a Declaration of Interests form in advance of the meeting. Three of the participants declared interest in the topic under consideration. Markus Lacorn and Eva Södergren declared significant interests connected with their employment, and Clare Mills declared interests connected to investments that exceeded the FAO/WHO's threshold. It could not be excluded that the declared interests may be perceived as a potential conflict of interest. Therefore, while all three persons mentioned above had been invited to participate in the meeting, they had been excluded from the decision-making process regarding final recommendations and participated only as technical resource people.

All remaining experts were not considered by FAO and WHO to have declared any interest that may be perceived as a potential conflict with regard to the objectives of the meeting.

All the declarations, together with any updates, were made known and available to all the participants at the beginning of the meeting.

All the experts participated in their individual capacities and not as representatives of their countries, governments or organizations.

EXECUTIVE SUMMARY

BACKGROUND AND OBJECTIVE

At its 45th session in May 2019, the Codex Committee on Food Labelling (CCFL) requested FAO and WHO to provide scientific advice to validate, and if necessary, update the list of foods and ingredients in section 4.2.1.4 of the *General standard for the labelling of prepackaged foods* (GSLPF) (FAO and WHO, 2019). In December 2020, the initial meeting of the Ad hoc Joint FAO/WHO Expert Consultation on Risk Assessment of Food Allergens, addressed the request by first identifying and agreeing upon the criteria for assessing additions and exclusions to the priority food allergen list, then evaluating the available evidence for foods of concern (FAO and WHO, 2022a).

The Codex Committee on Food Hygiene (CCFH) has developed a code of practice (CoP) to provide guidance to food business operators (FBO) and competent authorities on managing allergens in food production, including controls to prevent or minimize allergen cross-contact. In relation to this CoP, the 50th session of CCFH requested FAO and WHO to provide scientific advice with respect to the list of priority allergens and the use of allergen threshold levels to inform allergen risk management for foods (FAO and WHO, 2018a). In March 2021, the Expert Consultation convened to establish threshold levels for priority allergenic foods and recommend analytical methods for detection in food and food-processing environments. This second meeting addressed a part of the CCFH request by establishing recommended reference doses, based on health-based guidance values (HBGV) (FAO and WHO, 2022b).

The CCFL is also developing guidance on the use of precautionary allergen labelling (PAL) (FAO and WHO, 2021). Following those two meetings, FAO and WHO convened the Expert Consultation for a third meeting to address the remaining requests from the CCFH, and also to support the ongoing work of CCFL.

CONCLUSIONS

- > Precautionary allergen labelling (PAL) based on a comprehensive allergen risk management programme and implemented using a single clear unambiguous advisory statement, supported by effective risk communication, is an effective strategy to protect consumers from unintended allergen presence (UAP).
- > Current use of PAL is voluntary and often not part of a standardized risk assessment process. This leads to non-uniform and indiscriminate application of PAL (including a multitude of different phrases) and/or inappropriate absence of PAL.

Consumers find the information currently provided by PAL to be confusing. This results in poor communication and misinterpretation of the risks posed by UAP, a reduction in consumer trust in allergen labelling, and proven health risks to the allergic consumer.

- > The available evidence indicates that some manufacturers, consumers and other stakeholders do not understand current strategies to communicate precautionary messages relating to risks posed by UAP in products. Current data indicate a preference for wording that conveys that a food is *not suitable* for consumers with a particular allergy. Education of consumers, healthcare providers, FBOs, risk assessors and risk managers is critical to PAL management.
- > Individual allergy management considerations:
 - The use of a PAL system based on risk-based reference doses (RfDs) would be protective for the vast majority of food-allergic individuals.
 - In this framework for PAL, it is recommended that all individuals with a particular food allergy avoid foods when a PAL to that food is present on the food package. However, this system may be overprotective and restrictive for some of the less sensitive individuals with food allergies.
 - Similarly, a small proportion of individuals with a particular food allergy who react to smaller amounts of allergen (at or below the RfD) might not be fully protected, although they would be informed as to potential UAP exposure above the RfD (which might cause more severe reactions). Further work may be needed as to how to ensure these individuals can receive appropriate information to make informed safe food choices.
 - Any deviations from this recommendation (for food-allergic individuals to avoid all products with PAL to the relevant allergens) should be taken into consideration for individual allergy management advice, as discussed between an allergic individual and their healthcare providers.
- > RfDs recommended in the second meeting are not intended to be used for making a claim that a food is free from specified allergens.
- > Risk assessment (RA) for considering ingredient exemptions from priority allergen labelling is proposed for a future meeting.

RECOMMENDATIONS

The safety of consumers with food allergies is a shared responsibility of all stakeholders including (but not limited to) consumers, FBOs, healthcare providers and regulatory bodies.

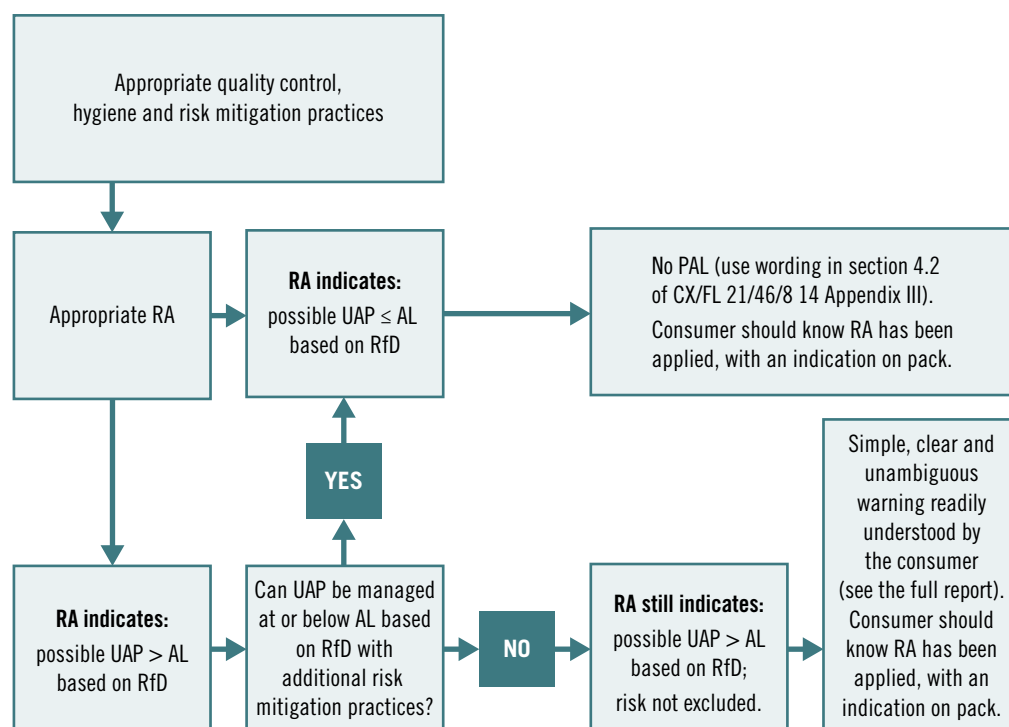
- > The Expert Committee recommends that the decision whether or not to use a PAL statement be part of a regulatory framework that requires FBOs to denote PAL when UAP exceeds the relevant RfD (i.e. ED₀₅-based RfD for priority allergenic foods as recommended in the second meeting of the FAO/WHO consultation) and not to use PAL when UAP does not exceed the relevant RfD.

Moreover, FBOs should/must provide an indication on the label (e.g. using a symbol) that a qualified RA to inform the need (or not) for PAL has been undertaken, irrespective of whether the RA outcome indicates that a PAL should be used or not.

- > If an RfD is not established for a particular priority allergenic food, an estimated RfD can be used provided it is determined following the guiding principles elaborated by the second meeting of the FAO/WHO consultation.
- > Compliance with existing Codex codes of practice, good allergen management and allergen control programmes are a prerequisite for FBOs. The use of PAL is not appropriate where deviations from these programmes may occur, such as UAP due to production errors.
- > Decisions about whether or not to use PAL should be based on hazard identification and risk characterization (refer to the diagram below). Adherence to the *Code of practice on allergen management for food business operators* (FAO and WHO, 2020b), good manufacturing practices (GMP), and hazard analysis and critical control points (HACCP) combined with an appropriate UAP risk assessment should ensure that the level and frequency of UAP is minimized, consistent with the principles elaborated for PAL. The use of PAL should be restricted and applied to those situations where UAP cannot be prevented and may result in an exposure above the RfD for a priority allergenic food.
- > The use of PAL, to communicate potential risk from UAP above the RfD to the consumer, should be simple, clear, unambiguous and not false or misleading:
 - A consistent and harmonized approach is needed.
 - This includes the use of a single unified phrase, which should convey to consumers that the product with PAL poses a health risk to individuals with an allergy to that particular food and is thus not suitable for them.
 - The precise wording of the single phrase for PAL needs to be decided by CCFL in conjunction with all relevant stakeholders and should consider local linguistic nuances.
 - Education of allergic consumers (or those providing food for them, including FBOs) and other relevant stakeholders (e.g. risk assessors, risk managers, and healthcare providers) is critical to ensure understanding of the applied principles and the implications of the chosen phraseology.
- > FBOs should retain documented evidence of compliance with COP/HACCP and their UAP RA process if an indicator that RA has been applied is used on the label.
- > Analytical methods used to inform the risk assessment process and validate or verify cleaning processes should have a demonstrated fitness-for-purpose (including e.g. matrix-matched assay validation with a limit of quantification at least threefold below the action level [AL] for the specific food being analysed) and report in units of mg total protein from the allergenic source/kg food analysed (ppm total protein from the allergenic source).

These recommendations are summarized in **Figure 1** below.

FIGURE 1. **OVERVIEW OF THE RECOMMENDED SINGLE PRECAUTIONARY ALLERGEN LABELLING (PAL) SYSTEM**



Note: ^a. RA, risk assessment; ^b. UAP, unintended allergen presence; ^c. AL, action level; ^d. RfD, reference dose.

Source: Authors' own elaboration.



CHAPTER 1

INTRODUCTION

1.1 BACKGROUND

The overall aims of the series of Ad hoc Joint FAO/WHO Expert Consultations on Risk Assessment of Food Allergens held during the period 2020–2022 were to (i) validate and update the list of foods and ingredients in section 4.2.1.4 of the *General standard for the labelling of prepackaged foods* (GSLPF) based on risk assessment, (ii) establish threshold levels in foods for the priority allergens, and (iii) evaluate the evidence in support of precautionary allergen labelling (PAL).

Several meetings of an Ad hoc Joint FAO/WHO Expert Consultation on Risk Assessment of Food Allergens were planned. The establishment of the priority allergens for the GSLPF occurred at the first meeting (FAO and WHO, 2022a). At the second meeting, reference doses (RfDs), reflecting exposure without appreciable risk to health, were derived as were analytical considerations with consequences for the application of RfD in quantitative or other risk assessments (FAO and WHO, 2022b).

Food regulations in most regions of the world prescribe the mandatory labelling of specified priority allergenic foods, including some or all ingredients derived from these, when used as or added to food (e.g. Regulation [EU] No. 1169/2011, FSANZ Standard 1.2.3, FSANZ P1044; Food Allergen Labelling and Consumer Protection Act of 2004). However, allergenic proteins may also unintentionally end up in food, for instance, due to cross-contact during food manufacture. The subject of the third meeting related to the application of RfDs established in the second meeting in addressing unintended allergen presence (UAP) due to cross-contact and providing guidance on the use of PAL for this issue. Some other remaining questions related to topics not completely covered in or deferred from the first and second meetings were also discussed. The terms of reference (ToR) for the meetings can be found on the FAO and WHO website (FAO and WHO, 2020a).

In the context of the questions from the ToR, during the third meeting, the Expert Committee considered and applied information gathered from the first two meetings. In particular, the Expert Committee agreed that the value and meaning of RfDs established at the second meeting was a valid benchmark for the concept of “thresholds” represented in the ToR questions.

Other focused questions and topics included:

- > Can RfD levels be used to determine if and when UAP due to cross-contact does not negatively impact human health and does not need to be communicated by precautionary allergen labelling?
- > How can RfDs, or action levels derived from these, be used as benchmarks by FBOs in managing food production operations?
- > What is effective use of precautionary allergen labelling?

1.2 CURRENT STATUS, USE AND RISK PERCEPTIONS OF PRECAUTIONARY ALLERGEN LABELLING (PAL)

Precautionary allergen labelling (PAL) originated in the 1980s as an attempt by the food industry to remedy the issues arising from the lack of data to characterize the risk to health posed by unintended allergen presence (UAP), also referred to as UAP risks, in food products. PAL is used as a consumer-facing measure to warn or provide information to food-allergic people that a product poses a potential risk to health. In prepackaged foods, UAP due to cross-contact (also referred to as cross contamination, previously) can occur when food products with different allergen profiles are produced in the same facility using shared equipment or on the same production line (Zurzolo *et al.*, 2013a; Taylor and Baumert, 2010; FoodDrinkEurope, 2022). Statements such as “may contain X”, “may contain traces of X”, “produced in a facility that uses X”, “not suitable for someone with X allergy” are common examples of PAL statements used by manufacturers, though in reality these statements can take many forms. The main intent of PAL is to help food-allergic consumers make informed decisions about safe food choices (Barnett *et al.*, 2011).

In most countries, PAL is a voluntary communication not mandated by regulatory or other authoritative bodies, and there is no harmonized guidance regarding when and when not to apply PAL, or what wording to use. While many countries have legislated the mandatory declaration of allergenic foods and their derivatives when present as intentional ingredients in a food product, PAL falls into a legislative grey area that is often unregulated and not standardized. In some jurisdictions, there are regulations over the nature of voluntary information relating to UAP (Allen *et al.*, 2014; Madsen *et al.*, 2020). Many countries have issued guidance on the voluntary use of PAL, advising that such statements should always be truthful and not used in instances when cross-contact can and should be prevented by effective manufacturing practices and controls. In the European Union (EU), the *Provision of food information to consumers regulation* (EU) No. 1169/2011 (EU, 2011) stipulates in Article 36 that voluntary information (including that related to food allergens) should not be misleading, ambiguous or confusing and should be based on relevant scientific data where appropriate. Some countries prohibit PAL (e.g. Argentina) while others have taken steps to mandate labelling UAP above a detectable level, i.e. 10 ppm (Japan). Still, other countries (e.g. Belgium and the Kingdom of the

Netherlands) have proposed RfDs – based on similar principles as VITAL® (Voluntary Incidental Trace Allergen Labelling) (see section 1.4) – for allergen management; however, the proposed RfDs have varied widely between these countries (Madsen *et al.*, 2020; FAVV SciCom, 2022). This broad range of practices causes non-uniformity in the application of PAL for addressing and communicating the risks of UAP at the global level (Allen *et al.*, 2014; Madsen *et al.*, 2020), impacting hazard assessments, trade and other global harmonization efforts.

Given that priority food allergens are ingredients commonly encountered during food manufacture and that products with complex and different food allergen profiles are often produced on the same equipment within food production facilities, the potential for allergen cross-contact is great. Lack of a uniform standardized (and regulated) process to address UAP risks in food products has likely contributed to a high proportion of products carrying PAL statements. For example, a 2011 survey of Australian supermarkets (Zurzolo, 2013b) found that the majority (65 percent) of surveyed products had a PAL for one or more allergens. A 2019 survey of over 10 000 product labels from Latin American supermarkets (Ontiveros *et al.*, 2020) found that 63.3 percent and 33.2 percent featured allergen labelling and/or PAL, respectively. Also, a consumer survey of food-allergic individuals undertaken by the United Kingdom Anaphylaxis Campaign (published in 2002) reported that 69 percent of breakfast cereals and 56 percent of confectionery items in the United Kingdom of Great Britain and Northern Ireland (UK) shops were labelled as containing traces of nuts, despite none listing tree nuts as an ingredient. Despite changes in labelling legislation, the situation had not really changed in 2014 when the United Kingdom Food Standards Agency commissioned further research which reported that 55 percent of products had PAL for peanuts or hazelnut while 11 percent had PAL for cow's milk or gluten (Food Standards Agency, 2014). Precautionary allergen labelling thus remains common on food products globally at the present time.

The high rate of PAL on food products has led to a perception that PAL statements are being used indiscriminately (Ward *et al.* 2010; Turner *et al.* 2011). Products with a variety of non-uniform and different PAL statements add to this perception. For example, a 2006 survey of supermarket products in the United States of America (Pieretti *et al.* 2009) found that, while 17 percent of products surveyed carried a PAL, 25 different types of statements were used. Ontiveros *et al.* (2020) identified 33 different types of PAL statements on Latin American food products. Also, surveys of imported foods sold in Australia reported that 22–38 percent of products carried nine different PAL statements, mostly in both the manufacturer's language and English (translated by the importers), but a considerable number of PAL statements were only in the manufacturer's language (Uraipong *et al.*, 2021; Yee *et al.*, 2021). These findings underscore the wide range in frequency and types of PAL on food products that can lead to uneven communication of UAP risks and potential confusion in interpreting food product allergen information by consumers.

To better understand UAP risks in food products, several analytical studies have been conducted to assess the presence and levels of UAP in domestic and imported products

with or without PAL (Pele *et al.*, 2007; Spanjersberg *et al.*, 2010; Remington *et al.*, 2015; Waiblinger and Schulze, 2018; Blom *et al.*, 2018; Uraipong *et al.*, 2021; Yee *et al.*, 2021; Robertson *et al.*, 2013; Do, Khuda and Sharma, 2018; Hefle *et al.*, 2007; Bedford *et al.*, 2017; Crotty and Taylor, 2010). Together, these data show that products with PAL statements may contain highly variable concentrations of the stated food allergens ranging from a few mg/kg of the allergenic food (in most products) to thousands of mg/kg. These differences in UAP content can pose significant differences in reaction risks (and reaction severity) for allergic consumers. Furthermore, the presence and amounts of UAP varied greatly depending on the type of food allergen and types of products investigated. For example, in some specific food types or commodities, more than 50 percent of products with PAL sampled had UAP detected, e.g. dark chocolate and unintended milk (Crotty and Taylor, 2010; Bedford *et al.*, 2017), while allergens mentioned in the PAL statement were never or rarely detected in some product categories (Do, Khuda and Sharma, 2018). Data also showed that the type of PAL phraseology bore no relationship to UAP risk (Bedford *et al.*, 2017; Hefle *et al.*, 2007). Thus, different wordings used in PAL are generally not an indicator of the different levels of UAP risk whatever the allergen considered (Hefle *et al.*, 2007; Pele *et al.*, 2007; Crotty and Taylor, 2010; Barnett *et al.*, 2011). Finally, many of these surveys found that UAP could also be detected in products without PAL (Do, Khuda and Sharma, 2018; Allen and Taylor, 2018; Blom *et al.*, 2018; Uraipong *et al.*, 2021; Yee *et al.*, 2021) and not at insignificant amounts (Bedford *et al.*, 2017; Blom *et al.*, 2018; Do, Khuda and Sharma, 2018; Uraipong *et al.*, 2021; Yee *et al.*, 2021).

While these analytical survey findings largely support the precautionary nature of PAL (i.e. the allergenic substance can be present but is not necessarily always present), there are some notable observations:

- > PAL may be overused, given the high rate of products with PAL with no evidence of UAP. As a consequence, consumers with an already restricted diet due to their food allergy may avoid a number of nutritious products that pose no risk to them.
- > Some products with PAL appear to have frequent and/or high levels of UAP, but consumers would not be alerted to these differences based on presence or type of PAL alone.
- > Products without PAL may still pose UAP risks. Thus, absence of PAL cannot be assumed to imply no UAP risk. This observation further suggests that UAP risk assessments may not be uniformly conducted for determining when or when not to use PAL for all food products which have potential for UAP.

Based on these observations, the current state of PAL and UAP communication is not frequently informed by actual presence and, therefore, increased risk of UAP to consumers. This has potential downstream consequences for consumers. For example, some consumers may take a conservative approach to PAL and treat PAL as communicating or indicating an allergen is *always* present in the product. Avoiding products with PAL and no UAP leads to unnecessary avoidance of many products that may be safe to consume. At the same time, consumers who tolerate a product with PAL on one or more occasions often assume that the same product will *always* be tolerated by them in the future.

Some may then associate a particular PAL statement with products that are more likely to be tolerated. However, in some cases products with that same PAL statement may actually contain significant UAP risks. Thus, the next time the product with PAL is consumed, it could be the one with UAP risks and lead to adverse reactions.

Consumers may not understand that PAL does not imply a UAP risk in *every* food product where PAL is present, and that the wording used for the PAL statement cannot be taken to imply a higher or lower risk of UAP. As a result, the value of PAL as an indicator of UAP risk becomes diminished. These factors – and most importantly, the perception that PAL is overused – have contributed to PAL losing its informational value and credibility as a means to warn allergic consumers about potential UAP risk (Madsen *et al.*, 2020; DunnGalvin *et al.*, 2019a and 2019b). This assertion is substantiated by recent consumer surveys which report that up to 70 percent of allergic individuals (depending on the PAL statement) report consuming prepackaged food products with PAL at least some of the time (Marchisotto, Harada and Kamdar, 2017; Cochrane *et al.*, 2013; Zurzolo *et al.* 2013a; Holleman *et al.* 2021; Allen and Taylor, 2018). These data are summarized in **Table 1**.

