

Proposal of 0.5 mg of protein/100 g of processed food as threshold for voluntary declaration of food allergen traces in processed food—A first step in an initiative to better inform patients and avoid fatal allergic reactions: A GA²LEN position paper

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Abstract

Background: Food anaphylaxis is commonly elicited by unintentional ingestion of foods containing the allergen above the tolerance threshold level of the individual. While labeling the 14 main allergens used as ingredients in food products is mandatory in the EU, there is no legal definition of declaring potential contaminants. Precautionary allergen labeling such as “may contain traces of” is often used. However, this is unsatisfactory for consumers as they get no information if the contamination is below their personal threshold. In discussions with the food industry and technologists, it was suggested to use a voluntary declaration indicating that all declared contaminants are below a threshold of 0.5 mg protein per 100 g of food. This concentration is known to be below the threshold of most patients, and it can be technically guaranteed in most

food production. However, it was also important to assess that in case of accidental ingestion of contaminants below this threshold by highly allergic patients, no fatal anaphylactic reaction could occur. Therefore, we performed a systematic review to assess whether a fatal reaction to 5mg of protein or less has been reported, assuming that a maximum portion size of 1kg of a processed food exceeds any meal and thus gives a sufficient safety margin.

Methods: MEDLINE and EMBASE were searched until 24 January 2021 for provocation studies and case reports in which one of the 14 major food allergens was reported to elicit fatal or life-threatening anaphylactic reactions and assessed if these occurred below the ingestion of 5mg of protein. A Delphi process was performed to obtain an expert consensus on the results.

Results: In the 210 studies included, in our search, no reports of fatal anaphylactic reactions reported below 5 mg protein ingested were identified. However, in provocation studies and case reports, severe reactions below 5 mg were reported for the following allergens: eggs, fish, lupin, milk, nuts, peanuts, soy, and sesame seeds.

Conclusion: Based on the literature studied for this review, it can be stated that cross-contamination of the 14 major food allergens below 0.5 mg/100 g is likely not to endanger most food allergic patients when a standard portion of food is consumed. We propose to use the statement “this product contains the named allergens in the list of ingredients, it may contain traces of other contaminations (to be named, e.g. nut) at concentrations less than 0.5 mg per 100 g of this product” for a voluntary declaration on processed food packages. This level of avoidance of cross-contaminations can be achieved technically for most processed foods, and the statement would be a clear and helpful message to the consumers. However, it is clearly acknowledged that a voluntary declaration is only a first step to a legally binding solution. For this, further research on threshold levels is encouraged.

KEYWORDS

anaphylaxis, food allergy, nutrition

1 | INTRODUCTION

Allergic reactions to foods are a major health problem that has increased in prevalence in recent years and affects 5%–10% of the population in industrialized countries.¹ In children and adolescents, food allergy is common and considerably impacts the quality of life in these patients, as well as their families and caretakers.² In this age group, food allergens are also most commonly the cause of anaphylaxis, the most severe form of an allergic reaction. Although fatalities are rare, these reactions to food allergens are potentially life-threatening. Anaphylaxis elicited by food allergens is most commonly reported after unintentional ingestion of foods containing the relevant allergen.

While labeling food products with the 14 main allergens is mandatory in the EU, precautionary allergen labeling such as “may contain,” “may contain traces of” or “manufactured in a setting where ‘allergen’ is processed” is voluntarily placed by food manufacturers. The inconsistent food labeling approaches are met with the

uncertainty of consumers, among whose knowledge about the regulations and meaning of this labeling is largely missing.³ It also has implications for the manufacturers since consumers with a history of severe allergic reactions are less likely to buy food products with the current precautionary allergen label even though other products without precautionary labeling may contain the allergen in the same quantities and the same likelihood as the labeled product.³