TABLE 1 SUMMARY OF CONSUMER SURVEYS REPORTING THE PROPORTION OF INDIVIDUALS WHO WOULD ALWAYS AVOID PURCHASING PRODUCTS WITH PRECAUTIONARY ALLERGEN LABELLING (PAL) DUE TO FOOD ALLERGIES, AND HOW THIS IS IMPACTED UPON BY THE PHRASEOLOGY USED

PAL WORDING	"MAY CONTAIN"	"MAY CONTAIN TRACES"	"MANUFACTURED IN A FACILITY THAT ALSO PROCESSES..."	"NOT SUITABLE FOR"	REFERENCE
United Kingdom of Great Britain and Northern Ireland (n=184)	80% avoid	60% avoid	40% avoid	n/a	Noimark, Gardner and Warner, 2009
Canada (n=127)	56% avoid	47% avoid	40% avoid	80% avoid	Ben-Shoshan <i>et al.</i> , 2012
Australia (n=246)	75% avoid	45% avoid	35% avoid	n/a	Zurzolo <i>et al.</i> , 2013a
Netherlands (Kingdom of the) (n=179)	64% avoid	43% avoid	36% avoid	n/a	DunnGalvin <i>et al.</i> , 2015
Ireland (n=87)	67% avoid	59% avoid	49% avoid	n/a	
United Kingdom of Great Britain and Northern Ireland (n=161)	70% avoid	61% avoid	53% avoid	81% avoid	
Germany (n=474)	70% avoid	45% avoid	39% avoid	82% avoid	
United States of America (n=5 507)	~90% avoid	n/a	59% avoid	n/a	Marchisotto, Harada and Kamdar, 2017
Canada (n=1 177)	77% avoid	n/a	64% avoid	n/a	
United States of America (n=2 729)	81% avoid	86% avoid	50–80% avoid	n/a*	Gupta <i>et al.</i> , 2021
Netherlands (Kingdom of the) (n=42)	~90% avoid	~70% avoid	~30% avoid	n/a	Holleman <i>et al.</i> , 2021

Note: *Avoidance numbers were derived from actual study data numbers or related information. Avoidance data not available, but this term ("not suitable for") was found to be most preferred by consumers (29.3%), followed by "May contain allergen" (22.1%).

Source: Authors' own elaboration.

Holleman *et al.* (2021) further investigated the understanding of allergen labelling information by allergic and non-allergic consumers and concluded that both allergic and non-allergic consumers find allergen information difficult to interpret and misunderstand PAL, wrongly attributing different risk levels to different PAL wordings. The authors of this study advocate the use of a single PAL wording as the best approach for clear communication of PAL.

There is clear evidence that the diminished value of PAL as an indicator of UAP risk has potential for adverse health consequences for the population of allergic consumers. The potential health impact resulting from this situation is informed by a prospective study of 157 food-allergic Dutch adults over a one-year period (Blom *et al.*, 2018; Michelsen-Huisman *et al.*, 2018). The study collected data on accidental reactions to prepackaged food products in allergic individuals and analysed both the use of PAL and presence of unintended allergen in those food products associated with culprit reactions. The authors found that over the study period 46 percent of participants experienced, on average, two accidental allergic reactions – many of at least moderate severity, for a total of 153 food product reactions. Forty-one percent of reactions involved prepackaged products. Only 50 percent of participants reported always checking the label before consumption, with participants commenting that total avoidance of PAL was impossible and that PAL was mostly used by food businesses to avoid litigation. Of 51 causative food products analysed, 21 (41 percent) had a PAL statement. Nineteen products (37 percent) had one or more non-ingredient allergens detected which could have caused the allergic reaction; 9 of these 19 products had a relevant PAL statement, implying that the accidental reaction was likely to have been caused by the patient consuming (and ignoring) product with a PAL statement. Also, UAP was identified in approximately 20 percent of products linked to allergic reactions, which lacked a declaration of the allergen, either in the ingredients or with a PAL statement. These findings further underscore both the diminished understanding by consumers of PAL as UAP risk communication and the decreased effectiveness of current PAL in identifying UAP risks and preventing allergic reactions in allergic consumers. Thus, many consumers may choose to ignore PAL and consume products that have hazardous levels of UAP while other consumers may inadvertently react to products carrying no PAL or other warnings for UAP risks.

A review of the literature finds that current approaches and practices for applying PAL are not readily effective in communicating risk information to consumers about products posing a high likelihood of UAP risk and should be improved. Madsen *et al.* (2020) evaluated the current status and uses of PAL and the way various authorities deal with UAP and PAL and concluded that PAL currently:

- > is not related to the actual risk;
- > does not always cover the correct allergens;
- > limits food choices unnecessarily;
- > is misinterpreted;
- > is increasingly ignored; and
- > is of limited value for patients due to the inconsistencies in its application.

The authors, who represented multiple stakeholder groups including consumers with food allergy, considered the current use (and non-use) of PAL and their utility to consumers (see **Figure 2**). They concluded that the most helpful PAL would be a system which conveys that a food product has undergone a proper risk assessment and that levels of UAP are unavoidable (despite adherence to GMP) and pose an actual reaction risk that is unsafe for consumers.

FIGURE 2. SCENARIOS FOR THE PRESENCE OR ABSENCE OF PRECAUTIONARY ALLERGEN LABELLING (PAL)

	Product without PAL	Product with PAL
Helpful to allergic consumers	1. Product without PAL with low or no risk of inducing an allergic reaction, i.e. is safe • Proper risk assessment by the food manufacturer • Conclusion that the allergen is not present in the product at a level that is likely to cause an allergic reaction	2. Product with PAL a real risk of inducing an allergic reaction, i.e. unsafe to consume • Proper risk assessment by the food manufacturer • Conclusion that the allergen may be present in the product despite allergen management and good manufacturing practice (GMP)
Not helpful to allergic consumers	3. Product without PAL with unknown risk of inducing an allergic reaction, i.e. may be safe or unsafe to consume • No proper risk assessment by food manufacturer resulting in possible allergen presence without being mentioned on the label • No conclusion can be drawn about the presence of the allergen	4a. Product with PAL with unknown risk of inducing an allergic reaction, i.e. may be safe or unsafe to consume • No proper risk assessment and allergen management to reduce the risk of unintended presence by manufacturer • No conclusion can be drawn about the presence of the allergen 4b. Product with PAL with unquantifiable, possibly high risk of inducing an allergic reaction • Risk assessment by manufacturer of some but not all allergens • Misleading PAL: incomplete list of allergens in the PAL statement/some allergens are present but not mentioned on the label • No conclusion can be drawn about the presence of the allergens not mentioned 5. Product with PAL with low or no risk of inducing an allergic reaction • Proper risk assessment by manufacturer • Decision to use PAL nevertheless by risk-averse manufacturer

Source: Madsen, C.B., van den Dungen, M.W., Cochrane, S., Houben, G.F., Knibb, R.C., Knulst, A.C., Ronsmans, S. *et al.* 2020. Can we define a level of protection for allergic consumers that everyone can accept? *Regulatory Toxicology and Pharmacology*, 117: 104751. <https://doi.org/10.1016/j.yrtph.2020.104751> (Reproduced under a Creative Commons CC-BY 4.0 license)

1.3 CONSUMER KNOWLEDGE AND ATTITUDES REGARDING PRECAUTIONARY ALLERGEN LABELLING (PAL)

Fear of accidental reactions from exposure to intended or unintended allergen exposure is common in the food-allergic community, and the constant vigilance in avoiding allergen hazards on a daily basis contributes to social anxiety, economic burden and a decreased quality of life (ASCIA 2007; Lieberman and Sicherer, 2011; Gupta *et al.*, 2013; Safefood, 2022; Cardwell *et al.*, 2022). These factors play an important role in forming consumer attitudes and behaviours towards PAL. PAL statements are useful if they provide clear and reliable information about UAP risks (DunnGalvin *et al.*, 2015; Madsen *et al.*, 2020). However, inconsistency in wording and a lack of standardization when using PAL to communicate UAP risks increases uncertainty and negatively impacts consumer perception of control and trust (DunnGalvin, 2015). The reality is that consumers have little knowledge as to why PAL might be present on a food package, and what the true risks to health posed by UAP on those products might be. As a result, consumers frequently perceive that PAL is used by manufacturers as a “safety net” to convey an unspecified risk or probability of cross-contact rather than an actual risk to health (DunnGalvin *et al.*, 2015; Pádua *et al.*, 2016). Consumers thus make their own risk assessment decisions about PAL, in many cases choosing to ignore PAL altogether (see section 1.2). When they consume products with PAL without incident, they assume that PAL is irrelevant to them. This diminishes the intended benefit of PAL for allergic consumers and contributes to risk-taking behaviours.

There are also data to suggest that consumers will use other proxy markers to guide their decision as to whether to heed PAL or not: for example, the product brand, manufacturer, or retailer (Barnett *et al.*, 2011, 2013; Ben-Shoshan *et al.*, 2012; Cochrane *et al.*, 2013). However, this can work both ways. Some brands may be viewed as using PAL carefully, so consumers might be less likely to ignore PAL on those products; on the other hand, a consumer might eat a product with PAL from one brand without reaction, and then consider that as “proof” that PAL has been indiscriminately applied and therefore ignore the presence of PAL on other foods of the same brand.

A survey undertaken in the United States of America and published in 2021 (Gupta *et al.*, 2021) analysed in more detail consumers’ underlying knowledge with respect to the use of PAL. In this survey of 3 008 consumers, 56 percent thought the use of PAL was regulated by legislation (rather than being voluntary); 44 percent responded that the use of PAL was based on “specific amounts of the allergen present in the foods”; and 41 percent thought that the phraseology used on PAL reflected the actual amount of allergen detected in the food product, indicating different levels of risks. These data demonstrate the poor knowledge base amongst allergic consumers with respect to PAL.

Of note, similar attitudes are expressed by healthcare professionals advising food-allergic individuals. Turner *et al.* (2016) reported a survey of healthcare professionals in the United Kingdom of Great Britain and Northern Ireland and Australia.

One third of respondents thought that the use of PAL was subject to a standardized risk assessment, while 13 percent believed that PAL was regulated by legislation. Around 40 percent regarded PAL as “generally helpful” while 40 percent believed that PAL was harmful. Most (82 percent) considered that PAL “increased anxiety or abnormal food behaviours” and that PAL was used by manufacturers to reduce risk of litigation due to UAP.

1.4 EXAMPLE OF RISK-BASED PRECAUTIONARY ALLERGEN LABELLING (PAL) APPROACHES – THE VITAL® PROGRAM

The VITAL® (Voluntary Incidental Trace Allergen Labelling) Program developed by the Allergen Bureau of Australia & New Zealand is a voluntary, standardized allergen risk assessment process for the food industry.

The VITAL® approach has evolved over time. VITAL® 1.0 was originally introduced in 2007. The aim was to limit the use of PAL relating to UAP by using "Action Levels" based on the application of risk assessment principles to the potential doses of exposure, to inform the need for standardized PAL messages. Three action levels were initially proposed: Green (low risk; no PAL); Yellow (possible risk; precautionary “may be present: xxx” labelling recommended); Red (higher risk; definitive “contains xxx” labelling recommended). The initial action levels were established on the basis of the threshold doses of protein from allergenic foods for subjective and objective responses cited by the 2006 US Food & Drug Administration (FDA) Threshold Working Group (Buchanan *et al.*, 2008). Due to uncertainties surrounding the FDA estimates and the general paucity of data at the time relating to allergen thresholds, a tenfold uncertainty factor was applied (Taylor *et al.*, 2014). A subsequent analysis demonstrated the potential benefits of using the VITAL® approach to improve PAL and reduce the use of unnecessary PAL (Turner *et al.*, 2011).

In 2011, the VITAL® Scientific Expert Panel conducted a thorough review of data relating to allergen thresholds and established appropriate reference doses to inform these action levels (VITAL® 2.0), on the basis of statistical modelling of the available threshold data. Given that allergic individuals react to amounts of protein, rather than concentrations, the reference doses were given as mg total protein for the allergenic food, based upon either the ED₀₁ (for peanut and cow’s milk), the 95 percent lower confidence interval of the ED₀₅ (for wheat, soybean, cashew, shrimp, sesame seed, mustard and lupine), or both (for egg and hazelnut) using all appropriate statistical dose-distribution models. Reference doses were established for 11 allergenic foods, but not for fish, celery (due to poor model fits) nor tree nuts beyond hazelnut and cashew because of the absence of relevant data. No uncertainty factor was applied since the data was derived from allergen challenges in allergic human volunteers and the uncertainty captured by the statistical modelling. A further change was the recommendation for just two action levels:

- > Action level 1: Precautionary allergen labelling is not recommended when the VITAL® risk assessment indicates the concentration of the total cross-contact protein from an allergenic food in the finished product is less than the Action Level transition point.

- > Action level 2: Precautionary allergen labelling is recommended when the risk assessment indicates the concentration of the total cross-contact protein from an allergenic food is at or greater than the action level transition point.

At the core of VITAL® is a robust allergen management plan designed to complement a food businesses' existing food safety systems. The first stage in the development of a VITAL® allergen management plan is a quantitative risk assessment. When a risk assessment determines that a PAL statement is needed, VITAL® recommends the use of the PAL statement: "May be present: allergen x, allergen y".

The approach was subsequently refined in 2022, when the VITAL® Scientific Expert Panel undertook a further review of 3 400 clinical data points from clinical (low-dose oral) food challenges (both published and unpublished studies) undertaken in Australia, the United States of America and the European Union. The data set was analysed by applying a new Stacked Model Averaging programme (Wheeler *et al.*, 2019) for each allergenic food, and the ED₀₁ adopted as the Reference Doses for VITAL® 3.0 (VITAL®, 2022b; Allergen Bureau, 2021).

Use of VITAL® is not a legislated requirement, but the Allergen Bureau has recently implemented the VITAL® Standard, an audited certification programme to allow manufacturers to inform consumers about its use. Manufacturers that achieve VITAL® Standard certification may use the VITAL® Mark on all products within their scope of certification irrespective of whether the VITAL® assessment has indicated that PAL is required or is not recommended (VITAL®, 2022a). This recommendation was adopted to solve the previous issue whereby if no PAL was present, the consumer would not know if this was because the manufacturer had conducted an appropriate risk assessment according to VITAL® and concluded that no PAL was needed.

As of April 2022, there have been more than 30 000 individual VITAL® risk assessment reports generated using the online tool. The Allergen Bureau does not have visibility of whether this has resulted in more or fewer PAL statements by the industry (personal communication with Allergen Bureau).

In a survey conducted with the Australasian food manufacturers to examine the factors influencing the industry's uptake of the VITAL® process (Zurzolo *et al.*, 2017), 76 percent agreed that VITAL® was a science-based effective tool for allergen risk assessment, 52 percent indicated that it was too time consuming, and 36 percent indicated a concern with the process not being endorsed by the government.

1.5 OVERVIEW OF MEETING PROCESS

REFERENCE DOSES (RfDS) IN RELATION TO THRESHOLDS, DERIVATIVE EXEMPTIONS AND "FREE-FROM" CLAIMS

Before beginning discussions regarding use or application of risk assessment principles for PAL, the Expert Committee discussed several unaddressed issues

from prior meetings. Since RfDs were discussed and determined at the second meeting, this information was not available for discussion at the first meeting. As such, questions regarding which foods and/or ingredients (i.e. derivatives) could be exempted from mandatory declaration were not fully addressed in the prior meetings. The Expert Committee considered data relating to specific examples of derivatives – highly refined oils, fish gelatin and gluten in soy sauce, and agreed that their use in food products is intentional rather than as a result of cross-contact. The committee acknowledged that the objectives for establishing RfDs at the second meeting were mainly designed to inform allergen exposure risks that are unintended and sporadic, rather than to inform risks from regular presence of allergens as an intentional ingredient. It was agreed that this question of applying RfDs to assess derivative exemptions be addressed at a later time, in a follow-up meeting of the Expert Committee. New data and information on derivatives discussed in the third meeting are included in Annex 3 of this report.

Another question regarding the application of RfDs to address “free-from” claims and other types of non-PAL labelling was deemed to be outside the scope of this consultation, although the Expert Committee agreed that it should be reinforced that the RfDs recommended in the second meeting are not intended to be used for making a claim that a food is free from specified allergens.

At this meeting, the Expert Committee agreed to adopt the term “reference dose (RfD)” from the report of the second meeting of this Expert Consultation as a more accurate term to describe the concept of “threshold” in this report. The Expert Committee found that “threshold” is a term that can be used in many different contexts (e.g. regulatory thresholds, analytical thresholds, reactivity thresholds) and thus may be too broad for the purposes of this consultation. The preferred term of RfD is thus used in place of threshold throughout most of this report.

SINGLE LEVEL RISK-BASED REFERENCES DOSES (RFDS) VS MULTIPLE LEVEL RISKS-BASED RfDs

The second meeting adopted an approach for identifying a single RfD for the priority allergenic foods identified in the first meeting described as “without appreciable risk to health”. The reference dose was based on the quality, quantity, availability and accessibility of eliciting dose data for the established priority allergens, as well as on supporting data relating to health manifestations (i.e. severity, including severe or life-threatening anaphylaxis) at the proposed RfD.

The process of identifying RfDs also took into consideration different levels of risk from UAP (e.g. low, medium versus high). More detail can be found in the second report (FAO and WHO, 2022b). While the Expert Committee agreed that different or higher levels of UAP risks could be assessed and determined from available data, the Expert Committee did not identify data on how these different risks are perceived by and/or influence consumers in their food choice or avoidance practices.

The Expert Committee decided that a single set of RfDs for the priority allergens would be most effective, informative and beneficial to consumers and other stakeholders as it would be based on a defined health-based guidance value (HBGV) to “reflect a range of exposure without appreciable health risk”. Reference doses were also based on a clearly defined safety objective to, as stated in this Expert Consultation:

minimise, to a point where further refinement does not meaningfully reduce health impact, the probability of any clinically relevant objective allergic response, as defined by dose distribution modelling of minimum eliciting doses (MEDs).

Thus, without clearly defined HBGV or safety objectives for other levels of UAP exposure risks, including data uncertainties in how consumers perceive these risks, the committee did not identify criteria or set limits for other levels of UAP risk.

The safety objective was also supported by data demonstrating that even in those who react to very small amounts of allergen below the RfDs, the resulting symptoms would not be expected to cause reactions which are either life-threatening (using the description used by the World Allergy Organization [WAO]) or refractory to first-line treatment with adrenaline/epinephrine (Patel *et al.*, 2021; Resuscitation Council UK, 2021). Such reactions might therefore be considered “acceptable” from a population or public health perspective (although the committee noted that further stakeholder engagement, particularly with food-allergic individuals, would be needed to ensure that such an approach is indeed acceptable as part of a regulated and robust system to prevent reactions to UAP).

The scientific rationale for determining an “acceptable” level of risk at a level of exposure to the RfD (or below) was:

- > Ninety-five percent of individuals with a relevant IgE-mediated food allergy would not experience an objective allergic reaction.
- > In those who do develop objective symptoms to a food product with PAL:
 - the probability of anaphylaxis (according to the WAO definition) is <5 percent;
 - the risk of severe anaphylaxis (as per WAO definition) is <1:100 000 person-years in the population of individuals with a relevant IgE-mediated food allergy; and
 - there is a negligible risk of fatal anaphylaxis (on the basis of no confirmed reports of fatal reactions to an RfD-level of exposure).

Adverse safety outcomes from other food-allergic conditions were not considered in this RfD definition as they were either not in scope (e.g. coeliac disease) or there were too little data available (e.g. non-IgE-mediated food allergies) (see the first report) (FAO and WHO, 2022a).

RATIONALE FOR RISK-BASED REFERENCE DOSE (RfD) IN PRECAUTIONARY ALLERGEN LABELLING (PAL)/UNINTENDED ALLERGEN PRESENCE (UAP) SYSTEM

The Expert Committee at the third meeting reviewed the data on the current status and uses of PAL and unanimously agreed that current PAL systems used in many countries needed to be improved as they were neither uniform nor informative and were not consistently risk-based on amount and frequency of UAP found in food products. The Expert Committee also found that current PAL approaches led to widespread PAL that diminished information and value for consumers. This not only led to fewer food choices but could exacerbate risks for adverse health consequences in a high number of allergic consumers who disregard PAL because the information is considered not to be based on an assessment of actual risk. The Expert Committee reviewed again the principles and basis of RfD from the second meeting and reached a consensus that the RfD for each priority allergen, as described by the HBGV and safety objectives, was a valid risk assessment endpoint for determining when sporadic or unexpected UAP posed more than appreciable risk to consumers and needed to be communicated to consumers by PAL.

The Expert Committee then deliberated on whether or not PAL should be communicated for any level of UAP. The Expert Committee agreed that UAP is by its nature sporadic and can occur commonly due to the regular use of priority allergens in food production facilities (e.g. linked to shared production lines), although risk mitigation measures should be in place. As a result, many instances of UAP are found at relatively low amounts that pose a negligible risk to the allergic population. Applying PAL for any instance of UAP irrespective of amount would lead to PAL being present on a large number of food products, with the level of UAP posing a negligible health risk. This results in a situation not dissimilar to the current status quo where PAL does not correlate to the actual UAP risk, the common use of PAL causes reduced food choices, and consumers are unable to identify which products with PAL have health impact levels of UAP and pose a significant risk of reaction (**Figure 3A**).

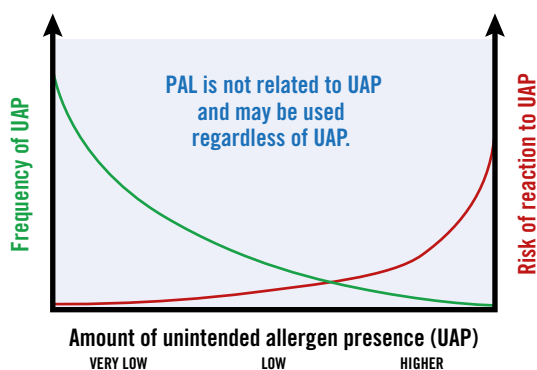
The Expert Committee agreed that to achieve the most effective communication of PAL, to limit its overuse, and to ensure that the use of PAL is best correlated to a potential risk of reaction, only UAP that is shown by risk assessment to pose a risk to health should be communicated. Using an AL (or “cutoff”) set at this UAP level to determine the need for PAL would more clearly identify products that posed true UAP risks and would better communicate this risk to allergic individuals.

The Expert Committee discussed at what level of UAP the AL should be set, keeping in mind that, at any AL chosen, there would always be some degree of residual risk of reaction to the food-allergic population. Setting a high AL would result in fewer products with UAP above the AL and therefore less PAL; however, this could result in products with no PAL communication but with UAP that posed unacceptable health risks to the population. Using a lower AL would result in more products with UAP above the AL and therefore more PAL; however, overall reaction risks would be significantly reduced.

Within this low-action-level framework, the committee agreed that setting an action level too low would not necessarily lead to more meaningful PAL and/or a reduction in health impact at a population level. Furthermore, very low action levels would be more difficult to verify, as they would be below the current limit of detection for analysis (see sections 3 and 4 below). Since assuring the absence of very low levels of UAP would not be feasible in most cases, setting an action level too low would likely lead to PAL being applied to many products with any level of UAP. Ultimately, this would not lead to a situation substantially different from the status quo for PAL (**Figure 3A**).

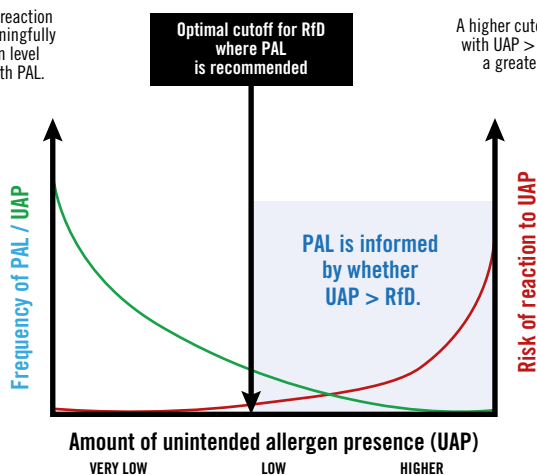
FIGURE 3. RELATIONSHIP BETWEEN THE AMOUNT OF UNINTENDED ALLERGEN PRESENCE (UAP) AND THE FREQUENCY AT WHICH UAP MIGHT BE PRESENT

3A STATUS QUO



3B PROPOSED APPROACH

With a lower cutoff for RfD, the risk of reaction is slightly lower, but this does not meaningfully reduce health impact at a population level and would result in more products with PAL.



Note: Currently, use of PAL is not related to UAP, which results in overuse of PAL and a poor relationship between PAL and risk of reaction (**Figure 3A, status quo**). If PAL is only used when $UAP > RfD$, then the use of PAL is more closely related to actual residual risk (**Figure 3B, proposed approach**). Using a more stringent RfD results in more products with $UAP > RfD$, and therefore more PAL. The optimal scenario is to set an AL at an RfD where residual risk from UAP exposure is minimized and a more stringent level does not meaningfully reduce the health impact at a population level (see the second report).

Source: Authors' own elaboration.

Thus, it was decided that the optimal scenario is to set an AL at a low amount of allergen exposure, which can be analytically verified, minimizes risk, and below which there is no meaningful reduction in health impact at a population level.

The Expert Committee therefore proposed using the risk-based RfDs established at the second meeting as the basis for calculation of the optimal AL since these are based on HBGV and safety objectives which also assessed analytical capabilities, severity and other factors to minimize risk. $UAP > RfD$ would represent unacceptable UAP risk that needed to be communicated by PAL, while $UAP < RfD$ would not specifically be communicated by PAL since the residual risk of reaction from UAP exposure would be negligible (or acceptable) and communicating UAP would not meaningfully reduce health impact at a population level (**Figure 3B**).

SINGLE PRECAUTIONARY ALLERGEN LABELLING (PAL) STATEMENT VS MULTIPLE PAL STATEMENTS

The Expert Committee discussed the value of a system using multiple PAL statements, where different wording formulations might convey different UAP risk levels (e.g. where potential UAP was high) or different frequencies of risk (e.g. where UAP might be present in every batch of a product, versus only a minority of batches of a particular product). Such a system would allow the ability to distinguish between a product where UAP might only cause a reaction in a minority of individuals allergic to a given food allergen, while other UAP (e.g. unintended milk presence in dark chocolate) might cause a reaction in 20 percent/30 percent/40 percent/50 percent or more of the population. A multiple PAL system was viewed as potentially providing more descriptive information on the relative risk of UAP to consumers.

While some Expert Committee members were in favour of considering such an approach, it was agreed that if proper risk management controls for UAP were instituted, products with a very high probability of UAP above the RfD would be relatively few and that a single PAL system (with a single AL, based on the recommended RfDs for the priority allergens in the second report) would already have established a PAL warning system for consumers to avoid products with UAP at levels associated with an appreciable public health risk (i.e. if the advice would be to avoid any PAL, then a “higher risk” PAL would not be needed). In addition, there has been limited research or regulatory guidance which focuses on the “upper level” for allergen cross-contact which may result in adverse reactions for a large proportion of the food-allergic population.

The Expert Committee, therefore, concluded that the best strategy was one where there was a single (rather than multiple) action level(s) based on a RfD that minimizes residual population risk but is practical and manageable – and therefore reduces the indiscriminate use of PAL. For products with $UAP > RfD$, a PAL statement should be used, and no PAL would be recommended for $UAP \leq RfD$ (**Figure 3**) – similar to the approach described by VITAL®. In turn, this would lead to better consumer

understanding and trust of PAL as a communication or warning that significant UAP risks are likely present. Given that there is general acceptance that health risks cannot be reduced to zero, there is arguably no cutoff for UAP associated with zero risk. Achieving an acceptable risk balance in which the level of UAP risk could be adequately managed by FBOs to reduce the proportion of products with PAL and allow a greater number of safe food choices while minimizing risk for adverse reactions was the preferred choice.

The Expert Committee acknowledged that UAP exposures below the RfD could pose a residual risk of objective allergic reaction in a small segment of the allergic population, specifically in the 5 percent of allergic individuals who react to levels of allergen at or below the RfD (see section 3.1 Other considerations). As per the established safety objectives underlying RfD established at the second meeting, the baseline residual risk of reactions can be described as up to 1 in 20 individuals experiencing an objective reaction, and the risk of severe outcomes (defined as anaphylaxis not readily responsive to first-line treatment) would be less than 1 per 60 000 exposures in the allergic population (Turner *et al.*, 2022a) or less than 1:100 000 person-years in the population of individuals with a relevant IgE-mediated food allergy. Given that using a more stringent (even lower) RfD would not meaningfully reduce health impact at a population level, the Expert Committee concluded that the residual risk posed by using the RfDs proposed in the second meeting was balanced by the potential benefits of a system underpinning the use of PAL that would identify products posing true UAP risks and still be protective for the vast majority of food-allergic individuals.

The Expert Committee considered whether (some) allergic consumers or other stakeholders might want to know if a food product with potential UAP at or below the RfD still poses a residual risk (i.e. to the 5 percent of allergic individuals who react to levels of allergen exposure below the RfD). However, the Expert Committee felt that general information about individual reactivity thresholds is currently lacking for consumers to understand what a “low risk” or “trace” amount means and/or what different risk levels above the RfD represent with regards to their individual thresholds and/or safe food consumption practices. This is an area requiring further multistakeholder engagement. For example, clinical testing can identify individuals at risk of reactions to exposures at or below the RfD and the nature of the symptoms (typically mild) that they might experience. Risk managers and healthcare professionals may wish to consider how these individuals could be informed as to the need to take additional steps when consuming food products with potential UAP at or below the RfD.

Residual risk could be further mitigated by education of consumers and healthcare professionals as to the correct interpretation of PAL and the need to remain alert to public health advisories about UAP risks in food products. Education and other efforts should lead to an approach that does not mimic the current situation where a high proportion of products have PAL and thus the vast majority of food-allergic individuals are deterred from consuming potentially safe products.

Lastly, considering that the decision to use PAL should be based on the results of a quantitative or qualitative risk assessment, it is expected that the residual amount of allergen(s) found in the final products would be low due to the mitigation measures which must be put in place to be able to use a PAL when UAP is above RfDs (notwithstanding that there may be some exceptions, such as milk in dark chocolate). Thus, at the current time, the multiple PAL system to communicate different levels of risk at exposures above the RfD was not endorsed by the Expert Committee. However, if consumer preference for such a system were identified in the future, then this conclusion might need to be reassessed.

RECOMMENDED WORDING FOR PRECAUTIONARY ALLERGEN LABELLING (PAL)

The Expert Committee also agreed that for effective application of PAL using this single-system approach, it is essential that a risk assessment be performed and that one, consistent PAL statement is used (while acknowledging there may be regional variations in the precise wording use in one geographical area compared to another). Thus, if consumers were to see this PAL statement (with an indication on the product label that the allergen RA has been performed), they would be more confident that a risk assessment had been undertaken which showed more than negligible UAP to be present and that they should therefore avoid the product. By the same token, if consumers knew that a risk assessment had been done and did not see PAL for their allergen, they could be confident that only a small risk posed by any UAP might be present, notwithstanding the above considerations (and potentially, a negligible risk if a further strategy was then used to identify the possible UAP at or below the RfD). Thus, the vast majority of allergic consumers could have more confidence in making the choice as to whether to consume the product or not.

There were additional discussions around what this one, consistent PAL statement might be. Since the intent of PAL was to communicate that the product had more than an appreciable risk to health due to UAP and should be avoided, some Expert Committee members advocated for language that explicitly told consumers not to eat the product. Some surveys have found “not suitable for someone with X allergy” to be a statement that most consumers were likely to avoid. There was also discussion as to whether there were specific scenarios where UAP may pose a higher frequency of UAP exposure to consumers (see section 4.2 Risk anomalies) that might require different wording. However, the preference was for a single PAL statement to cover all scenarios where there is UAP above the RfD. The interpretation of PAL statements may differ depending on cultural or other linguistic practices. Therefore, the phraseology for the PAL statement should be decided by Codex members. Also, the presentation of a PAL statement on the label was discussed briefly with reference to FSANZ’s *Plain English allergen labelling* (FSANZ, 2020), but the Expert Committee did not elaborate on this matter.

RECOMMENDED FOOD CONSUMPTION DATA FOR REFERENCE DOSES (RfDs) BASED ON UNINTENDED ALLERGEN PRESENCE (UAP) EXPOSURES AT ED₀₅

Following the discussions of the second meeting (see section 8 of the second report) (FAO and WHO, 2022b) and **Figure 3**, RfDs based on UAP exposures at ED₀₅ improved the overall ability of FBOs to assess analytical-based action levels and to apply risk-based approaches for determining the need or otherwise for PAL compared to RfDs based on UAP exposures at lower eliciting dose (ED) levels. Another important factor in using RfDs in a risk assessment context for establishing action levels is total estimated product consumption. Since food consumption patterns vary across the world, this approach allows action levels to be derived that reflect regional differences. This was illustrated in section 8 of the second report using the 75th percentile of consumption which provided extended compliance in previously published analyses within the framework of the iFAAM project (Blom *et al.*, 2019). However, the appropriateness of the 75th percentile resulted from analyses using the ED₀₁ as RfD. Since these analyses were performed, threshold datasets have been improved as have threshold modelling methods (Remington *et al.*, 2020; Houben *et al.*, 2020) and the current RfDs recommended by the Expert Committee were based on the ED₀₅ (FAO and WHO, 2022b). More recent analyses showed that for compliance with the ED₀₅, the 50th percentile of consumption could be as reliable a consumption marker with similar statistical uncertainty. At the third meeting, it was determined to use the 50th percentile of general population single-eating occasion consumption for the derivation of action levels at the RfDs based on ED₀₅. The Expert Committee further incorporated into their recommendations the action levels for the priority allergens, using approaches applied to other food hazards. The action levels were calculated for different intakes of the affected food (containing potential unintended allergen), ranging from 10 g to 1 000 g in 10 g increments.

TEST METHOD PERFORMANCE REQUIREMENTS

Examining assay capability in relation to the recommended RfDs, the Expert Committee observed that RfD can be implemented and monitored to some degree with current analytical capabilities but acknowledged that significant limitations in method performance guidance exist. The Expert Committee strongly recommended that the expression of analytical results be standardized as mg total protein of the allergenic food per kg food product analysed. This would facilitate result interpretation, cross-comparison of different tests and comparison with an RfD and its corresponding AL calculated from the 50th percentile of consumption for a particular food by users of analytical services. To address deficiencies in analytical methodology, the Expert Committee recommended the development of method performance criteria, as well as a more extensive provision of accessible reference materials for the priority allergenic foods (as recommended in the second report). Experts also identified the need for a better understanding of assay performance in different food matrices and greater transparency over assay-specific reagents,

such as antibodies used in ELISA, which are critical to assay performance. Improvements were also called for in sampling for analysis and curation of samples from originator to laboratory.

The derivation of action levels in this manner can inform allergen test method performance requirements, as presented in section 8.2 of the second report. Selected key recommendations from the second report are as follows:

- > It is preferable to use protein-based analytical methods, such as ELISA and mass spectrometry, which quantify total allergenic commodity protein, since this is what the HBGVs are based on.
- > The test methods should report quantitative test results as mg total protein from the allergenic source/kg food product. (Most currently available analytical tests report mg allergenic commodity food / kg. Thus, food needs to be converted to total protein amounts).
- > The test methods should be able to report quantitative test results threefold below the AL and given the variability in test methods, analytical laboratories should routinely monitor the limit of quantification (LoQ) of a given test method.
- > There is a need to ensure appropriate sampling plans are developed and applied to validate and verify allergen management – from cleaning processes to finished foods. Such plans should be informed by the likely form of an unintended allergen since testing of particulates (e.g. nuts and sesame seeds) and dust (e.g. flour) will require a different approach to foods where the allergen is homogeneously distributed.



CHAPTER 2

GUIDANCE ON PRECAUTIONARY ALLERGEN LABELLING

2.1 PURPOSE OF THE GUIDANCE FOR PRECAUTIONARY ALLERGEN LABELLING (PAL)

To facilitate consistent and harmonized approaches to effective risk-based use of PAL for communicating to consumers with food allergies about the risk from UAP in foods.

PROPOSED SCOPE FOR USE OF PRECAUTIONARY ALLERGEN LABELLING (PAL):

- > Presence of PAL denotes a product where a risk assessment has determined that consumption of the affected food or product may pose an appreciable risk of provoking an allergic reaction in more than 5 percent of the population allergic to that food or product (see the second report for more detailed risk characterization).
- > Conversely, absence of PAL denotes a product where an RA has determined that consumption of the food would not pose an appreciable health risk to individuals allergic to that food.

2.2 SCOPE OF GUIDANCE

This guidance applies to PAL when used to indicate the possible unintentional presence of protein from an allergenic source in prepackaged foods that are within the scope of the *General standard for the labelling of prepackaged foods* (FAO and WHO, 2018b). Similar principles can also be applied to other scenarios involving prepackaged food products, such as when these foods are part of non-packaged food products sold to consumers at retail.

The Code of practice on allergen management for food business operators (FAO and WHO, 2020b) provides guidance on effective management practices and controls

to prevent or minimize the potential for UAP due to cross-contact.

Other useful guidance documents include *Guidance on food allergen management for food manufacturers version 2* (FoodDrinkEurope, 2022); *Practical guidance on the application of food allergen quantitative risk assessment* (ILSI Europe) and *Food industry guide to allergen management and labelling* (FIGAMIL, Allergen Bureau).

2.3 GENERAL PRINCIPLES OF PRECAUTIONARY ALLERGEN LABELLING (PAL)

The decision to use PAL should be based on the findings of a RA which can include but is not limited to quantitative risk assessment. The use of PAL should be restricted to those situations where measures to prevent UAP cannot be feasibly implemented (despite GMPs) and will result in exposure above the RfD for a priority allergenic food. A reference dose is defined in this report as an HBGV based on quantitative hazard characterization (via dose-response modelling). Above the RfD, the safety of a food-allergic consumer cannot be assured. Consumption of a food allergen at or below the RfD would not pose an appreciable health risk to individuals allergic to that food, defined as:

- > a probability of objective symptoms of < 5 percent in the population of individuals with a relevant IgE-mediated food allergy; and
- > in those who do develop objective symptoms to a food product with PAL:
 - a probability of non-severe anaphylaxis (according to the World Allergy Organization definition) of < 5 percent;
 - the risk of severe outcomes (defined as anaphylaxis not readily responsive to first line treatment) would be less than 1 per 60 000 exposures in the allergic population (Turner *et al.*, 2022a) OR a risk of severe anaphylaxis (according to the World Allergy Organization definition) of < 1:100 000 person-years in the population of individuals with a relevant IgE-mediated food allergy; and
 - a negligible risk of fatal anaphylaxis (on the basis of no confirmed reports of fatal reactions to an RfD-level of exposure).

Furthermore, the public health impact of a more stringent RfD would be expected to be negligible, in terms of reducing significant public health risk.

Use of PAL should never be a substitute for good allergen management. It should be used within the context of existing Codex codes of practice (FAO and WHO, 2020b).

If a reference dose is not established for a particular allergenic food, an estimated reference dose can be used, provided that it is determined following the guiding principles elaborated by the second meeting of the FAO/WHO consultation.

A consistent and harmonized approach is the most effective use of PAL for

communicating to consumers with food allergy globally about the risk from UAP due to cross-contact. This includes use of standardized language and other indications that an RA has been performed. PAL should be clear, concise and truthful, and not misleading (unambiguous communication) and be able to be readily communicated to consumers (Turner *et al.*, 2022b).



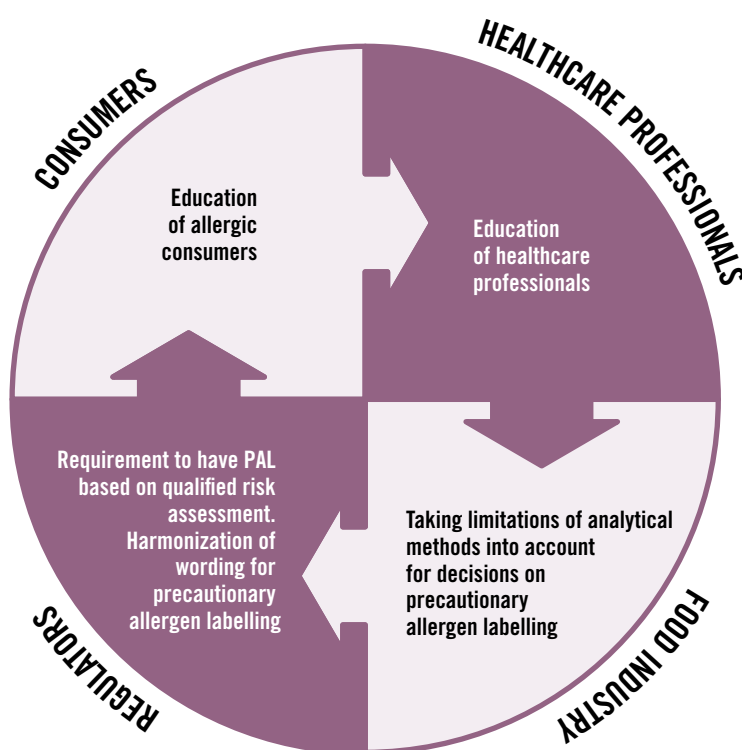
CHAPTER 3

RECOMMENDATION FOR PRECAUTIONARY ALLERGEN LABELLING (PAL) APPLICATION — A SINGLE PAL SYSTEM BASED ON THE RECOMMENDED REFERENCE DOSES (RfD) ESTABLISHED IN THE SECOND MEETING

The safety of consumers with food allergies is a shared responsibility of all stakeholders including, but not limited to, consumers, FBOs, healthcare providers and regulators (Roche *et al.*, 2022). The diagram below (**Figure 4**) shows the interconnectivity of the different stakeholder groups and the need for clear communication and rule setting for PAL. Numerous jurisdictions have identified the need to provide mandatory food allergen information on food products in order to protect the vulnerable group of allergic consumers from exposure to added allergenic ingredients.