The implementation of concentrations over which food allergen traces should be declared on the package would therefore be helpful for consumers as well as for manufacturers. The major problem is that the threshold for elicitation of allergic reactions against foods is different in different individuals. The vast majority of food allergic patients have no problems with contaminants and traces of the relevant allergen. For example, most pollen allergic patients with oral food allergy syndrome often only react to the pure cross-reacting food allergens if they are present in amounts above 1000 mg. On the other hand, there are some severely

affected food allergy sufferers, especially to peanuts with thresholds below 1mg. In addition, a true no observed adverse events level (NOAEL), as in cosmetic allergy, is not known for food allergens. In summary, this situation is unsatisfactory: overcautious reporting of potential contamination of allergens creates unnecessary fears in most food allergy sufferers and is not helpful. On the other hand, underreporting of potential contamination is endangering those severely affected by food allergies reacting to minimal amounts.

As this problem is internationally recognized, some national authorities have implemented threshold values over which food allergens have to be labeled on the package. Japanese authorities have decided on a threshold value based on the precision of ELISA test kits.⁴ As precision parameters of medical measurement equipment are subject to change, jeopardizing the scientific value of this rule, this approach is met with serious concerns. Switzerland obligates all food producers to list involuntary cross-contaminations above 1 g allergen per 1 kg food product as “may contain traces of ...”.⁵ The German authorities indicate that the threshold depends on the respective allergen.⁶ A similar approach is pursued in Australia and New Zealand, where there are no regulations regarding the mandatory declaration of unintentionally present allergens.⁷ The VITAL[®] (Voluntary Incidental Trace Allergen Labelling) program is a joint venture of Australia's leading food manufacturers and the Australian Food and Grocery Council (AFGC). It provides a standardized approach for assessment and declaration of food allergen contamination, recommending thresholds based on scientific data that has been processed in a stacked model averaging program using a range of statistical calculation models.⁸ However, this leads to modifying the thresholds for each allergen with every revision of the program. The aim is to protect the “vast majority of people with food allergy” and they state that below the thresholds, only 1% of allergic patients may develop an allergic reaction, this reaction however may be severe.^{9,10} The data processed must adhere to high-quality standards and to include only double-blind, placebo-controlled, food challenge studies.¹⁰⁻¹² While this is a very rigorous approach, some issues may cause bias. One is that especially severe allergic reactions are comparatively rare and are often published as case reports or case series only. As this form of study is considered low-quality evidence in medical science, such are not included in the data evaluated by VITAL. Therefore, it is likely that the most severe allergic reactions described in the literature are not included. Also, fatal reactions are not likely to happen while under clinical observation while unintentional ingestion of food allergen out of hospital may be more likely to lead to death and may be reported only in case reports. In this systematic review, an alternative solution for this dilemma is assessed.

Of course, it is acknowledged that some food allergy sufferers who have not undergone placebo-controlled tests may not know their thresholds but still may have a feeling for it based on previous experiences. Therefore, it would be beneficial to know that the allergens included in the food product do not exceed a certain level. However, this food contamination level, or concentration, needs to

be low enough to ensure that no life-threatening or fatal reactions have been observed at this level, but also one which can be easily measured with existing technologies in the food industry without increasing the cost of food production. Therefore, in this systematic review, we assess whether a level of 0.5 mg protein/100 g of food of allergenic protein would be less than the lowest published observed adverse effect level (LOAEL) for a fatal reaction. As portion sizes vary, a maximum portion size of 1 kg of processed food was assumed to exceed any meal and thus giving a sufficient safety margin. Therefore, we used 5 mg protein as a threshold in this investigation.

2 | METHODS

This systematic review was conducted according to the PRISMA guidelines for systematic reviews and meta-analyses.¹³ The review was registered on PROSPERO as CRD42018110170.