Due to the high probability of UAP from various food-processing practices which could also pose risks for the vulnerable allergic population, legislators consequently should also define the legal framework or requirements for communicating UAP risks through PAL. This may include the requirement of a preceding, qualified risk assessment on the one hand and the permitted terminology to be used for PAL, such as “may contain” or “not suitable for” on the other hand. Food manufacturers need to adhere to the legislators’ requirements. However, this often allows some flexibility with regards to labelling that appears on the final product. Here, healthcare professionals need to communicate to allergic consumers how such labelling needs to be interpreted, and consumers need to understand the risk associated with buying products that carry a precautionary label. Therefore, there is an interconnection between all four stakeholder groups, and only clear communication and understanding of the terminology prescribed by law and used by food manufacturers will have the potential to protect food-allergic consumers.

FIGURE 4. INTERACTIONS BETWEEN DIFFERENT STAKEHOLDERS



Source: Authors' own elaboration.

In a recent example of stakeholder engagement, Roche *et al.* (2022) presented a consensus statement to facilitate a harmonized allergen management approach that should be legislatively mandated. The stakeholder forums consisted of consumers, food manufacturers and retailers, regulators, researchers, and healthcare professionals and identified the following as issues to be addressed: 1) lack of PAL regulation, 2) lack of standardized risk-based assessment processes, 3) not unified allergen management practices, and 4) lack of consumer responsibilities. The stakeholder consensus statement emphasized the responsibilities of both consumers and food manufacturers. It stated that consumers should declare their food allergies, read food labels carefully and make their own judgements about which foods they choose to consume. Food manufacturers should follow robust food allergen management practices through a quantitative risk assessment and provide clear and consistent labelling on the allergen content of their products. As indicated by the Australasian food manufacturers in the industry survey by Zurzolo *et al.* (2017), although VITAL® is a science-based effective allergen risk assessment tool, there was a concern that it was not endorsed by the government. Hence, there was concern that voluntary adoption of a risk-based allergen management strategy would lead to slow or inconsistent uptake by certain sectors of the industry while mandatory PAL regulation would establish a more “level playing field”.

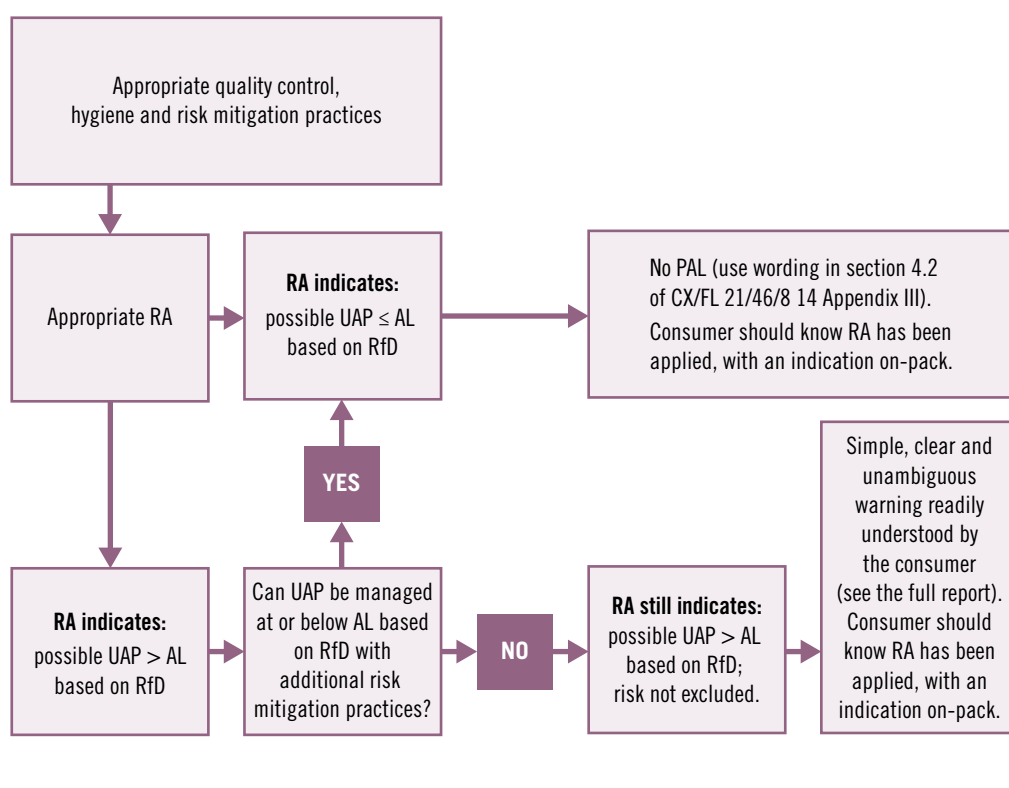
3.1 OVERVIEW OF THE RECOMMENDATION

The intention in applying a PAL is to warn consumers that the food poses a risk of causing a reaction and that they are advised not to eat that food. In this regard, the Expert Committee recommends a single PAL system based on action levels derived from the recommended RfDs established in the second meeting, as illustrated in **Figure 5**.

Step 1: Appropriate quality control (QC), hygiene and risk mitigation measures are crucial to UAP management and are “owned” by practices established by CCFH and should intrinsically undergo a continual process of review, refinement and improvement. These measures will be assisted by action levels informed by RfDs based on established HBGVs but should always be undertaken to keep UAP to the lowest possible level that can be mitigated. To this end the schema was modified to capture the need for the QC, hygiene and risk mitigation to have been done effectively at the outset and repeated if needed. Only if UAP cannot be mitigated to a level at or below the AL should the application of a PAL statement be considered.

Step 2: RfDs established during the second meeting (FAO and WHO, 2022b) provide a firm basis for risk-based approaches in determining when or not PAL is needed to communicate a UAP risk to allergic consumers. This decision was made by the Expert Committee based on the understanding that the risk of allergic reactions following exposure to protein from priority allergenic foods at or below the RfDs would not pose an appreciable health risk to individuals allergic to that food and that the impact or benefit of a more stringent RfD would be expected to be negligible in terms of meaningful reduction in health impact at a population level.

FIGURE 5. **OVERVIEW OF THE RECOMMENDED SINGLE PRECAUTIONARY ALLERGEN LABELLING (PAL) SYSTEM**



Note: ^a. RA, risk assessment; ^b. UAP, unintended allergen presence; ^c. AL, action level; ^d. RfD, reference dose.

Source: Authors' own elaboration.

The Expert Committee then discussed how to apply RfDs into action levels for use in risk-based approaches for applying PAL:

(1) The RfD is translated into an AL using a reference amount (RfA) of food intake; Blom *et al.* (in preparation) was reviewed and demonstrated that RfAs based on the p50 to p65 of the general population distribution of the single-eating occasion intake of foods result in compliance with the safety objective intended by using the RfDs (based on ED05) established at the second meeting (FAO and WHO, 2022b), without being over conservative. Based on these results, the Expert Committee recommended using the p50 as the RfA. If the p50 is not available, the mean of the population distribution of the single-eating occasion intake of food would be a good alternative, as analyses of the intake data showed that the mean generally is between the p50 and p65.

(2) Analytical methods will be used which can quantify protein from allergenic foods at about threefold below the AL. In practice, this means that FBOs will operate below the AL to take account of analytical uncertainties. This is the general practice for gluten-free foods which must be below 20 mg gluten/kg of food product although the Expert Committee could not identify any documents in the published literature describing this practice to use as evidence.

Step 3: A simple, clear and unambiguous communication to consumers is needed when risk assessment shows that UAP in a product is above the RfD. The PAL should convey a clear message or warning that is understood by allergic consumers to mean that the product has more than an appreciable risk to health and is not suitable and/or not to be consumed. When UAP due to cross contact is managed to be consistently at or below the RfD AL, there would be no need for PAL since the risk for serious reaction in the allergic consumer population is minimal.

Step 4: To promote consumer understanding of and confidence in this single risk-based PAL approach, some type of label communication on products is needed to make it clear to consumers that a risk assessment has been performed for all the priority allergenic foods. The Expert Committee recommended a marker or symbol to be used on product packaging to communicate this to consumers.

OTHER CONSIDERATIONS

Since the risk for severe reactions to UAP exposure at or below RfDs was minimal but some risk still existed for reactions in extremely sensitive individuals, the Expert Committee discussed the value of other options to no PAL. The term “trace” to describe $UAP < RfD$ was considered but not recommended because it is poorly defined and had unclear meaning to multiple stakeholders. Another option was to apply a specific statement to indicate the presence of UAP below the RfD, for example, “may contain residues of X”. The rationale was that consumers would have information when any level of UAP that could cause some risk for reaction was present in a product but also be informed by the type of statement description that UAP risks from product consumption are expected to be quite lower than UAP risks from consumption of products with PAL (denoting exposures above the RfD). Ultimately, this option was not recommended by the Expert Committee because it would not lead to less use of precautionary statements for negligible UAP, which was a desired advantage for a risk-based PAL approach. Also, any type of PAL or other precautionary statement may be seen as a warning to some consumers, and this has the disadvantage of discouraging these consumers from choosing products that are potentially safe choices for them. However, the Expert Committee noted that work needs to be undertaken to understand if such a strategy would be acceptable to allergic consumers.

It was also discussed that, because of a lack of a legal framework for managing or preventing UAP due to allergen cross-contact and applying or not applying PAL based on UAP risk level, many products with any analytical presence of UAP may be subject to enforcement action by government regulators. As such, industry stakeholders may be reluctant to not apply PAL when there is any UAP for fear of enforcement action. Thus, for effective application of a single PAL system, endorsement by all relevant stakeholders of a legal framework for PAL to address UAP risks was considered of high importance.

To address concerns about products with higher or particulate levels of UAP, the Expert Committee agreed that the main intent in applying a single PAL statement

is to warn consumers that the food poses a risk of causing a reaction and that consumers are advised not to eat that food. Importantly, PAL needs to provide sufficient warning not only for products with UAP at or near the RfD but also for products with potentially higher or consistent levels of UAP, as evidenced by milk in dark chocolate product scenarios (section 4.2) and/or for cross-contact issues involving particulate contamination (section 3.3.2.2).

Based on a review of consumer survey information and different phraseologies, most Expert Committee members agreed that a PAL phrase which conveys that a food is not suitable for, or not to be consumed by, consumers with a particular allergy would be preferred. Any statement should be tailored to local linguistic preferences and the level of consumer education. The Expert Committee noted that many food industry groups express a preference for “may contain” or “may be present”, although this was not always the preferred statement in consumer surveys. It was also noted that “may contain” or “may be present” are hazard-based communications, while the approach recommended by the Expert Committee is risk-based; the intended application of PAL is to advise allergic consumers not to eat a food product when there is a relevant risk. Nonetheless, the overriding consideration should be a PAL statement that is most meaningful in conveying UAP risk or warning information to allergic consumers.

There was a discussion about allergen communication issues posed by rework (where an unincorporated food product is kept for subsequent use or reprocessing, for example, re-use of ingredients such as reprocessing dough left over from a previous production). Rework can result in allergen presence due to cross-contact. The Expert Committee agreed that since most rework is added back to products as an ingredient, that rework of allergen-containing ingredients cannot be considered as an “unintended allergen presence” since it is intentionally added back on a production line.

3.2 BACKGROUND FOR RISK ASSESSMENT APPROACH USING REFERENCE DOSES (RfDs)

Establishing reference doses (RfD) which conform with the definition of health-based guidance values (HBGVs) constitutes a critical first step in assessing the risk from allergens, as they are a characteristic of the hazard that allergens present to the food-allergic population. Their establishment, which is a focus of the ToR for the second meeting (FAO and WHO, 2022b), is thus essential to develop guidance on evidence-based application of risk management and mitigation strategies, such as PAL.

The safety objective defined at the second meeting was described as follows:

to minimise, to a point where further refinement does not meaningfully reduce health impact, the probability of any clinically relevant objective allergic response, as defined by dose distribution modelling of minimum eliciting doses (MEDs) and supported by data regarding severity of symptoms in the likely range of envisioned RfD (FAO and WHO, 2022b, p. 87).

The Expert Committee further identified several important considerations to guide decisions. These included a clear definition of criteria to be met by quantitative data on which RfD are based; supporting data on health manifestations (severity) at the proposed RfD; quality, quantity, availability and accessibility of data (for priority allergens), as well as how to deal with priority allergenic foods for which information supporting one or more of those considerations was lacking.

The Expert Committee agreed as a general principle that the RfD values should be contextualized, taking into account the wider and possible unintended consequences. Importantly, they concluded that a guiding principle should be whether selecting a more stringent (lower) value would significantly improve the public health impact.

Considering both the proportion of individuals potentially affected and the severity characteristics of reactions at ED₀₁ and ED₀₅, including the absence of reports of severe anaphylaxis (based on the World Allergy Organization definition), the Expert Committee agreed that for all priority allergenic foods, the safety objective would be met by using as a basis for the RfD the ED₀₅ (with rounding, as evaluated using the data from the Remington *et al.*, [2020] and Houben *et al.*, [2020] publications). This decision was also informed by the current analytical limitations regarding the use of ED₀₁ versus ED₀₅ as RfDs. The Expert Committee had previously noted that the:

public health impact of choosing a more stringent RfD is expected to be negligible, in terms of reducing significant public health risk. A more stringent RfD would introduce considerable burdens and limitations for monitoring and potential unintended consequences on the application of PAL or other risk management strategies (FAO and WHO, 2022b, p. 93).

The resulting RfDs, expressed as mg of total protein from the priority allergenic source, are shown in **Table 2**.

TABLE 2 CONSENSUS REFERENCE DOSE (RfD) RECOMMENDATIONS FOR CODEX PRIORITY ALLERGENS (ADAPTED FROM THE SECOND REPORT)

PRIORITY ALLERGENS	RFD RECOMMENDATION (MG TOTAL PROTEIN FROM THE ALLERGEN IC SOURCE)
Walnut (and Pecan)	1.0
Cashew (and Pistachio)	1.0
Almond*	1.0
Milk	2.0
Peanut	2.0
Egg	2.0
Sesame	2.0
Hazelnut	3.0
Wheat	5.0
Fish	5.0
Crustacea	200

Note: *Provisional.

Source: Authors' own elaboration.

The Expert Committee further incorporated into their recommendations action levels, calculated for intakes of food (containing potential unintended allergen) ranging from 10 g to 1 000 g in 10 g increments.

For more details regarding the recommended RfDs, see the second report (FAO and WHO, 2022b).

3.3 RATIONALE FOR REFERENCE DOSE (RfD) AND PRECAUTIONARY ALLERGEN LABELLING TO ADDRESS UNINTENDED ALLERGEN PRESENCE (UAP)

The Expert Committee agreed that RfDs recommended in the second report were appropriate for assessing the need for use of PAL for UAP situations. Unintended allergen presence can be considered analogous to many other chemical contaminant hazard situations – it may become inherently present in food and unavoidable but not likely to be a significant public health concern if kept at or below established tolerances, or “tolerable risk” action levels, tied to no or minimal adverse health effects in the population of consumers. The most serious adverse health effect associated with food allergens is fatal anaphylaxis, but fortunately this is a very rare event (Umasunthar *et al.*, 2013). Thus, RfDs based on negligible risk for fatal anaphylaxis and very low risk of severe anaphylaxis or other serious adverse health consequences could represent this tolerable risk AL for UAP, and at or below this level unavoidable UAP would not pose a significant public health risk or need communication through food labelling.

As opposed to other chemical contaminants, UAP is not a hazard for all or the large majority of consumers. Thus, when UAP is found above RfD-based action levels and cannot be further managed to a level at or below this AL, the product is not an imminent hazard to the general public and labelling or product statements can be used to communicate the presence of potential UAP risks to specific populations of at-risk (i.e. allergic) individuals. In most countries, UAP is considered a chemical contaminant that is not part of the product formulation and thus the allergen is not allowed to be listed as an ingredient on the label. Hence, other forms of labelling or product statements are needed to communicate UAP risks in said products. Use of a PAL statement was still recognized by this Expert Committee as the most viable and practical risk management strategy for addressing and communicating UAP risks. However, to avoid potentially confusing messages about UAP risks, the Expert Committee proposed that a single, clear and unambiguous PAL statement be used and that this PAL also effectively communicates to the public (e.g. with a symbol or other marker) that the product has undergone a proper risk assessment and the presence or absence of listed priority allergens on PAL signifies the presence or absence of UAP risks in product(s).

Since RfD-based action levels for UAP, which are unexpected and sporadic, may not equate to absence of any risk from allergen exposures, the Expert Committee determined that these RfDs are not intended to be used as a basis for making a claim that a food is “free from” specified allergens or as a cutoff or other threshold for determining which derivatives of allergenic foods may be exempted from mandatory allergen labelling.

3.3.1 SOURCES AND MITIGATION OF UNINTENDED ALLERGEN PRESENCE (UAP) DUE TO CROSS-CONTACT

Adherence to the *Code of practice on allergen management for food business operators* (CXC 80-2020) (FAO and WHO, 2020b), GMP and HACCP combined with an appropriate UAP risk assessment ensures that the level and frequency of UAP risks are minimized in a manner consistent with the principles elaborated for PAL and that they are crucial for appropriate allergen risk management. Food business operators should maintain documentary evidence of compliance with CoP/ HACCP and of their UAP risk assessments.

Regarding the factors listed in the CoP, the Expert Committee emphasizes certain UAP factors that should or should not be considered for or addressed by PAL (**Table 3**). Production errors should be addressed using the HACCP plan and appropriate procedures. PAL is not appropriate for UAP due to production errors.

TABLE 3 KEY ELEMENTS TO CONSIDER IN DEVELOPING A GOOD MANUFACTURING PRACTICE (GMP)/ HAZARD ANALYSIS AND CRITICAL CONTROL POINTS (HACCP)-BASED UNINTENDED ALLERGEN PRESENCE (UAP) RISK ASSESSMENT TO IMPLEMENT PRECAUTIONARY ALLERGEN LABELLING (PAL) (SEE COP SECTION: FACTORS CONTRIBUTING TO EXPOSURE)

INCLUDES:	DOES NOT INCLUDE:
Identification of sources of potential UAP	UAP due to production errors
From supplied materials or ingredients	Labelling errors (e.g. mistakes during label development, label misprints, outdated labels, lost labels, wrong label applied to package, incorrectly translated labels or omitting the declaration of an allergen, product in the wrong package)
Due to processing or production plan	Errors in handling of rework
Hang up points during processing ^a	Improper use or handling of an allergen-containing ingredient
Maintenance and maintenance sequencing on shared lines	Inadequate or lack of employee training, education and/or awareness on managing food allergens including lack of understanding of the serious nature of food allergies
	Lack of change management for changes in formulation, ingredient supply and documentation processes

Note: ^a. For more information: Allergen Bureau. <https://info.allergenbureau.net/infographic/cleaning>.

Source: Authors' own elaboration.

3.3.2 CHARACTERIZATION AND QUANTIFICATION OF UNINTENDED ALLERGEN PRESENCE (UAP)

While UAP due to cross-contact can occur through many causes, not all UAP is the same or poses the same risks. Thus, for risk assessment purposes, quantifying the amount of UAP per product scenario is important as this will help determine not only which products may have UAP exposure that is likely to pose risk for reaction (above RfDs) but will also identify which processes pose the greatest concern for UAP exposure in a facility and need to be more effectively managed to minimize UAP. The main considerations for quantifying UAP in the processing environment rely on characterizing the nature, type or physical form of UAP, such as whether

it is highly dispersible (see section 3.3.2.1) versus particulate (see section 3.3.2.2), and how effectively it can be managed with preventive controls. Another important consideration is the frequency of the cross-contact problem leading to UAP. This likely depends on the type of equipment or processing and can vary from highly sporadic to frequent. For example, producing dark chocolate on the same line as milk chocolate has been shown to result in a relatively high frequency of milk protein cross-contact (Bedford *et al.*, 2017; Crotty and Taylor, 2010) and poses special risk considerations (Allergen Bureau *et al.*, 2019) (see section 4.2 Risk anomalies). Particulate cross-contact in general presents more challenges for risk assessment because it is often non-uniform and occurs more sporadically.