To find an acceptable threshold levels of allergen contamination in processed food that would benefit food allergy sufferers and would be feasible for the food manufacturers, the first talk was conducted on this topic at the BLL meeting of the allergens specialists committee that took place on 8 July 2019 in Berlin, Germany. The conference included representatives of the German food industry, including food technicians and food manufacturers. The main question was which level of food allergen contamination in processed food could be detected analytically and reproducibly in quality management of food production without increasing the price of the food? The level of 5 mg protein was discussed as it is a typical challenge dose in provocation studies. It was also discussed if voluntary labeling would be an option for food production companies. The discussion resulted in the proposal to use the concentration of 0.5 mg of protein per 100 g food as a threshold for voluntary declaration of allergen traces in processed food. In this systematic review, it was deemed mandatory that even if allergy sufferers would not know their personal threshold, that at this level, fatal reactions would have never been observed.

2.1 | Study eligibility

This systematic review includes provocation studies and case reports describing life-threatening anaphylactic reactions to one of the 14 main allergens in food products were reported. Main food allergens were defined in accordance with the European Union's Food Information Regulation No. 1169/2011: crustaceans, cereals containing gluten, eggs, fish, peanuts, soybean, milk, nuts (namely: almond, hazelnuts, walnuts, cashews, pecan nuts, Brazil nuts, pistachio nuts, macadamia, or Queensland nuts), celery, mustard, sesame seeds, sulfur dioxide and sulfites (*sensu stricto* and sulfites are not an allergen but known to induce intolerance reactions), lupin, and molluscs (Table 1). Anaphylactic reactions were considered life-threatening in case of a fatal outcome, potentially fatal outcome without intervention (ie, administration of epinephrine, severe dyspnea/asthma, loss of consciousness), positive

TABLE 1 Main food allergens according to the European Union's Food Information Regulation No. 1169/2011

| Allergen name | Including | Amount of protein per 100 g of food. |
|-----------------------------|--|--|
| Celery | | Celery root 2 g/100 g |
| Cereals containing gluten | Wheat (such as spelt and khorasan wheat), rye, barley, oats or their hybridized strains, and products thereof | Wheat 12 g/100 g Rye 9 g/100 g Barley 10 g/100 g Oats 12 g/100 g |
| Crustaceans | | Shrimp 19 g/100 g |
| Eggs | | 13 g/100 g |
| Fish | | Between 17-20 g/100 g |
| Lupin | | 40 g/100 g |
| Milk | | Cow's milk 3 g/100 g |
| Molluscs | | Mussel 11 g/100 g Cuttlefish 16 g/100 g |
| Mustard | | 6 g/100 g |
| Nuts | Almonds, hazelnuts, walnuts, cashews, pecan nuts, Brazil nuts, pistachio nuts, macadamia or Queensland nuts, and products thereof | Almond 19 g/100 g Brazil nut 14 g/100 g Cashew 18 g/100 g Hazelnut 12 g/100 g Macadamia 9 g/100 g Pecan nut 11 g/100 g Pistachio 18 g/100 g Walnut 14 g/100 g |
| Peanut | | 25 g/100 g |
| Sesame seeds | | 21 g/100 g |
| Soybeans | | Soybeans 38 g/100 g Soydrink 4 g/100 ml |
| Sulfur dioxide and sulfites | At concentrations of more than 10 mg/kg or 10 mg/L in terms of the total SO ₂ Sulfites are not an allergen but known to induce intolerance reactions | Not applicable |

shock index, and/or hypotension, and/or heart failure. Included studies and case reports had to give information on the approximate amount of ingested food, for example, "one bite." Publications had to be written in English. Animal studies were excluded.

There is also an abundance of scientific literature that is written in Spanish, French, German, and Japanese language for which quoted reviews in English exist.

2.2 | Search strategy and literature screening

MEDLINE and EMBASE electronic databases were searched via Ovid from their inception until January 2021. The exact search terms are presented in Appendix 1. Titles and abstracts of the retrieved references were screened by a team of three reviewers, duplicates were eliminated, and potentially relevant references were identified. A full-text review of the remaining references was performed. Studies in which relevance was unclear were discussed by the team

of reviewers. In addition, the bibliographies of included studies and case reports revealed by the search strategy were searched for eligible articles missed by the search strategy.

2.3 | Data extraction and analysis

Data regarding the type of ingested food, the approximately ingested amount of food, and the type of life-threatening anaphylactic reaction were extracted onto a predefined datasheet by the three reviewers. In addition, we searched and noted the usual concentration of allergenic protein for every food product used in the included provocation studies or described in the included case studies and calculated the amount of ingested allergenic protein. This process was verified by a registered dietitian. The studies were analyzed regarding the occurrence of life-threatening reactions and the reported amount of food protein provoking the reaction. Finally, the data were presented in a table and summarized narratively.

2.4 | Inclusion of authors and discussion with stakeholders

An open call for participation was made within the GA²LEN network, which includes EAACI and EFA as members. In addition, further patient organizations and other experts in the field of allergology and immunology were actively approached. Some non-GA²LEN members accepted the invitation. Participation was denied either due to a lack of time or stating a conflict of interest. A Delphi process was performed which included all participants. A consensus was obtained after two rounds of expert panel evaluations that took place on 10 October 2020 and 10 June 2021. The expert panel consisted of German patient organizations, the members of the CODEX alimentarius working group, food industry legal advisors, and food technologists. Additional data provided by the panel members were evaluated and included if eligibility of the study was given.

2.5 | Risk of bias

The approach that was used in this systematic review has a high level of evidence to suggest that at the concentration of 0.5 mg/100 g limited to no food fatal reactions will occur; however, there is a lower level of evidence regarding the no observed level threshold in severely affected allergy sufferers. This is based on the search string which will not find these provocation tests in which no life-threatening symptoms have occurred.

3 | RESULTS

The search in MEDLINE and EMBASE via Ovid yielded 3289 references, of which we included 90 provocation studies and 88 case studies. Figure 1 gives the PRISMA flowchart that presents an overview of the search results and study selection.

We analyzed double-blind, placebo-controlled provocation tests and case report different minimal threshold levels for different allergens. Some of the other 14 allergens, which must be declared in the European Union, such as mustard and molluscs, have not been reported as being the trigger of a severe allergic reactions at very low levels. Table 2 summarizes the findings from all studies included in this analysis that reported severe allergic reactions after ingestion of less than 5 mg allergen protein or where the ingested amount was unclear. In addition, a summary with all provocation studies and case reports included in this analysis is found in the Tables S1 and S2.

In a cohort of food allergic children used by Moneret-Vautrin et al.²³ for the evaluation of personalized care projects, 2 asthmatic reactions resulting from peanut protein amount lower than 5 mg have been described. However, the authors state in their paper that no fatal reactions were observed. One anaphylactic shock was observed in this study which occurred after ingestion of 965 mg peanut, which amounts to more than 240 mg protein.

Ebrahimi et al.²⁹ report respiratory distress after 3 drops of milk-based formula in one study subject who needed to be treated with epinephrine. They used BioMeal, Fassbel, Belgium, a formula which is no longer available. According to the EU regulations, infant