The most effective manner for quantifying UAP for risk assessment is usually by analytical testing of protein from allergenic food in samples from the specific production line where a potential UAP issue is noted and/or by testing in finished product(s), although this is not always needed. Analytical results in combination with likely food consumption estimates based on the p50 or mean of the general population single-eating occasion intake of food (reference amounts [RfA]) can be used to calculate a UAP protein exposure estimate per eating occasion of product and be compared to RfDs. However, analytical testing in all potential UAP situations is not often practical or feasible. In these circumstances, there may be other ways to obtain quantitative information about UAP and do an exposure assessment. This could depend on knowledge of the type of processing leading to UAP, the nature of the manufacturing facility, and recipe information. For example, if a hang up point is inside a pump, pipe or other area which is difficult to access, an engineer may be able to assist with estimating the amount of product that may be left in the line and become incorporated into a subsequent product. If UAP is in a powder residue, it may be able to be swept up and weighed. If the hang up cannot be reached, it may be necessary to estimate potential UAP levels based on the volume of the pipe or other factors. Visual inspection and observation of UAP are also important. Information about a particle size or characteristics can provide some quantitative information of UAP that may assist in estimating amount of protein for risk assessment in downstream products. For example, does the shared production line have formulations which only contain hazelnut pieces 2–6 mm in size or are there also formulations with pieces of half or whole hazelnuts in a finished product? This basic information can inform the risk assessor of what type of remaining particulates might be found in processing equipment and could form the basis of an exposure assessment.

Exposure assessments or AL calculations may be needed in a number of situations, including but not limited to:

- > Readily dispersible or homogenous cross-contact
 - Cross-contact source composition is 100 percent from the allergenic source
 - Cross-contact source recipe composition is < 100 percent from the allergenic source

- > Particulate cross-contact
 - Cross-contact source composition is 100 percent from the allergenic source
 - Cross-contact source recipe composition is < 100 percent from the allergenic source
- > Hang up cross-contact
 - Cross-contact source composition is 100 percent from the allergenic source
 - Cross-contact source recipe composition is < 100 percent from the allergenic source
 - Consideration: will the hang up cross-contact remain intact (lump or particulate exposure) or will it be redispersed throughout a larger batch of the product due to specific processes such as mixing after the hang up point?

While the translation of RfD to action levels is described in section 3.3.5, it is not the intention of this guidance to walk through exposure estimates and AL calculations for every possible scenario. Others have provided examples for calculations of this nature and how they may be used in cross-contact risk assessments (Allergen Bureau *et al.*, 2021; Remington *et al.*, 2022; Livsmedelsverket, 2022).

3.3.2.1 Readily dispersible or homogenous cross-contact allergens

Non-particulate allergens are materials such as powders or liquids, the individual components of which cannot be distinguished by the naked eye and which are not retained by a sieve (Remington *et al.*, 2022). This type of cross-contact is also referred to as “readily dispersible” (Allergen Bureau *et al.*, 2021; FoodDrinkEurope, 2022) and as “homogeneous amorphous” (Remington *et al.*, 2022).

Guidance for estimating the amount of dispersible or homogenous UAP has been described by others for various production scenarios (Allergen Bureau *et al.*, 2021; Remington *et al.*, 2022). For the purposes of this report, one example situation is as follows:

Calculation of the concentration of UAP in a finished product is a relatively straightforward process for readily dispersible or homogenous UAP identified in raw materials or ingredients which are added to the finished product. Unintended allergen presence would represent the total concentration of protein from a particular allergenic food in said materials, quantified by summing the concentrations for the unintended protein from each source, advised by the supplier or determined before production as below:

$$\begin{array}{ccccc}
 \text{Total protein} & & & & \\
 \text{concentration from} & & & & \\
 \text{cross-contact allergenic} & = & \text{The concentration of} & & \text{The relative amount} \\
 \text{food in formulation} & & \text{cross-contact protein} & \times & \text{of ingredient in the} \\
 \text{(ppm, mg / kg)} & & \text{from allergenic food in the} & & \text{formulation (\%/100)} \\
 & & \text{ingredient (ppm, mg / kg)} & &
 \end{array}$$

Depending on the needs of the specific risk assessment, this total protein concentration result could be compared with an AL or used in an exposure assessment for comparison to the RfD.

$$\text{Exposure}^a = \text{Concentration}^b \times \text{RfA}^c$$

Note: ^a Exposure in mg total protein from the allergenic food. ^b Concentration: in mg total protein from the allergenic food / kg food containing the UAP. ^c RfA: in kg intake value per single-eating occasion of product containing the UAP.

For other scenarios, such as due to plant design hang-ups in which UAP cannot be completely eliminated by preventive controls, UAP quantification and calculations may be more difficult to quantify. Considerations will need to include whether the cross-contact due to a hang-up point remains intact and results in a lump or particulate exposure, or whether the cross-contact due to a hang-up point will be redispersed throughout a larger batch of the product due to specific processes such as mixing after the hang-up point.

3.3.2.2 Particulate unintended allergen presence

Particulate allergenic ingredients were defined by Remington *et al.* (2022, p. 79) as “materials in which the physical form of the allergen consists of pieces visible to the naked eye. They can be retained if passed through an appropriately sized sieve.”

Particulates could 1) originate entirely from an allergenic source, such as pieces of nuts or 2) could contain the allergenic source in a mixture of other components, such as pieces of dough with a percentage of the recipe coming from allergenic sources. In order to properly characterize the risk of particulate cross-contact, three different particulate variables are of potential importance: 1) size and mass, 2) composition, and 3) distribution. These parameters will enable an exposure assessment for particulate UAP and a characterization of the risk incurred by an allergic individual being exposed to one or more particles in a (portion of) product (Remington *et al.*, 2022).

Particulates may be identified in ingredients, raw materials, or production environment or equipment. Particulate UAP may occur infrequently, in uneven numbers and in non-uniform distribution in the product. As such, particulate allergen cross-contact poses difficult risk assessment challenges. Guidance on managing particulate cross-contact remains extremely limited (FSA, 2006; Madsen *et al.*, 2014). Because of this, historically, any risk from particulate UAP is usually managed through the use of PAL, without any attempt to apply quantitative methodologies.

The application of a PAL system around risk-based RfDs may allow for particulate situations to be quantitatively assessed on a case-by-case basis. Evaluation of the public health dimension of this risk will also require estimates of how frequently the product in question contains one or more particles, and how frequently the product will be consumed by an allergic individual reactive to the amounts present.

Visual inspections and sampling plans are crucial when establishing valid estimates of particulate numbers, distribution and the probability that a particle will be present in the product (Remington *et al.*, 2022; FAO and WHO, 2020b).

The frequency of particulate exposure may be difficult to ascertain in some, but not all, cases. A potential scenario identified by the Expert Committee in which risk-based RfD principles could be used to assess potential particulate UAP risks and PAL need is sesame seeds. Cross-contact from sesame seeds is notoriously difficult to manage because small seeds can be easily dispersed and difficult to remove from hang-up points during food production. In a hazard-based system, visual detection of just one dispersed seed in a food production facility or prepackaged product could lead to PAL or other labelling for sesame. However, using risk-based RfDs, it is estimated that 4 or 5 seeds would need to be ingested to reach an exposure equivalent to or above the FAO / WHO recommended RfD of 2.0 mg sesame protein.¹ Food business operators could thus use this information to better assess need for PAL in circumstances involving sesame seed dispersion scenarios. Finally, this is only one example of particulate allergen cross-contact for one priority allergen. Particulate examples such as this can be found for all priority allergens and different product scenarios, and this example was chosen to highlight the potential shift in thinking required for allergen cross-contact when moving from a hazard-based Precautionary allergen labelling system to a risk-based system.

3.3.2.3 Ingredients intended for further processing (e.g. bulk product)

PAL is only relevant for products which are intended for presentation to consumers. In any case, FBOs should be aware of UAP in all food products, including bulk products not intended for immediate sale to consumers. Food business operators should supply their customer(s) with at least the following information about UAPs and allergens present due to cross-contact:

- > the presence and size/mass of any particulate allergen; and
- > the total concentration of any readily dispersible allergens.

For scenarios involving a mixture of allergens, a RA should be conducted using the allergen of greatest prominence/presence.

3.3.3 OUTPUT OF RISK ASSESSMENT FOR UNINTENDED ALLERGEN PRESENCE (UAP) FROM PROCESSING AND FREQUENCY CONSIDERATIONS

Risk assessment applying the considerations above should achieve a final characterization and quantitative output of likely UAP from processing which describes:

¹ Sesame seeds range in size and have been measured at 2.9 ± 0.3 mg per seed (see Meima *et al.*, 2020). Using a protein conversion value of 17% protein in “sesame seeds, whole, roasted and toasted” ([link to SR Legacy USDA database](#)) there would be an estimated 0.493 ± 0.051 mg sesame protein per seed. At these protein levels, 4 to 5 sesame seeds are needed to reach an exposure equivalent to or above the FAO/WHO recommended RfD of 2.0 mg sesame protein. The range of 4 to 5 sesame seeds to reach the FAO/WHO recommended RfD is calculated from a minimum of 4 larger seeds (0.544×4 seeds = 2.176 mg sesame protein) and a maximum of 5 smaller seeds (0.442×5 seeds = 2.21 mg sesame protein) to reach a minimum exposure dose of 2.0 mg sesame protein.

- > type of cross-contact problem;
- > frequency of cross-contact; and
- > potential range of concentration profile (or range of exposures) for protein from each allergenic food of concern.

Based on this information, if the identified UAP concentrations lead to an estimated concentration of protein from an allergenic food in the affected product that is higher than the RfD-based action level, it is first recommended to return to review all processes, HACCP, GMP and so forth to see if additional risk mitigation measures can be applied. If yes, the risk assessment should be repeated after additional risk mitigation measures are applied. If, despite risk mitigation measures, UAP allergen concentrations are not at or below the action levels, then the use of PAL may be warranted, which is consistent with the overall guidelines. However, it should be noted that there are very limited published data in terms of the frequency and potential range of UAP concentrations (batch-to-batch variation as well as within-batch variation) for any given product, and this data gap would benefit from further research. There is also a data gap in assessing UAP frequency and the need to ensure appropriate sampling plans are developed and applied when investigating allergen cross-contact. The data gap for appropriate sampling plans would also benefit from further research.

Incorporation of inputs regarding the frequency of UAP risk, considerations for the concentration profiles (or exposure profiles) and agreement on appropriate sampling plans involve multistakeholder discussions and, ultimately, will require risk management framework decisions to be made. For example, should a product with a frequency of cross-contact found in 10 percent of batches with concentrations always above the AL have the same PAL outcome as a product with a frequency of cross-contact in 1 percent of batches with only 1 percent of concentrations found just above the AL? Both products will eventually result in an exposure scenario that would be above the RfD, but these two products would present different risk profiles. As such, while these inputs and considerations were discussed, the Expert Committee was unable to make recommendations regarding these inputs at this time.

Thus, within the currently recommended framework, PAL should be used even when UAP risk above the RfD is infrequent. The Expert Committee recognized that additional inputs on UAP frequency could be incorporated into a future update of this PAL framework, and then both the frequency and concentration profile of UAP could be a factor in determining the need for PAL. The area would benefit from more extensive multistakeholder discussions.

3.3.4 VALIDATION OF AN UNINTENDED ALLERGEN PRESENCE (UAP) RISK ASSESSMENT

The concentrations of UAP in a final product may be validated using analytical testing, although this is not essential. Analytical results should not be considered in isolation from a comprehensive HACCP-based UAP risk assessment.

While UAP residues may not be absent from all surfaces that are visibly clean (Bedford *et al.*, 2020), there is no evidence that residues left on surfaces have concentrations of protein from allergenic foods higher than RfD-based action levels. Thus, demonstration that adequate preventive controls are in place and that all surfaces, including hang-up spots, are visibly clean represents likely validation of adequate UAP management. This also aligns with the *Code of practice on allergen management for food business operators* (CXC 80-2020) which states:

Validation of the cleaning process provides a means of assuring that cleaning processes are adequate to reduce or eliminate allergens and thereby prevent or minimise allergen cross-contact. The validation process should be specific to the allergen, process and product matrix combination. Cleaning processes should be verified through visual observation (checking that equipment is visibly clean) and, where feasible and appropriate, through an analytical testing program (FAO and WHO, 2020b, p. 16).

Where the concentration of protein from allergenic foods identified by analytical testing is greater than that found during the UAP risk assessment, the FBO should consider reviewing the risk assessment for other contributing factors. Consideration should be given to the type of analysis, and the nature and form of the allergenic material. It is important to consider the impact of food processing as some processes may reduce the amount of detectable protein. Where analytical results are significantly higher than expected, a comprehensive review of the UAP risk assessment is essential to identify possible GMP and HACCP errors.

3.3.5 TRANSLATION OF REFERENCE DOSES (RfDs) TO ACTION LEVELS (ALs)

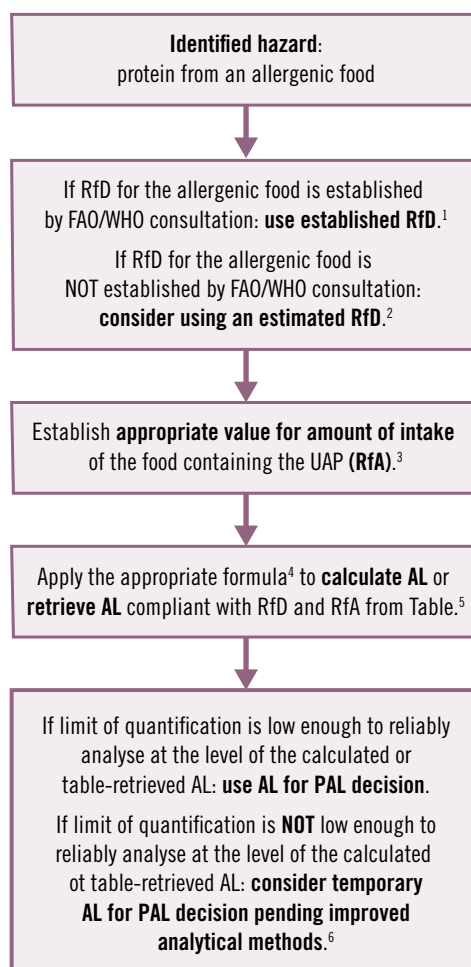
Reference doses (RfDs) are expressed as doses of mg total protein from the allergenic food. The second report fully describes the approach to translate RfD values for priority allergenic foods (expressed in mass of protein) into action levels and the performance requirements for test methods for those allergenic foods (FAO and WHO, 2022b). Briefly, the action levels are determined by dividing the RfD by an appropriate value for the amount of food consumed (reference amount [RfA]), using the formula:

$$AL^1 = \frac{RfD^2}{RfA^3}$$

Note: ¹ AL: in mg total protein from the allergenic food/kg food containing the UAP. ² RfD: in mg total protein from the allergenic food. ³ RfA: in kg containing the UAP.

One approach to identify the appropriate food intake figures to use for the conversion of RfDs to ALs to avoid under- or overestimating the appropriate ALs is illustrated in **Figure 6**.

FIGURE 6. THE QUANTITATIVE PROCESS OF DERIVING ACTION LEVELS (ALS) FOR PRECAUTIONARY ALLERGEN LABELLING (PAL) DECISIONS



Notes: a. RfD: reference dose; b. UAP: unintended allergen presence; c. RfA: reference amount; d. AL: action level

1. Reference dose as established by the second meeting of the FAO/WHO consultation.

2. An estimated reference dose can be used providing it is determined following the guiding principles elaborated by the second meeting of the FAO/WHO consultation.

3. Food intake data from the general population are suitable. From these data, the p50 or mean of the single-eating occasion population intake distribution of the food is recommended.

4. $AL \text{ (in mg total protein from the allergenic food/kg food containing the UAP)} = RfD \text{ (in mg total protein from the allergenic food)} / RfA \text{ of the food containing the UAP (in kg)}$.

5. See Table 4.

6. Calculated or table-retrieved AL can guide the desired analytical sensitivity for improvement of analytical methods.

Source: Authors' own elaboration.

Food intake figures representing the use of food items by individuals on single-eating occasions (single meals) should be used. Blom *et al.* (2020) further showed that for food allergen risk assessment, such single-eating occasion intake data may be derived from food consumption surveys based on the general population, as

these were found not to lead to a relevant under- or overestimation of the risk for the food-allergic population. Blom *et al.* (2019) in the framework of the EU iFAAM project previously showed that the 50th percentile value of the population distribution of the single-eating occasion intake of foods within a food group resulted in compliance with the safety objective achieved by using the ED₀₁ as the HBGV in 99 percent of the numerous scenarios assessed. Use of the 75th percentile extended compliance with that safety objective to 100 percent of the scenarios.

Based on these analyses, they suggested that the 75th percentile was the optimal point estimate for use in deterministic food allergy risk assessment required to meet the safety objective of compliance with the ED₀₁ and is adequately conservative in the public health context. At the second meeting, the FAO/WHO Expert Committee considered that when using ED-values greater than ED₀₁ as the basis for the HBVG, the optimal percentile of the distribution will likely fall within a similar range (in the 50th–75th percentile range) but may need verification by additional sensitivity analyses as conducted by Blom *et al.* (2019). The second report also recommended that the consumption quantities should be appropriate to the intended protection level.

In support of the preparation of the third meeting of the FAO/WHO consultation, TNO (Netherlands Organisation for Applied Scientific Research) performed the suggested verification by additional sensitivity analyses, similar to those conducted by Blom *et al.* 2019, to establish the optimal percentile of the food intake distribution for compliance with the ED₀₅ based RfDs established at the second meeting of the FAO/WHO consultation (Blom *et al.*, forthcoming). In these analyses, the latest improved threshold datasets and model averaging methodology were used (Houben *et al.*, 2020; Remington *et al.*, 2020). The results were presented and discussed at the third meeting. The sensitivity analyses showed that RfAs based on the p50 to p65 of the population distribution of the single-eating occasion intake of foods within a food group resulted in compliance with the safety objective intended by the RfDs established in the second meeting, without being overly conservative. Based on these results, the Expert Committee recommends using the p50 of the population distribution of the single eating occasion intake of a food as RfA. If the p50 is not available, the mean of the population distribution of the single-eating occasion intake of food would be a good alternative, as analyses of the intake data showed that the mean generally is between the p50 and p65.

Action levels can be calculated from RfDs using the equation given above ($AL = RfD / RfA$) or by using a Table based on a list of predefined narrow categories of RfAs, such as < 10 g, 10 to < 20 g, 20 to < 30 g and so forth calculated using the upper bound of the interval. For easier reference, the calculated ALs can be rounded down as illustrated in **Table 4**. The use of predefined intake categories with 10 g increment steps has advantages both at the lower as well as the higher intake ranges. In the lower intake ranges, the increment steps are relatively large, which pushes the relatively high action levels down for food products with intakes below the upper bound of the category. In the higher intake ranges, this effect is negligible, and the relatively small incremental steps hardly change the action levels and put less pressure on the analytical sensitivities required.