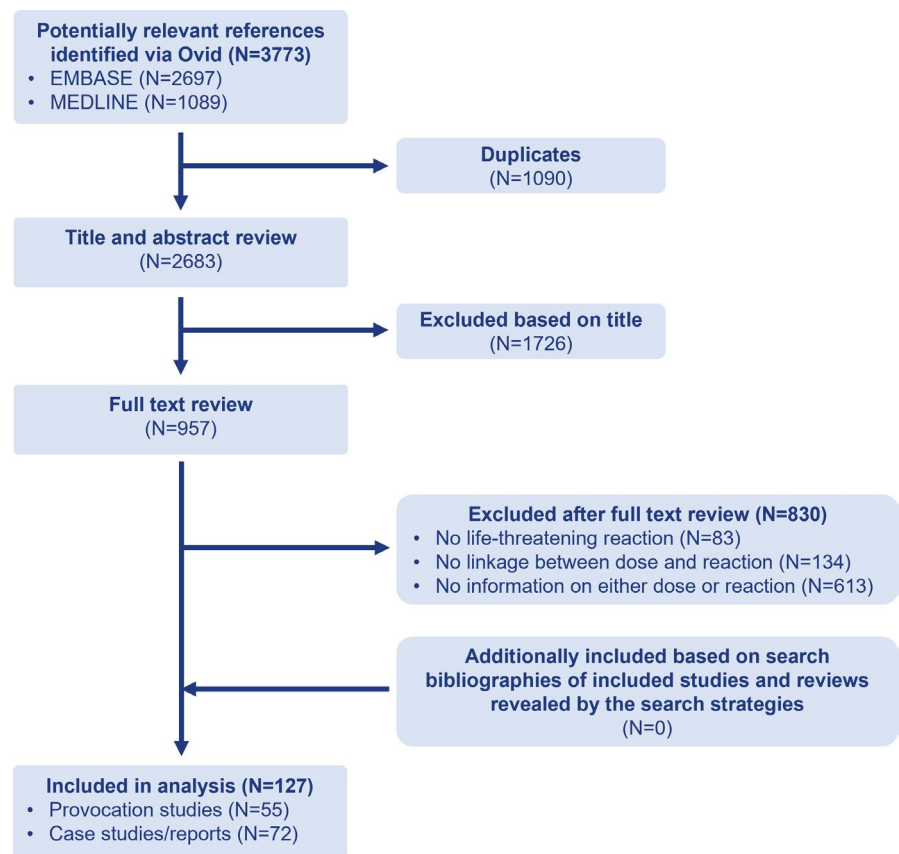


FIGURE 1 Search results and selection of studies

TABLE 2 Summary of data from provocation studies and case reports in which ingestion of less than 5 mg of allergen protein elicited a severe allergic reaction

| Allergen | Food product | Nature of life-threatening allergic reaction | No. of participants (no. experiencing a severe reaction) ^a | Amount of food that provoked a severe reaction | Amount of allergen protein (mg) that provoked a severe reaction | Study |
|------------|---|--|---|--|---|---|
| Cereals | No report found for reactions at or below 5 mg | | | | | |
| Celery | No report found for reactions at or below 5 mg | | | | | |
| Crustacean | No report found for reactions at or below 5 mg | | | | | |
| Egg | Mortadella | abdominal pain, throat itching, vomit, dyspnea | 1(1) | Mortadella 25 mg | 0.0503 | Tripodi et al. 2009 ¹⁴ |
| Fish | Fish | Asthma or mild anaphylaxis | 1(1) | Fish 8 mg | 1.36 | Lefevre et al. 2016 ¹⁵ |
| Lupin | Short crust pastry containing lupin flour as minor ingredient | asthma | 2(1) | Small amount | Not determinable | Bansal et al. 2014 ¹⁶ |
| Milk | Cow's Milk | Asthma or mild anaphylaxis | 5 | CM <0.05 mg | 0.0015 | Lefevre et al. 2016 ¹⁵ |
| Milk | Cow's milk | Systemic symptoms | | Even traces | Not determinable | Poza-Guedes et al. 2014 ¹⁷ |
| Milk | Cow's milk | | 10(?) | Trace amounts | Not determinable | Paiva et al. 2009 ¹⁸ |
| Milk | Cow's milk | Syncope, hypoxia, and drop in blood pressure treated with epinephrine | 1(1) | Accidental ingestion of trace amounts | Not determinable | Lisann et al. 2014 ¹⁹ |
| Milk | Cow's milk | Syncope, hypoxia, and drop in blood pressure treated with epinephrine | 1(1) | Accidental ingestion of trace amounts | Not determinable | Lisann et al. 2014 ¹⁹ |
| Molluscs | No report found for reactions at or below 5 mg | | | | | |
| Mustard | No report found for reactions at or below 5 mg | | | | | |
| Nut | Cashews (Placed in same jar as walnuts) | loss of consciousness | | Some nuts +febrile infection | Not determinable | Laliotou et al. 2018 ²⁰ |
| Nut | Pinon nut (SPT extract) | dyspnea | | One drop cutaneously | Not determinable | Sindher et al. 2015 ²¹ |
| Nut | Walnut | Acute anaphylactic reactions including angioedema, dyspnea, and cyanosis | 1(1) | Trace amount | Not determinable | Noh et al. 2009 ²² |
| Peanut | Peanut | Asthma | 33(1) | 15 mg | 3.75 | Moneret-Vautrin 2001 ²³ |
| Peanut | Peanut oil | Asthma | 33(1) | 5 mL | Not determinable | Moneret-Vautrin 2001 ²³ |
| Peanut | Peanut oil | Asthma and/or FEV ₁ , vomiting and/or abdominal pain | 103(6) | 5 mL | Not determinable | Morisset et al. 2003 ²⁴ |
| Peanut | Peanut oil | Asthma | 62(14) | 5 mL Peanut oil | Not determinable | Moneret-Vautrin et al. 1998 ²⁵ |