TABLE 4 ACTION LEVELS (ALS) BASED ON REFERENCE DOSES (RFDs) AND REFERENCE AMOUNT (RFA) CATEGORIES, ROUNDED DOWN FOR EASIER REFERENCE

RFD in mg	SHRIMP	FISH	WHEAT	HAZELNUT	SESAME	MILK	EGG	PEANUT	CASHEW	WALNUT
RfA in g	200	5	5	3	2	2	2	2	1	1
10	20 000	500	500	300	200	200	200	200	100	100
20	10 000	250	250	150	100	100	100	100	50	50
30	6 500	150	150	100	65	65	65	65	30	30
40	5 000	100	100	75	50	50	50	50	25	25
50	4 000	100	100	60	40	40	40	40	20	20
60	3 000	80	80	50	30	30	30	30	15	15
70	2 500	70	70	40	25	25	25	25	10	10
80	2 500	60	60	35	25	25	25	25	10	10
90	2 000	55	55	30	20	20	20	20	10	10
100	2 000	50	50	30	20	20	20	20	10	10
110	1 500	45	45	25	15	15	15	15	9	9
120	1 500	40	40	25	15	15	15	15	8	8
130	1 500	35	35	20	15	15	15	15	7	7
140	1 000	35	35	20	10	10	10	10	7	7
150	1 000	30	30	20	10	10	10	10	6	6
160	1 000	30	30	15	10	10	10	10	6	6
170	1 000	25	25	15	10	10	10	10	5	5
180	1 000	25	25	15	10	10	10	10	5	5
190	1 000	25	25	15	10	10	10	10	5	5
200	1 000	25	25	15	10	10	10	10	5	5
210	950	20	20	10	9	9	9	9	4	4
220	900	20	20	10	9	9	9	9	4	4
230	850	20	20	10	8	8	8	8	4	4
240	800	20	20	10	8	8	8	8	4	4
250	800	20	20	10	8	8	8	8	4	4
260	750	15	15	10	7	7	7	7	3	3
270	700	15	15	10	7	7	7	7	3	3
280	700	15	15	10	7	7	7	7	3	3
290	650	15	15	10	6	6	6	6	3	3
300	650	15	15	10	6	6	6	6	3	3
310	600	15	15	9	6	6	6	6	3	3
320	600	15	15	9	6	6	6	6	3	3
330	600	15	15	9	6	6	6	6	3	3
340	550	10	10	8	5	5	5	5	2	2
350	550	10	10	8	5	5	5	5	2	2
360	550	10	10	8	5	5	5	5	2	2
370	500	10	10	8	5	5	5	5	2	2
380	500	10	10	7	5	5	5	5	2	2

TABLE 4 ACTION LEVELS (ALS) BASED ON REFERENCE DOSES (RFDS) AND REFERENCE AMOUNT (RFA) CATEGORIES, ROUNDED DOWN FOR EASIER REFERENCE (continued)

RFD in mg	SHRIMP	FISH	WHEAT	HAZELNUT	SESAME	MILK	EGG	PEANUT	CASHENW	WALNUT
RfA in g	200	5	5	3	2	2	2	2	1	1
390	500	10	10	7	5	5	5	5	2	2
400	500	10	10	7	5	5	5	5	2	2
410	450	10	10	7	4	4	4	4	2	2
420	450	10	10	7	4	4	4	4	2	2
430	450	10	10	6	4	4	4	4	2	2
440	450	10	10	6	4	4	4	4	2	2
450	400	10	10	6	4	4	4	4	2	2
460	400	10	10	6	4	4	4	4	2	2
470	400	10	10	6	4	4	4	4	2	2
480	400	10	10	6	4	4	4	4	2	2
490	400	10	10	6	4	4	4	4	2	2
500	400	10	10	6	4	4	4	4	2	2
510	350	9	9	5	3	3	3	3	1	1
520	350	9	9	5	3	3	3	3	1	1
530	350	9	9	5	3	3	3	3	1	1
540	350	9	9	5	3	3	3	3	1	1
550	350	9	9	5	3	3	3	3	1	1
560	350	8	8	5	3	3	3	3	1	1
570	350	8	8	5	3	3	3	3	1	1
580	300	8	8	5	3	3	3	3	1	1
590	300	8	8	5	3	3	3	3	1	1
600	300	8	8	5	3	3	3	3	1	1
610	300	8	8	4	3	3	3	3	1	1
620	300	8	8	4	3	3	3	3	1	1
630	300	7	7	4	3	3	3	3	1	1
640	300	7	7	4	3	3	3	3	1	1
650	300	7	7	4	3	3	3	3	1	1
660	300	7	7	4	3	3	3	3	1	1
670	250	7	7	4	2	2	2	2	1	1
680	250	7	7	4	2	2	2	2	1	1
690	250	7	7	4	2	2	2	2	1	1
700	250	7	7	4	2	2	2	2	1	1
710	250	7	7	4	2	2	2	2	1	1
720	250	6	6	4	2	2	2	2	1	1
730	250	6	6	4	2	2	2	2	1	1
740	250	6	6	4	2	2	2	2	1	1
750	250	6	6	4	2	2	2	2	1	1
760	250	6	6	3	2	2	2	2	1	1

TABLE 4 ACTION LEVELS (ALS) BASED ON REFERENCE DOSES (RfDs) AND REFERENCE AMOUNT (RfA) CATEGORIES, ROUNDED DOWN FOR EASIER REFERENCE (continued)

RfD in mg	SHRIMP	FISH	WHEAT	HAZELNUT	SESAME	MILK	EGG	PEANUT	CASHEW	WALNUT
RfA in g	200	5	5	3	2	2	2	2	1	1
770	250	6	6	3	2	2	2	2	1	1
780	250	6	6	3	2	2	2	2	1	1
790	250	6	6	3	2	2	2	2	1	1
800	250	6	6	3	2	2	2	2	1	1
810	200	6	6	3	2	2	2	2	1	1
820	200	6	6	3	2	2	2	2	1	1
830	200	6	6	3	2	2	2	2	1	1
840	200	5	5	3	2	2	2	2	1	1
850	200	5	5	3	2	2	2	2	1	1
860	200	5	5	3	2	2	2	2	1	1
870	200	5	5	3	2	2	2	2	1	1
880	200	5	5	3	2	2	2	2	1	1
890	200	5	5	3	2	2	2	2	1	1
900	200	5	5	3	2	2	2	2	1	1
910	200	5	5	3	2	2	2	2	1	1
920	200	5	5	3	2	2	2	2	1	1
930	200	5	5	3	2	2	2	2	1	1
940	200	5	5	3	2	2	2	2	1	1
950	200	5	5	3	2	2	2	2	1	1
960	200	5	5	3	2	2	2	2	1	1
970	200	5	5	3	2	2	2	2	1	1
980	200	5	5	3	2	2	2	2	1	1
990	200	5	5	3	2	2	2	2	1	1
1 000	200	5	5	3	2	2	2	2	1	1

3.3.6 TEST METHOD PERFORMANCE REQUIREMENTS TO MEET THE P50 PERCENTILE-BASED REFERENCE AMOUNTS (RfAs)

The second meeting reviewed the methods available for allergen analysis and what would be required for their implementation to provide data on UAP in foods in light of proposed ALs (see section 8.2 of the second report) (FAO and WHO, 2022b). Using the 75th percentile of food consumption and the HBGV identified in the second meeting, the review of analytical methodology concluded that the RfD identified by the second meeting could be implemented and monitored in part with current analytical capabilities but identified a number of significant limitations which users of the test methods need to understand in order to allow for those limitations in the interpretation and use of allergen test results.

Specific aspects that are iterated here are that analytical test methods must have a demonstrable fitness-for-purpose regarding the following:

- > Analytical targets should be specific for the allergenic commodity protein. The only exception might be monitoring of hygiene practices (such as monitoring rinse waters) where a general protein-specific method may be applied. However, data on validation and comparison of different methods for monitoring cleaning are lacking.
- > The test methods should provide a quantitative result, reporting in mg of protein from the allergenic food kg of food analysed.
- > The test methods should operate with a limit of quantification at least threefold lower than the AL for that food.
- > The test methods should have been appropriately validated for the relevant food matrix or type of food matrix using approaches such as the AOAC International triangle.
- > The test methods are of the required specificity which may be problematic when analysing allergenic foods, notably fish, crustacea and wheat. A lack of knowledge on specificity or cross-reactivity of test methods makes this even more challenging.
- > Wider availability of certified reference materials for priority food allergens, both as ingredients and incurred into food matrices where UAP can be more common, will be essential to harmonize test method results and integrate them with HBGVs identified for allergens in foods as well as to provide a means for ongoing monitoring of test method LoQ.
- > There is also a need to ensure appropriate sampling plans are developed and applied to validate and verify allergen management – from cleaning processes to finished foods. The sampling plan will need to be informed by the form of an unintended allergen that is likely to be in the product since testing of particulates (e.g. sesame seeds) and dusts will require a different approach to foods where the allergen is homogeneously distributed.

In the second report (FAO and WHO, 2022b), an analysis of the RfDs and published data on test methods, focusing on ELISA and mass spectrometry methods, was presented. This analysis indicated that many test methods would be able to quantify protein from priority allergenic foods at the RfD-based ALs if the ED₀₅ level was used as a basis for the RfD. This analysis made use of 75th percentile data on food intake. As reported earlier in this report (see section 3.3.5), based on new analyses considered at the third meeting, the Expert Committee now recommends using the 50th instead of the 75th percentile of the population distribution of the single-eating occasion intake of a food as an RfA. Use of the 50th percentile, i.e. a lower intake in comparison with using the 75th percentile, would imply higher ALs and thus higher LoQs required. Thus, this would imply a more favourable outcome regarding the suitability of method performances (i.e. achievability of required LoQs) in analysing at the concentrations required (action levels). Comparison of ALs calculated using predefined intake categories for

iFAAM food groups based on the 50th and the 75th percentiles of food intake (i.e. ALs as calculated in Table 11 of the second report) showed that 50th percentile-based ALs on average are a factor of 1.5 higher than those based on the 75th percentiles (range: 1.0–2.0). This would translate into a slight increase in required LoQs (i.e. lower sensitivity of methods needed). If the p50 is not available, the Expert Committee recommended the mean of the population distribution of the single-eating occasion intake of food to be a good alternative. Mean-based ALs using predefined intake categories are on average a factor of 1.2 (range 1.0–1.4, except for one outlier: 2.0 for binding agent) higher than those based on the 75th percentile, with again a small favourable impact on required LoQs.

3.4 RECOMMENDED WORDING FOR PRECAUTIONARY ALLERGEN LABELLING (PAL)

The Expert Committee unanimously agreed that current PAL approaches used in most countries in which multiple statements or phrases express messages about UAP risks, without any clear guidance on what the associated risks are, needed to be improved. Multiple PAL statements not only cause consumer confusion but have led to lack of trust in such labels (Mills *et al.*, 2004; DunnGalvin *et al.*, 2015; Roche *et al.*, 2022; FSA-FSANZ, 2000). Moreover, surveys have shown that allergic and non-allergic consumers find allergen information difficult to interpret and misunderstand PAL, incorrectly distinguishing different risk levels for different PAL wordings (Hefle *et al.*, 2007; Holleman *et al.*, 2021; Marchisotto, Harada and Kamdar, 2017).

The UK Food Standards Agency together with Food Standards Australia New Zealand (FSANZ) recently undertook a joint literature review of consumer response to allergen declarations and PAL and reported a general consensus amongst stakeholders that PAL wording should be standardized. However, research into defining the preferred wording across different regions and consumers has not yet been undertaken (Food Standard Agency, 2021).

FoodDrinkEurope (2022) has proposed a single harmonized statement for PAL to be “may contain (allergen)”, on the basis that this is a well-known phrase for consumers which has been in use for many years, as well as being a purely factual statement. DunnGalvin *et al.* (2019a, b) surveyed 1 560 adults with food allergy and parents of food-allergic children across Germany, Ireland, the Kingdom of the Netherlands, Spain and the United Kingdom of Great Britain and Northern Ireland. The most popular statement was “this product is not suitable for consumers with XX allergy”, with 46 percent of respondents selecting this as their first choice. This was closely followed by “may contain (allergen)” (44 percent), with “accidental presence of (allergen)” preferred the least (7 percent). There were significant regional preferences, with “not suitable for” ranked more highly by respondents from the United Kingdom of Great Britain and Northern Ireland, Ireland and Germany, while “may contain” was preferred more by respondents in the Kingdom of the Netherlands. Sixty-eight percent of respondents preferred the use of a single PAL statement phrase, rather than multiple phrases, to represent different levels of potential risk or allergen cross-contact. In addition, there was a clear desire amongst 66 percent of respondents for additional information relating to a potential risk

to be available, perhaps through the use of a symbol indicating that a formal risk assessment had been performed.

These findings are similar to a survey conducted by the FDA amongst 1 243 individuals (530 consumers with food allergy, 209 with food-allergic dependents and 504 with no food allergies or food-allergic dependents), to evaluate preferred PAL choice with respect to possible peanut presence. The preferred wording was “may contain,” but only one third expressed this view (Verrill and Choinière, 2009). A more recent survey of United States of America allergic consumers found that the top preference for a PAL statement was “not suitable for people with ‘blank’ allergy” (29.3 percent) and “may contain {allergen}” (22.1 percent) (Gupta *et al.*, 2021). Also, a survey commissioned by FSANZ in Australia and New Zealand (2008, n = 1028) reported almost half of respondents thought that PAL statements using “may contain traces of...” and “may be present...” were not very useful, and one third expressed similar non-favourable preferences with respect to PAL statements referring to food products being “made in the same premises” or on the “same equipment.” This survey methodology did not specifically ask about “not suitable for” or other similar statement and so does not allow for a comparison with DunnGalvin (2019a, b) or other surveys. On the basis of this evidence, the Expert Committee reached consensus that a single preferred phrase for PAL is most ideal and effective. Whichever type of phrase or statement is chosen, this PAL phrase should convey the message of the risk assessment conducted by the FBO that the product contains UAP at levels above appreciable risk and *should not be consumed by allergic individuals*. It should also be easily translated into other languages to maintain transparency of meaning. Whatever PAL phraseology is chosen, it should communicate the conclusion from the risk assessment process and convey the message that the product is not suitable for people with a food allergy to a specific priority allergen.

Some Committee members found “not suitable for ... allergic individuals” to be one PAL example that could convey the intended message not to consume product as per the conclusion of the risk assessment. However, there was some disagreement over whether this statement accurately described the risks from UAP that was present at the ED₀₅ AL cutoff but would be tolerated by and thus “suitable” for up to 95 percent of allergic consumers. There was a brief discussion about the word “traces” and whether a PAL phrase that denotes a product has “likely traces of X allergen from cross-contact” could capture the message of the risk assessment. However, the Expert Committee felt that the term “traces” is often very ill-defined and would not convey a consistent message of the risk assessment that levels of UAP pose an appreciable risk of serious reaction and thus products with this PAL phrase should be avoided. Healthcare professionals have also expressed misgivings over the use of the term “traces”, which is arguably a misrepresentation of the amounts of allergen that are implicated in accidental reactions to food and also risks the perception that someone who reacts to a “trace” has a more severe food allergy while the truth is that the vast majority of allergic reactions occur due to detectable allergen amounts and not “traces” (Turner and Gowland, 2016). Furthermore, other proposed PAL phrases such as “may contain...” or “may be present” were discussed.

These phrases were not specifically endorsed by the committee as they were found to be hazard-based statements (whether the material is present or not) and do not represent the risk-based outcome of the risk assessment process (whether the product is considered safe or not). Also, it was noted that absence of a “may contain...” statement may actually be considered misleading if UAP at or below the RfD or AL is known to be (potentially) present. Notwithstanding these discussions about individual types of PAL statements, the overriding consideration should be for use of a word formulation for a PAL statement that is most meaningful to allergic consumers.

Whichever PAL statement is adopted, a single, clear and concise phrase should mitigate against the current situation in which many PAL statements are ignored by consumers, and products with potential UAP hazards are being consumed by allergic individuals leading to potential adverse reactions. The Expert Committee agreed that more research is needed to understand consumer PAL phrase preferences in different regions. Other single PAL phrases could work in different regions as long as there are communication and education efforts in these regions to reinforce what these chosen PAL phrases represent and that they convey the message of the risk assessment.

Setting different PAL statements based on different AL risk tiers (low, medium, high) was ultimately not pursued by the Expert Committee because of a paucity of data on what are considered “high” (versus low) population risk levels and a lack of information or evidence that most consumers could understand their individual reactivity thresholds enough to know which risk tier of products can or cannot be safely consumed. The Expert Committee acknowledged that further work is needed to establish consumer preferences with respect to risk communication of UAP using PAL, and whether consumers might consider (some) higher-risk scenarios (or risk anomalies, see 4.2) as requiring additional flagging in some way, for example, in the case of unintended presence of cow’s milk in dark chocolate.

Also, to improve consumer trust in and understanding of PAL and what it represents, the Expert Committee favoured an approach that risk assessments be either mandated for every food product and/or that there is a clear indication on the label that a risk assessment has been undertaken to the priority food allergens. In the iFAAM PAL survey, 73 percent of allergic consumer respondents reported that their trust in a product would be improved if an RA process had been used to make a decision about whether or not to apply PAL. Overall, 66 percent reported that a “statement + symbol” on the label indicating a quantitative risk assessment (QRA) would help them to understand the risk assessment process that had been used by the food manufacturer (DunnGalvin *et al.*, 2019b). Two multistakeholder workshops held in the iFAAM project confirmed there was a need for an indication on a food product that a risk assessment had been undertaken to remove ambiguity as to whether a product without PAL would be suitable for an allergic consumer in the event the risk assessment was not made mandatory (DunnGalvin *et al.*, 2019b).

The Expert Committee also noted that introduction of a VITAL® Standard certification scheme and VITAL® Mark in 2019 has been welcomed by consumer groups who thought it was a positive step towards being transparent about products that have undergone proper risk assessment (Roche *et al.*, 2022). Adopting such an approach was encouraged by the Australian House of Representatives (Parliament of the Commonwealth of Australia, 2020) who noted that the approach would improve transparency and aid allergic consumers in making safe food choices but would need to be accompanied by education for them, their caregivers and health professionals providing advice on food avoidance. The presentation of a PAL statement on the food label had been presented with the reference to *Plain English allergen labelling* (PEAL) that was implemented in Australia in 2021 (FSANZ, 2020), but the Expert Committee did not discuss this matter extensively.

The Expert Committee agreed that a communication on the product label that an allergen risk assessment had been performed would give allergic consumers greater confidence that products with PAL likely had relevant UAP while products that did not have a PAL would not pose an appreciable public health risk to individuals allergic to that food. How this communication should be presented (e.g. a symbol on packaging) may require further research in order to understand the most practical and cost-effective method for both food businesses and consumers.



CHAPTER 4

ADDITIONAL CONSIDERATIONS

4.1 UNINTENDED ALLERGEN PRESENCE (UAP) RESIDUAL RISKS AND NO PRECAUTIONARY ALLERGEN LABELLING (PAL)

Adopting a single, clear and unambiguous risk-based PAL statement will be a great improvement in risk communication over the current plethora of multiple (mostly hazard-based) phrases used for PAL that are confusing and potentially misleading. However, in addition to proposing a risk assessment approach for when and when not to communicate UAP through PAL, the Expert Committee also acknowledged that there is a potential evidence gap in the best way to communicate what no PAL information means to food-allergic consumers (or those purchasing foods for them) – particularly in terms of the residual risk posed to those (“highly sensitive”) food-allergic individuals with lower reaction thresholds who might react to levels of UAP at or below the RfDs proposed for PAL. The current non-risk-based PAL landscape often errs on the side of more PAL for any possible UAP. While this leads to overuse of PAL and reduces safe food choices with negligible UAP risks (**Figure 3A**), highly sensitive consumers would likely be alerted to most products with possible UAP and have the opportunity to avoid any UAP exposure and the possibility for adverse reactions.

With the proposed risk-based PAL approach endorsed by the Expert Committee, there would be an accepted small number of products with no PAL statement or other warning that yet have possible UAP that could pose some residual risk for reaction, although overall risk for severe reactions would be minimized. There were still some severe residual risk considerations to delineate for the subpopulation of the highly sensitive allergic population who are known to react adversely to exposures below the RfD. Also, the Expert Committee recognized that many consumers with food allergy do not just want to avoid severe reactions, they also want or would prefer to avoid *any* reaction due to allergens – whether intended or unintended – in food products. To better understand the residual risk for all allergic and highly sensitive allergic consumers, the Expert Committee reviewed data relating to the expected rate of any objective reaction vs anaphylaxis at RfDs based on ED₀₅ (**Table**

5). The results for all foods analysed showed that the highly sensitive population did not have a higher rate of severe reactions (i.e. anaphylaxis) compared to the overall rate for objective reactions for the entire allergic population.

TABLE 5 RESIDUAL RISK ASSOCIATED WITH THE PROPOSED REFERENCE DOSES (RfDs)
(95% CIs in parentheses)

	RfD (mg)	% OF INDIVIDUALS ALLERGIC TO THIS FOOD EXPECTED TO REACT TO THIS DOSE WITH OBJECTIVE SYMPTOMS	EXPECTED RATE OF ANAPHYLAXIS* TO AN ALLERGEN EXPOSURE AT THIS LEVEL IN:	
			INDIVIDUALS REACTING TO ED ₀₅ EXPOSURE WITH OBJECTIVE SYMPTOMS	ALL INDIVIDUALS ALLERGIC TO THIS FOOD
Walnut	1.0	5% (1–11%)	5.3% (2.0–13%)	2.7 per 1 000 (1.0–6.7 per 1 000)
(Pecan)	1.0	5% <i>estimated</i>		
Cashew	1.0	4% (1–8%)	4.9% (2.2–10.5%)	2.0 per 1 000 (0.9–4.2 per 1 000)
(Pistachio)	1.0	5% <i>estimated</i>		
Almond	1.0	5% <i>estimated</i>		
Peanut	2.0	3% (2–4%)	4.5% (1.9–10.1%)	1.4 per 1 000 (0.6–3.0 per 1 000)
Egg	2.0	8% (5–12%)	1.5% (0.02%–55%)	1.2 per 1 000 (0–44 per 1 000)
Hazelnut	3.0	4% (2–6%)	2.5% (0.3–15.8%)	1.0 per 1 000 (0.1–6.3 per 1 000)
Wheat	5.0	3% (1–6%)	2.2% (0.02%–75%)	0.7 per 1 000 (0–23 per 1 000)
Fish	5.0	2.5% (0.4–6%)		
Crustacean	200	3% (0.6–7%)		
Milk	2.0	4% (2–6%)	4.0% (1.5–10.2%)	1.6 per 1 000 (0.6–4.1 per 1 000)
Sesame	2.0	4% (0.5–8%)	3.0% (0.8%–11%)	1.2 per 1 000 (0.3–4.4 per 1 000)

Note: *Generally mild anaphylaxis; refractory reactions would be rare.

Source: Authors' own elaboration.

The Expert Committee then discussed the value of minimizing residual risk for reaction in the allergic population to products with possible UAP and no PAL by comparing potential trade-offs between establishing RfDs for UAP risks at the proposed ED₀₅ versus a lower, and more conservative, ED value (such as ED₀₁). Reference doses (RfDs) based on ED₀₁ could theoretically reduce the absolute number of reactions by 80 percent, from 5 percent to 1 percent of sensitive consumers. Five percent of these reactions would be expected to be anaphylaxis with both cutoffs, although again the absolute number of anaphylaxis episodes would be 80 percent fewer with an ED₀₁-based RfD (Table 6).

TABLE 6 ESTIMATED RATE OF REACTIONS BASED ON REFERENCE DOSES (RfD) BASED ON ED₀₅ AND ED₀₁

RfD BASED ON	PROPORTION OF EXPOSURES IN PEOPLE ALLERGIC TO THE FOOD EXPECTED TO CAUSE AN OBJECTIVE ALLERGIC REACTION	PROPORTION OF THESE REACTIONS EXPECTED TO RESULT IN:		ESTIMATED RATE OF FATAL REACTIONS TO THIS EXPOSURE
		ANAPHYLAXIS	REFRACTORY (SEVERE) ANAPHYLAXIS	
ED ₀₅	5% = 5 000 reactions per 100 000 exposures	5% = 250 events per 100 000 exposures	<1 event per 60 000 exposures	<1 event per 1 000 000 exposures
ED ₀₁	1% = 1 000 reactions per 100 000 exposures	5% = 50 events per 100 000 exposures	<1 event per 350 000 exposures	<1 event per 1 000 000 exposures

Source: Authors' own elaboration.

The Expert Committee also found that a more stringent RfD (such as ED₀₁) would potentially introduce considerable limitations for monitoring UAP and for the application of PAL or other risk management strategies. The mitigation measures needed to comply with RfDs based on ED₀₁ or lower would be too difficult to achieve in a consistent manner. Difficulty in establishing a clear AL based on analytical method could result in a situation similar to the status quo, where food businesses do not make risk-based decisions and default to using PAL for *any* potential UAP. This would result in a paradoxical increase in the use of PAL statements, since food businesses and regulators would not be able to verify allergen presence at or below ED₀₁ for many allergens and matrices. Furthermore, one may argue that an RfD based on ED₀₁ might still be unacceptable in principle, since 1 percent of the allergic population would still be expected to react with an objective allergic reaction.

The Expert Committee considered the trade-off of using the RfDs proposed in the second meeting (based on ED₀₅), where use of PAL could be informed by existing analytical capabilities. This would allow a greater number of products to undergo risk-based assessments and decisions, and likely reduce the number of products with PAL statements. This would not only improve risk communication of PAL but would offer consumers a greater range of safe food choices. Given that there is likely to be an increase in PAL and reduced food choices with a more stringent RfD (based on the ED₀₁ or lower) without a meaningful reduction in population health risk, the Expert Committee agreed that using the RfDs (based on ED₀₅) would be more advantageous at a public health level. This advantage was apparent when also considering the disadvantages of a slightly higher residual risk of reaction at the ED₀₅-based RfD since the expected severity would be limited and not significantly improved in terms of public health impact with a more stringent RfD.

A final trade-off in favour of the proposed RfD risk-based approach was the observation from analytical surveys of products associated with consumer reactions (Blom *et al.* 2018) that the current non-risk-based PAL system has also led to some

scenarios in which products with significant UAP risks did not have PAL and likely contributed to inadvertent moderate to severe reactions in consumers. Since levels of UAP could be well above the RfD, the risk of severe reactions from this scenario is potentially greater than for product scenarios with $UAP < RfD$; also, this risk would adversely impact not just the highly sensitive individuals but all allergic consumers. With the proposed RfD risk-based approach, all products with significant UAP risks $> RfD$ would now carry PAL (**Figure 3B**), and thus the overall residual risk of severe reactions posed by products with no PAL to the allergic population would be greatly minimized.

4.2 RISK ANOMALIES

Certain processing scenarios (involving shared lines that are difficult to clean) may represent distinct risk anomalies due to a combination of particulate and non-particulate UAP and/or due to a relatively high frequency of cross-contact leading to UAP. This may lead to large variations in UAP that cannot be easily or consistently quantified by routine sampling or risk assessment methods.

The production of dark chocolate on the same lines as milk chocolate is a prime example. Because of certain processing factors (e.g. wet cleaning not typically used for some equipment, types of equipment are difficult to disassemble/inspect), the consistency of chocolate makes it difficult to remove from equipment, the effectiveness of preventive control measures (e.g. push through, pig purging of pipes) is not consistent, and there are inherent difficulties in preventing milk cross-contact from the equipment to dark chocolate. This results in almost ubiquitous and unavoidable presence of milk UAP, at times at concentrations in great excess of the RfD-based action levels. Analytical surveys of dark chocolate with PAL statements have shown that over 70 percent of these products have detectable milk allergen and that over 50 percent of these products have milk concentrations at 1 000 ppm or higher; thus, at concentrations much higher than Rfd-based AL for milk (Bedford, 2017). For this reason, milk cross-contact in dark chocolate has been treated as a Risk Review Anomaly in the Australia-New Zealand VITAL[®] programme and is managed outside the scope of VITAL[®] risk assessment. By agreement between the confectionary industry and the Australian State & Territory food law enforcement agencies, manufacturers of affected dark chocolate product may choose to treat the milk UAP as a subingredient and include it at the end of the ingredient list, or they may add an additional advisory statement to alert the allergic consumer to the potential presence of traces of milk (Allergen Bureau *et al.*, 2019).

Another example of special risk management measures due to milk UAP in chocolate is from Sweden, where chocolate and chocolate products were identified as risk products by the Swedish Food Agency based on data from a Nordic project investigating undeclared allergens in food (Bolin and Lindeberg, 2016). Milk was commonly detected both in products without PAL (12 percent) and with PAL (51 percent), mainly in chocolate, candy and bakery products and was also reported in high levels (range 2.7–8 800 mg casein / kg with PAL and range 2.0–2 600 mg

casein/kg without PAL). These data led to a special risk management measure with a recommendation to severe cow's milk allergic consumers to discuss with their health care professional about complete avoidance of chocolate and chocolate products (SFA Report, 2017). The Expert Committee did consider whether a different form of wording might be needed for such scenarios, but the preference was for a single PAL statement to cover all scenarios where there is UAP above the RfD.

4.3 RECOMMENDATION TO MANDATE RISK-ASSESSMENT-BASED SINGLE PRECAUTIONARY ALLERGEN LABELLING (PAL) SYSTEM

In the scenario where UAP may be present in food products, the Expert Committee debated some of the pros and cons for the proposed PAL versus no PAL risk assessment approach. The Expert Committee acknowledged that at present there are no regulations in most countries mandating use or non-use of PAL for UAP. Because of this, FBOs may be subject to regulatory actions if their products are found to have any UAP, even if UAP levels are clearly below RfD-based action levels. The same may also be true if both UAP and PAL are present, especially in cases in which UAP is found at high levels and/or has injured an allergic consumer. Thus, the Expert Committee agreed that for a risk assessment approach to be accepted and effective, it was necessary that regulations or other policies mandating the use or non-use of PAL based on risk assessment be accepted by all relevant industry, consumer and regulatory stakeholders. Mandated UAP risk assessments would set a more level playing field for food products denoting PAL as all sectors of the food industry would need to comply. This would be a very significant improvement from the current (voluntary) practice which leads to non-uniform and inconsistent use of PAL. Also, if consumers had confidence that all products with or without PAL have undergone a risk assessment for priority allergenic foods, this would increase consumer safety, reliance on and trust in PAL.



CHAPTER 5

CONCLUSION

- > Precautionary allergen labelling (PAL) based on a comprehensive allergen risk management programme and implemented using a single clear unambiguous advisory statement, supported by effective risk communication, is an effective strategy to protect consumers from risks of unintended allergen presence (UAP).
- > Current use of PAL is voluntary and often not part of a standardized risk assessment process. This leads to non-uniform and indiscriminate application of PAL (including a multitude of different phrases) and/or inappropriate absence of PAL. Consumers find the information currently provided regarding UAP to be confusing. This results in poor communication and misinterpretation of the risks posed by UAP, reducing consumer trust in allergen labelling, and in a proven health risk to the allergic consumer.
- > The available evidence indicates that some manufacturers, consumers and other stakeholders do not understand current strategies to communicate precautionary messages relating to risks posed by UAP in products. Current data indicate a preference for wording which conveys that a food is not suitable for consumers with a particular allergy. Education of consumers, healthcare providers, food business operators (FBOs), risk assessors and risk managers is critical to PAL management.
- > Individual allergy management considerations:
 - The use of a PAL system based on risk-based RfDs as set out in previous sections of this report would be protective for the vast majority of food-allergic individuals.
 - In this framework for PAL, it is recommended that all individuals with a particular food allergy avoid foods when a PAL to that food is present. However, this system may be overprotective or restrictive for some of the less sensitive individuals with food allergy.
 - Similarly, a small proportion of individuals with a particular food allergy who react to smaller amounts of allergen (at or below the RfD) might not be fully protected; further work is needed as to how to ensure these individuals can receive appropriate information to make informed safe food choices.

- Any deviations from this recommendation (for food-allergic individuals to avoid all products with PAL to the relevant allergens) should be taken into consideration for individual allergy management advice, as discussed between an allergic individual and their healthcare provider.
- > Reference doses recommended in the second meeting are not intended to be used for making a claim that a food is free from specified allergens.
- > Risk assessment for considering ingredient exemptions from priority allergen labelling is proposed for a future meeting.

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ANNEX 1

DEFINITIONS

TABLE A1 DEFINITIONS USED IN THIS REPORT.

Aerosols	Readily dispersible liquid particulates
Allergen	For the purposes of this report an allergen is defined as a molecule in an allergenic food or ingredient, which can bind to IgE (van Ree, 2014).
Allergen cross-contact	Allergen cross-contact occurs when an allergenic food, or ingredient, or residues thereof, is unintentionally incorporated into another food that is not intended to contain that allergenic food. This is sometimes also referred to as allergen cross-contamination.
Allergen profile	Food allergens present via intentional addition as well as those inadvertently present (or the absence of any allergens) in a food (FAO and WHO, 2020).
Coeliac disease	Coeliac disease is a chronic immune-mediated intestinal disease in genetically predisposed individuals induced by exposure to dietary gluten proteins that come from wheat, rye, barley and triticale (a cross between wheat and rye) (FAO and WHO, 2022a).
Derivative	An ingredient derived from main food allergen source through various forms of processing. This term includes ingredients exempted from mandatory labelling for priority allergens with reduced allergenic protein content.
Dust	Airborne particulates
Food allergy	Food allergy is defined as an adverse health effect arising from a specific immune-mediated response that occurs reproducibly on oral exposure to a given food, which may or may not be mediated by food-specific immunoglobulin class E (IgE) antibodies (FAO and WHO, 2022a).
Food intolerances	Food intolerances are non-immune mediated adverse reactions. They can be categorized into three types: enzymatic, pharmacological, and undefined or idiopathic food intolerances. The most common foods implicated in intolerances include dairy products, products containing sulfites, salicylates, FODMAPs (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols), biogenic amines, lactose, and food additives (FAO and WHO, 2022a).
Hang up	Points in food processing/machinery where food substances can build up or accumulate instead of flowing through freely and are difficult to clean (Allergen Bureau, 2021)
Homogenous or dispersible	Terms to describe non-particulate allergens or materials such as powders, etc, the individual components of which cannot be distinguished by the naked eye and which are not retained by a sieve. The current guidance describes this type of cross-contact as “homogeneous amorphous” and the Australia-New Zealand VITAL® 2.0 scheme described this type of cross-contact as “readily dispersible”.
Particulate	A particle of food is in the form of discrete pieces, chunks, fragment or lumps, normally visible to the naked eye. May be retained by a sieve.
Precautionary allergen or advisory labelling	Precautionary allergen labelling is a statement indicating (a more than appreciable risk of) possible unintended allergen presence (based on the recommended single PAL system). It may also be referred to as advisory labelling.
Reference dose	Reference dose (RfD) is a health-based guidance value (HBGV) based on quantitative hazard characterization information (dose-response modelling) (see FAO and WHO, 2022b for further details).
Rework	Clean, unadulterated food that has been removed from processing at any point up to and including final packaging for reasons other than insanitary conditions or that has been successfully reconditioned by reprocessing and that is suitable for use as food or a food component (FAO and WHO, 2020).
Unintended allergen presence (UAP)	The presence of protein from a priority allergenic food source in another food which is not intended (e.g. due to cross-contact) at any point in the food supply chain.
Visibly clean	Having no visible food, debris and other residues (FAO and WHO, 2020).

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ANNEX 2

TERMS OF REFERENCE QUESTIONS FOR PRECAUTIONARY ALLERGEN LABELLING (PAL) GUIDANCE

Should such labelling be restricted to those situations in which allergen cross-contact cannot be controlled to the extent that the product no longer poses a potential risk to the allergic consumer?

Yes, only after appropriate quality control, hygiene and risk mitigation practices are performed.

There may be other situations in which a firm can control allergen cross-contact the majority (e.g. 99 percent) of the time but cannot ensure that particulates that pose a risk are present.

Should such labelling not be used? Must a risk assessment be carried out identifying either a risk (allergen PAL/labelling) or no risk (no PAL/labelling) for the allergic consumers?

Yes, a risk assessment should be performed for all cases of UAP. When a risk assessment shows that exposure risk from UAP does not exceed the RfD, then no PAL is warranted. If the exposure risk from UAP is above the RfD, then PAL is warranted.

In what way should allergy severity/class be taken into account for precautionary labelling?

There is a concern about using the same PAL for products with significantly different UAP risks – low vs high (higher risk for severe reactions). One option is to use a statement that is most likely to deter most consumers from consuming product

with PAL. This will deter consumers from consuming any product with UAP risks greater than RfDs, whether the risks are low or the risks are even higher for severe reaction. A potentially feasible statement that conveys a message to consumers to not consume a product with significant UAP risk could be a “not suitable for” statement. This statement has been reported to be the PAL most likely to be avoided in consumer surveys.

ANNEX 3

DERIVATIVES AS A SOURCE OF UNINTENDED ALLERGEN PRESENCE (UAP) AND LABELLING CONSIDERATIONS

A3.1 INTRODUCTION

Numerous food ingredients are derivatives of priority allergenic foods (milk, egg, fish, crustacean shellfish, peanut, tree nuts, sesame seeds, or cereal sources of gluten). These food ingredients can serve numerous technical functions in formulated food products including flavours, colours, sweeteners, antioxidants, preservatives, emulsifiers and others. Depending on the process by which they are produced, some of these derivatives can have very high levels of allergenic protein from a priority allergenic source; examples include caseinates and whey protein concentrate from milk, egg white and whole egg powder, semolina from wheat, wheat gluten, and tahina from sesame seed. A few derivatives contain high levels of protein from the priority allergenic food, but the protein profile of the ingredient may not include very much of the key allergenic proteins; fish gelatin is a primary example. At least one derivative (lysozyme from egg) is a known allergenic protein from a priority allergenic food. Other derivatives contain very low, sometimes undetectable, levels of protein from the priority allergenic source; examples include highly refined (solvent extracted, neutralized, bleached and deodorized) peanut oil; fish oil; butter oil, butter ester, and starter distillate from milk; ethanol, vinegar, and glucose syrup from wheat; and possibly others. Some derivatives contain low but detectable amounts of protein from the priority allergenic source; examples include lactose from milk, wheat starch (excluding “Codex” wheat starch), egg lecithin, cold-pressed tree nut and other not highly refined vegetable oils, such as sesame seed oil.

In 1999, a list of eight foods or food groups causing IgE-mediated food allergy was compiled and incorporated into the *General standard for the labelling of prepackaged foods (GSLPF)* under section 4.2.1.4. The listing recommends labelling the foods and ingredients (derivatives) of those foods. The recommendations in 1999 relating to derivatives indicated that all derivatives from these allergenic sources should be declared on the ingredient label regardless of the level of allergenic protein present in the derivative. Subsequently, as countries globally began to implement the recommendations in the GSLPF, the labelling of derivatives of these allergenic foods became a provision of labelling regulations. However, some regulatory jurisdictions recognized that certain derivatives of these allergenic foods had very low allergenic risk due to methods of manufacturing and very low, sometimes non-detectable, levels of allergenic proteins. As a result, some countries developed processes to allow source labelling exemptions for derivatives considered to represent low allergenic risk. In these cases, decisions of promulgation of source labelling exemptions were made on a case-by-case basis considering scientific and technical information provided by the manufacturers of such derivatives. However, due to a litany of factors, source labelling exemptions were not made uniformly. Global harmonization of the labelling of the various derivatives of the allergenic foods has not been achieved, hampering global trade.

More recently, this Ad hoc Joint FAO/WHO Expert Consultation on Risk Assessment of Food Allergens recommended a revised list of eight priority allergenic foods or food groups (milk, egg, fish, crustacean shellfish, peanut, tree nuts, sesame seeds, and cereal sources of gluten) with the addition of sesame seed and the removal of soybean. The Expert Consultation also recommended that derivatives from these foods known to cause IgE-mediated allergic reactions should be evaluated on a case by-case basis for possible exclusion from source labelling on ingredient lists appearing on prepackaged foods (FAO and WHO, 2022).

Derivatives of priority allergenic foods may be intentionally added to food formulations during the food manufacturing process. Food business operators should determine if intentional food ingredients are derived from priority allergenic foods. Additionally, derivatives may enter the food ingredients unintentionally through the use of shared manufacturing facilities and/or equipment. If so, the potential for UAP should be evaluated and controlled using the allergen management approaches outlined in the *Code of practice on food allergen management for food business operators* (CXC 80-2020; CoP). The level of allergenic protein present in the derivative is an important factor in labelling considerations for intentional food ingredients and for the potential for UAP.

The Expert Consultation recognized that the topic of derivatives is complex with a diversity of manufacturing operations leading to a myriad of food ingredients offering a wide range of technical attributes with variable composition including protein levels and allergen profiles used in differing amounts in food products. The Expert Consultation discussed three derivatives as examples of the complexity of the risk assessment of derivatives for consideration for ingredient labelling and PAL.

These examples are provided below to assist FBOs in the selection of implementation approaches for ingredients that are derivatives of priority allergenic sources. In some regulatory jurisdictions, certain derivatives are exempted from mandatory labelling but these exempted ingredients, and the requirements for exemption, vary by regulatory jurisdiction. The first example, highly refined soybean oil, illustrates a situation where a highly defined and reproducible process, supported by a Code of Practice, consistently assures the production of a virtually protein-free derivative. The second example (fish gelatin) highlights a situation where the final product, derived from a highly heterogeneous and variable raw material, contains by design a substantial amount of protein. Furthermore, the process, which is not standardized, results in the removal of the known allergenic proteins, albeit perhaps to different degrees that have not been systematically evaluated. Demonstrating the safety of the end product to consumers with the relevant (fish) allergy is thus clearly very challenging for fish gelatin. However, certain specific uses of fish gelatin have received exemptions primarily due to demonstrated low doses of exposure to the major allergenic fish protein. In the case of the third example (soy sauce), while the raw materials are defined agricultural commodities, which meet prescribed standards, the end product is the result of process conditions (e.g. fermentation) that alter these raw materials. Some processes can result in different allergen profiles, and safety to sensitive consumers cannot be assumed merely from adherence to the process.