TABLE 2 (Continued)

| Allergen | Food product | Nature of life-threatening allergic reaction | No. of participants (no. experiencing a severe reaction) ^a | Amount of food that provoked a severe reaction | Amount of allergen protein (mg) that provoked a severe reaction | Study |
|----------|--|---|---|--|---|-------------------------------------|
| Peanut | Peanut dust | Severe anaphylaxis treated with epinephrine | 1(1) | Peanut dust sprinkled on meal | Not determinable | Robertson et al. 2017 ²⁶ |
| Sesame | Sesame seed oil | "Anaphylactic shock" | 12(1) | 1 mL | Not determinable | Morisset et al. 2003 ²⁴ |
| Sesame | Sesame seed | Throat closure, generalized urticaria, and vomiting | 1(1) | 5 seeds | 3.15 | Dua et al. 2011 ²⁷ |
| Soy | Soy milk | "Systemic reaction" | 2(1) | 0.01 mL | Not determinable | Hudes et al. 2019 ²⁸ |
| Sulfites | No report found for reactions at or below 5 mg | | | | | |

Note: Fatal reactions were not reported at all at this level.

^aTotal number of participants in the study mentioned, while number in brackets give the number of participants experiencing the reaction described. If no number is given, only the total number of participants is listed.

formula may contain 1.08–3.6 g protein/100 ml³⁰ provided correct preparation. The volume of a "drop" depends on the viscosity of the liquid, however, in pharmacy and medicine, a drop is generally defined as being 0.05 mL. The amount ingested may therefore range between 1.6 mg and 5.4 mg, although given that the formula is no longer on the market, the protein content cannot reliably be verified. We therefore do not know the amount of milk protein which resulted in the described reaction. The same holds true for the reaction described by Hudes et al²⁸ which reported a "systemic reaction" to 0.01 ml of soy milk. However, the amount of soy protein differs widely between the different brands of soy milk, so the exact amount ingested by the patient is not determinable. Furthermore, the authors do not describe the systemic reaction in detail and any life-threatening potential cannot be determined.

Tripodi et al¹⁴ report a case of a 11-year-old with egg allergy developing dyspnea after ingestion of a mortadella sandwich. They analyzed the mortadella and found the reactive amount being 0.45 mg hen's egg, which would mean a protein content of 0.05 mg. They did, however, not analyze the other components of the sandwich so there is no way to know if this is the real threshold dose.

Dua et al. describe one patient who experienced "throat closure" after ingestion of 5 sesame seeds. We weighed different sesame seeds on a high precision scale and found an average of 15 mg per 5 seeds, and could determine that 5 seeds contain approximately 3.15 mg sesame protein. However, the patient was not treated with epinephrine but with oral antihistamines and intravenous hydrocortisone only,²⁷ excluding the likelihood that treating physicians regarded it as a truly life-threatening situation.