A3.2 LACK OF ALLERGENICITY OF HIGHLY REFINED NEUTRALIZED/ REFINED BLEACHED AND DEODORIZED (N/RBD) SOYBEAN OIL

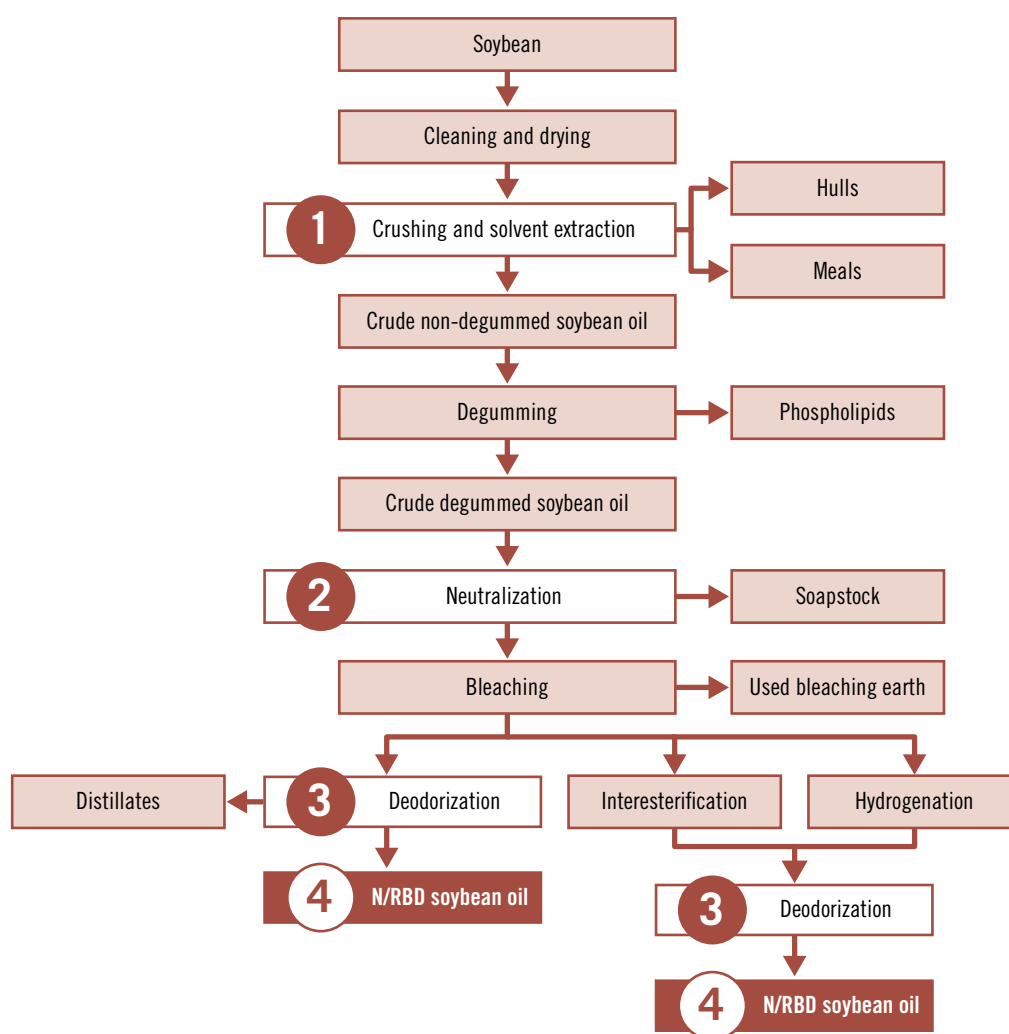
Highly refined soybean oil is an edible vegetable oil used widely and in large quantities in the food industry. Any requirement to declare its presence as an allergen therefore carries significant operational implications as well as potential unintended consequences for soy-allergic consumers (e.g. precautionary allergen labelling). In some jurisdictions (i.e. the United States of America), the use of highly refined oils from priority allergens are statutorily exempted from allergen labelling (USFDA, 2004). No reasons are provided as to why these oils are exempted and how “highly refined” oils are defined. As part of its allergens legislation, the European Union introduced a formal two-stage process whereby an initial temporary exemption for derivatives could be granted, based on a dossier describing the available scientific evidence supporting the exemption, together with studies planned to support a later permanent exemption. Exemption of highly refined soybean oil from allergen labelling fits in this context. The studies and data presented here followed the European Food Safety Authority’s (EFSA, 2007) conclusion in its Opinion on the temporary exemption dossier “that it is not very likely that N/RBD soybean oils will cause a severe allergic reaction in the majority of soybean allergic individuals.”

In that Opinion EFSA also requested information on the level and identity of the residual soy protein and protein fragments, as well as more clinical information concerning the effects of neutralized/refined bleached and deodorized (N/RBD) soybean oil in soybean- and peanut-allergic patients. Specifically, they required

additional data about the patients from the challenge study which had been presented in the temporary exemption dossier (the “Nebraska study”), as well as further clinical challenge trials to demonstrate that soybean oil was safe for soy- and peanut-allergic individuals up to the worst-case scenario described in the original notification.

The material studied was neutralized/refined bleached and deodorized (N/RBD) soybean oil (“highly refined soybean oil”). The N/RBD oil was commercially refined in accordance with the FEDIOL Code of Practice (FEDIOL, 2020).

FIGURE A1. **SIMPLIFIED ILLUSTRATION OF THE PRODUCTION PROCESS FOR NEUTRALIZED/REFINED BLEACHED AND DEODORIZED (N/RBD) SOYBEAN OIL**



Source: Authors' own elaboration.

A blend of N/RBD oils from different European refineries was prepared so that the test material was representative of the oils available on the European market. Highly refined canola oil was used as the placebo. Crude, degummed soybean oil was also used in the analytical and immunochemical studies (Figure A1).

In addition, the protein content of a representative selection of oils used in the “Nebraska” study (included in the temporary exemption dossier) was measured by the same method as used for the above oils (Figure A2).

Initially three different extraction methods were assessed, but because of technical issues arising from the very low protein levels and in order to improve reproducibility, a further, low-volume extraction method was developed during the studies (micro-borate method). Protein content was quantified by the ATTO-TAG method (You *et al.* 1997) and proteins characterized by proteomic approaches, including 1D- and 2D-SDS PAGE, and mass spectrometry.

Immunoblotting was used to investigate specific IgE binding of the proteins using sera from soy-allergic donors.

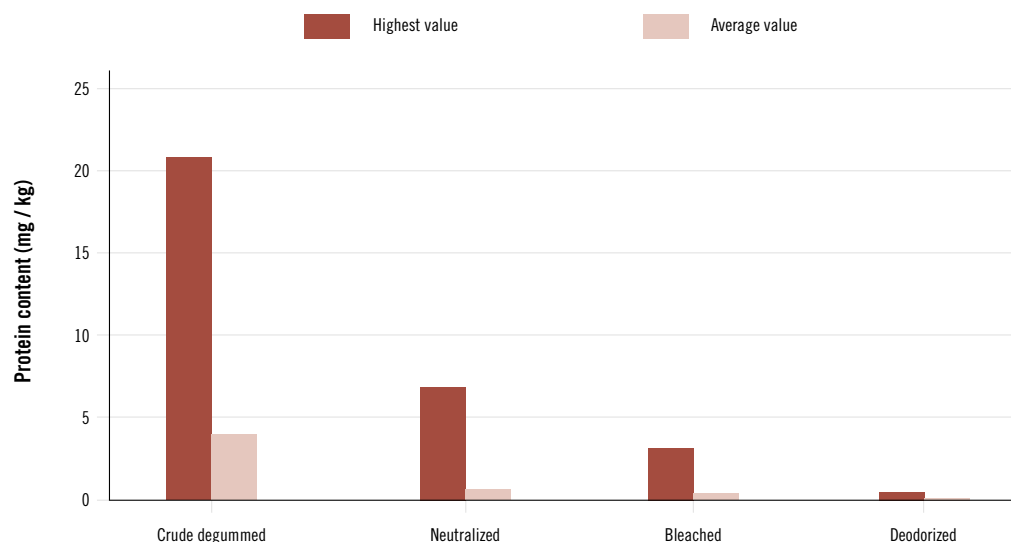
The European Food Safety Authority had requested clinical challenge studies in both peanut-allergic and soy-allergic individuals. Two clinical double-blind placebo-controlled challenge studies with the prepared soybean oil blend were therefore undertaken.

In the first study, 30 individuals (18–57 years, 13 males) with a history of exquisite peanut food allergy, confirmed by double-blind placebo-controlled challenge, were recruited at each of two participating clinics (university clinics in Berlin and Utrecht) experienced in conducting double-blind placebo-controlled food challenges. They consumed by mouth increasing doses of soybean (12, 24 and 48 ml) or placebo oil mixed in a mashed potato vehicle (up to 400 g in total) up to a dose representing the worst-case intake for a single-eating occasion (84 ml).

In the second study, 32 individuals (12–62 years, 10 males) with demonstrated soy allergy, confirmed by challenge, were recruited at each of three participating clinics (university clinics in Berlin, Utrecht and Zurich). All patients were challenged under the same conditions and using the same doses as in the first study.

The protein content of a range of oils was measured, including several N/RBD, partially hydrogenated, and interesterified soybean oils and the N/RBD oils used in the clinical challenge studies, all supplied by FEDIOL member companies, and a representative selection of 29 oils previously used in the Nebraska study. The reduction of protein content through the refining process was clearly demonstrated with crude non-degummed soybean oil containing about 340 times more protein than its corresponding N/RBD oil (average 87 250 ng / g versus 256 ng / g), as well as in the analysis of the Nebraska samples. The protein content of the Nebraska samples measured by the micro-borate/ATTO-TAG correlated with the results obtained by the PBS / total amino acid method. The quantification of protein in these oils showed that the levels in N/RBD oils and other oils that undergo a full refining process were very significantly lower than the level in the crude non-degummed oils.

FIGURE A2. **RESIDUAL TOTAL PROTEIN CONTENT OF SOYBEAN OIL MEASURED AT THE END OF DIFFERENT STAGES OF REFINING**

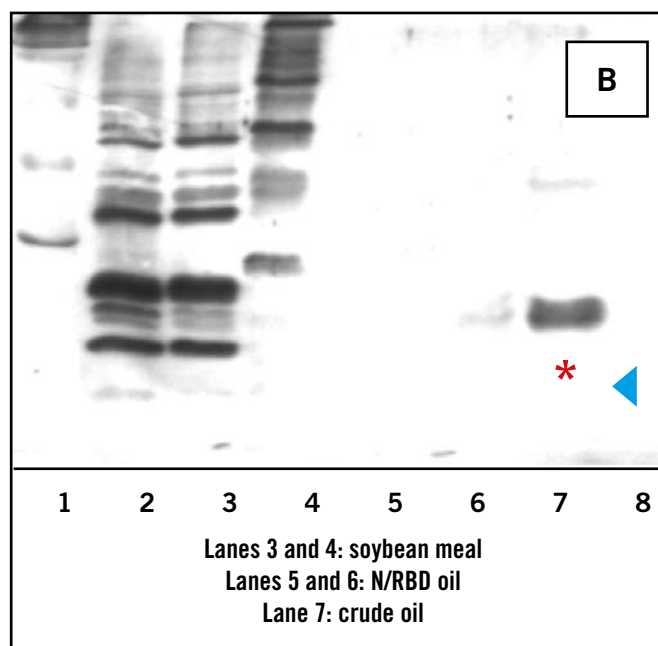


Source: Authors' own elaboration adapted from data by Nordlee *et al.* (2002).

Further characterization by proteomic techniques was confined to the residual protein from crude non-degummed oil because the very low protein content of the N/RBD oils meant that not enough could be extracted for this purpose. One-dimensional SDS-PAGE analysis indicated that all extracted proteins were ones which had already been identified in soybean extracts, including some implicated as allergens. However, significantly there was no evidence that the major soy allergens Gly m Bd 30k or Gly m 4 were present in the crude non-degummed soybean oil. Two-dimensional SDS-PAGE analysis of crude non-degummed soybean oil showed only a few proteins compared to the same analysis performed on a soybean meal or flour extract. Analysis of the proteins from the oil was complicated by the fact that they did not yield focused protein bands because of their hydrophobicity. Only one protein from the oil gel, identified as a Kunitz trypsin inhibitor, gave a significant MOWSE score from MALDI-ToF mass spectrometric characterization.

The IgE binding properties of several extracts of soybean meals and oils were also examined. Extracts from soybean meal bound IgE well in the immunoblotting, showing that the serum pool used contained a full spectrum of IgE binding capacity. The extract from crude non-degummed soybean oil showed IgE binding to two antigens of which one was weak. Extracts from N/RBD soybean oil showed either no or only very weak traces of IgE binding, as would indeed be expected from the extremely low protein content of N/RBD soybean oil.

FIGURE A3. IMMUNOBLOTTING WITH A POOL OF 5 HUMAN ANTI-SOY IGE SERA SHOWING EXTENT OF BINDING TO A WHOLE SOYBEAN MEAL EXTRACT, NEUTRALIZED/REFINED BLEACHED AND DEODORIZED (N/RBD) SOYBEAN OIL AND CRUDE SOYBEAN OIL



Source: Authors' own elaboration.

First study: challenge of peanut-allergic individuals. Nearly 75 percent of volunteers (22 / 30) reported no symptoms at all. In the remainder, all reported symptoms were mild, subjective and self-limiting and approximately equally distributed between soybean oil challenges only (2 / 30), placebo challenges only (4 / 30) and both placebo and soy oil challenges (4 / 30). These results thus confirm the conclusion in the temporary exemption dossier that soybean oil is very unlikely to trigger allergic reactions in peanut-allergic individuals.

Second study: challenge of soy-allergic individuals. The majority of the volunteers (21 / 32 – 70 percent) reported no symptoms at all (3 / 32 – 9 percent after challenge with soybean oil). In the remainder, all reported symptoms were mild, subjective and self-limiting. More reactions were reported with the placebo challenges. These results thus confirm the conclusion that soybean oil is very unlikely to trigger allergic reactions in soy-allergic individuals.

In summary, the data presented corroborate the conclusion of the original notification, endorsed by the EFSA (EFSA, 2007). They confirm that N/RBD soybean oil is extremely unlikely to trigger allergic reactions in either soy- or peanut-allergic individuals. This conclusion is based on the following evidence:

- > Initial review of the clinical and epidemiological data indicated extremely rare (and poorly-documented) cases of reactions to soybean oil.

- > There is confirmation that N/RBD soybean oils have an extremely low total protein content.
- > The major soy allergens are not found in extracts from crude non-degummed soybean oil and therefore cannot be found in N/RBD oils which are derived from them.
- > Clinical challenge studies showed no qualitative or quantitative differences between the response of soy- or peanut-allergic volunteers to soybean oil and placebo.
- > The use of the amount calculated from a worst-case scenario provides a significant margin of safety compared to commonly consumed amounts of soybean oil.

A3.3 GELATIN

Although most food gelatin ingredients are derived from beef and pork, some gelatin is derived from fish. Fish gelatin is produced by extraction and hydrolysis of fibrous, insoluble collagen from the skin and bones of various species of fish; skin and bones are by-products of fish manufacturing. Numerous global manufacturers of fish gelatin exist. The Expert Consultation is not aware that fish gelatin is made by any standardized manufacturing procedure. However, generally, the manufacturing process involves treatment with acid and/or alkali, followed by several water rinses, pH adjustment, extraction by heating one or several times in succession, and purification by filtration and/or ion exchange and finally sterilization. Various fish gelatin manufacturers use the skin and bones from different fish species. Fish gelatin has numerous ingredient uses, including the encapsulation of vitamins and carotenoids, and as a fining agent for wines and beers. Fish gelatin is almost entirely composed of protein from fish, a priority allergenic source as identified in the first report. The reference doses were defined in the second report in terms of total protein from fish. However, the primary protein in fish gelatin is collagen, while the major panallergen from fish is a muscle protein known as parvalbumin (Ruethers *et al.*, 2018). Collagen has also been identified as a fish allergen but does not appear to sensitize as many fish-allergic patients in most countries with the possible exception of Japan (Kobayashi *et al.*, 2016; Kalic *et al.*, 2020). Parvalbumin is the primary allergen of concern for risk assessment of food products containing fish gelatin. The parvalbumin content of fish gelatin is probably relatively low since the amount of muscle tissue in the bones and skin is modest and parvalbumin residues are reduced by the water rinses used in their manufacturing (Koppelman *et al.*, 2012). Also, the amount of parvalbumin in fish muscle varies from one species to another with comparatively higher levels in cod and rather low levels in tuna (Lee *et al.*, 2011; van Do *et al.*, 2005). Both cod and tuna are used as sources of fish gelatin by different manufacturers. However, the level of residual parvalbumin in commercial fish gelatin is unknown for the majority of fish gelatin manufacturers. A clinical trial demonstrated that cod-allergic patients could tolerate gram exposure levels of a commercial fish gelatin primarily derived from cod (Hansen *et al.*, 2004). Thus, any risk assessment of fish gelatin should take into account its parvalbumin content

(whether known or unknown, conservatively assume that all protein in fish gelatin is parvalbumin), the levels of usage of fish gelatin in the food product, and the results of any relevant oral challenge trials. The European Union has exempted source labelling of fish gelatin for uses as an encapsulating agent for vitamins and carotenoids and as a fining agent for wines and beers. In both cases, exposure of consumers to fish gelatin was estimated to be quite low. The increasing recognition of collagen as a fish allergen (Kobayashi *et al.*, 2016; Kalic *et al.*, 2020) merits consideration as well.

A3.4 GLUTEN IN SOY SAUCE

Soy sauce is a popular condiment and seasoning agent used in Asian and other cuisines. There are two major types of soy sauces: Chinese-style soy sauce, which is manufactured using soybeans alone as the major ingredient, and Japanese-style soy sauce, which is produced with a mixture of soybeans and wheat, a priority allergen defined in the first report. There are five categories of Japanese soy sauces (koikuchi, usukuchi, tamari, shiro and saishikomi) which differ in the ratio of soybeans to wheat used as raw materials (Fukushima, 1981; Kobayashi *et al.*, 2004). Soy sauces can also be classified according to the processes by which they are manufactured. Naturally brewed or fermented soy sauces are produced by mixing steamed soybeans, roasted wheat (for Japanese-style soy sauce) and spores of *Aspergillus oryzae* or *Aspergillus sojae* to produce what is known as “koji”. Next, the koji is mixed with brine to generate mash or “moromi”, which is typically fermented and aged for up to six months under controlled conditions. During the fermentation process soy and wheat proteins are enzymatically hydrolysed to amino acids and peptides. Starches from soybeans and wheat are degraded to monosaccharides which are subsequently fermented to lactic acid and ethanol by lactic acid bacteria and yeasts present in the moromi (Fukushima, 1981; Luh, 1995; Liu, 2008). There have been several reports on the design and use of bioreactors to reduce the fermentation time needed to produce naturally brewed soy sauce (Hamada *et al.*, 1991; Luh, 1995). In contrast to the natural brew process, the acid hydrolysis method uses acid to hydrolyse soy and wheat protein, followed by neutralization. “Chemical soy sauce” produced by the acid hydrolysis method tends to be of lesser quality than naturally brewed sauce due to the lack of flavour development that accompanies the fermentation process (Liu, 2008).

The fate of wheat proteins, including gluten, during production of Japanese-style soy sauce was examined in several research studies. Using IgE antisera from five wheat-allergic children, Kobayashi *et al.* (2004) found that antigenic elements in soy sauces were no longer detected after 48 days of moromi fermentation. Similar results were found by Cao *et al.* (2017) who reported that gluten levels in traditional Japanese soy sauce after one month of moromi fermentation were below the LoQ of commercially available ELISA kits that target intact and hydrolysed gluten. No wheat allergen was detected in ten commercial soy sauces by inhibition ELISA or direct ELISA using the sera of five wheat-allergic patients (Kobayashi *et al.*, 2004).

Similar results were reported by Cao *et al.* (2017) and Li *et al.* (2018) who found that gluten concentrations in 15 and 10 store-purchased soy sauces, respectively, were below the LoQ of commercial ELISA kits that target intact and hydrolysed gluten. Li *et al.* (2018) used discovery proteomics to identify gluten-derived peptides and targeted proteomics using LC-MRS-MS to confirm the presence of gluten in store-purchased soy sauces. Although gluten was not detected in any of the soy sauces, wheat proteins (LTPs (lipid transfer proteins) and ATIs) were identified in 5 out of 7 sauces that were labelled as having wheat as an ingredient. The studies described above suggest that the fermentation process used in soy sauce production extensively hydrolyses wheat proteins including gluten. However, since the enzymatic processes and fermentation conditions used in the production of soy sauces are not always known or standardized, it is difficult to conclude that gluten is hydrolysed to the point where all gluten immunopathogenic sequences are removed. Altering the processing conditions used in soy sauce production may result in variable hydrolysis of gluten, and the product may thus pose a risk to consumers with celiac disease (Li *et al.*, 2018).

A3.5 CONCLUSIONS

Due to the wide-ranging diversity of possible derivatives and the resulting complexity involved with assessment of the potential risks posed by derivatives of priority allergenic foods and food groups, the Expert Consultation recommends that a separate joint FAO/WHO Expert Consultation should be convened in the near future to discuss derivatives in more depth. Recommendations on labelling, labelling exemptions, and risk assessment for UAP relating to derivatives are needed to achieve global harmonization and facilitate global trade while also protecting food-allergic consumers. Without such recommendations, the labelling of derivatives may curtail the progress achieved by the current Expert Consultation on allergen and precautionary allergen labelling.

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RISK ASSESSMENT OF FOOD ALLERGENS

PART 3: REVIEW AND ESTABLISH PRECAUTIONARY LABELLING IN FOODS OF THE PRIORITY ALLERGENS

MEETING REPORT

FAO and WHO reconvened a third meeting to review and evaluate the evidence in support of precautionary allergen labelling to address unintended allergen presence in foods.

The Expert Committee at the third meeting reviewed the data on the current status and uses of PAL and unanimously agreed that current PAL systems used in many countries needed to be improved as they were neither uniform nor informative and were not consistently risk based on amount and frequency of UAP found in food products. The Expert Committee also found that current PAL approaches led to widespread PAL that diminished information and value for consumers. The Expert Committee reviewed again the principles and basis of RfD from the second meeting and reached a consensus that the RfD for each priority allergen, as described by the HBGV and safety objectives, was a valid risk assessment endpoint for determining when sporadic or unexpected UAP posed more than appreciable risk to consumers and needed to be communicated to consumers by PAL.

FOOD SYSTEMS AND FOOD SAFETY - ECONOMIC AND SOCIAL DEVELOPMENT

WEBSITE: WWW.FAO.ORG/FOOD-SAFETY

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