Both, Morisset et al.²⁴ and Moneret-Vautrin et al.²⁵ described potentially life-threatening reactions after the ingestion of sesame or peanut oil. As the protein content of oil varies considerably and protein amounts have not been measured for the oils used, it is not possible to determine an amount.

Houri-hane et al.,³¹ Leung et al.,³² and Lefevre et al.¹⁵ list reactions to allergenic amounts <5 mg, but do not describe them further. Therefore, those reactions cannot be evaluated further to determine their life-threatening potential, which is acknowledged to be a problem. The same holds true for the following reports where no amounts are stated, with one of them being however a clear outlier. Robertson et al.²⁶ report on a criminal case where a wife spread peanut dust on her husband's meals. It can be expected that the amount was more than 5 mg protein. Poza-Guedes,¹⁷ Paiva,¹⁸ and Lisann¹⁹ report potentially life-threatening reactions to accidental ingestion of trace amounts of cow's milk. As the amounts are not specified, it is not possible to determine the allergenic threshold. Laliotou²⁰ and Noh²² also state "trace amounts" as triggering an anaphylactic reaction to nut. Again, the missing quantification does create a problem and it is possible that a whole nut has been ingested.

The same holds true for the report of Bansal et al.¹⁶ where a "small amount" of lupin flour in short crust pastry triggered a reaction.

Levin et al³³ described the case of a 9-month-old child reacting with episodes of asthma, vomiting, and urticaria after ingestion of a soy formula which was contaminated with 32.4 mg milk protein

per liter. Here, it is unclear how much of the formula was administered but if it were the typical amount of one bottle containing 150–200 ml, this would be most likely more than 5mg, and furthermore, it is unclear if the reactions were life-threatening.

Yunginger et al.³⁴ reported 7 fatal cases, 6 of whom had eaten at least “one bite” but mostly one cookie or one piece of cake, without further specification of the amount of the relevant allergen. In one case of a fish allergic patient, French fries had been consumed, which other guests reported tasted of fish. Unfortunately, there is no way to estimate in this case, as it is unclear if the reaction was due to the sauce offered with the fries.

Azmi et al.³⁵ describe two cases of allergic reactions to vegan ice cream containing lupin flour, one of them potentially life-threatening. The amount of lupin flour is however not stated and is likely more than 5 mg protein since vegan ice cream usually has lupin flour as the main ingredient.

4 | DISCUSSION

4.1 | Interpretation of results

Remarkably, none of the case reports or provocation tests in a clinical setting reported a LOAEL, the lowest ingested dose at which there was an observed adverse effect, less than the evaluated threshold of 0.5 mg protein/100 g of food, to cause a life-threatening or even fatal reaction. The case reports have revealed 8 cases of fatal food allergy reactions, however, all at higher levels than 0.5mg/100 g of food. Looking at the list of the 14 different allergens which need to be declared (celery, cereals containing gluten (such as barley and oats), crustaceans (such as prawns, crabs, and lobsters), eggs, fish, lupin, milk, molluscs (such as mussels and oysters), mustard, peanuts, sesame, soybeans, sulfur dioxide, and sulfites), the following statements can be made:

No severe reactions to trace amounts of molluscs or mustard have been reported.

Sulfite is added as an allergen in the list; however, sulfite is in reality a cause for pseudoallergic reactions. Life-threatening or fatal reactions against sulfites were never reported at all. Still, it is important to also look at sulfite as severe asthmatic reactions have been described in a single report with a threshold of 50 mg.

No severe reactions have ever been reported to low amounts of any other allergen that is not listed in the 14 which have to be declared according to the EU regulations.

No fatal reactions have ever been reported with levels clearly documented below 5mg of protein for any allergen.

In a small subset of patients allergic but not life-threatening reactions can occur at levels below 5mg of protein.

The most important finding of our search is that no fatal allergic reactions to food were reported below an estimated amount of 5 mg protein.

Any interpretation of the results regarding the reporting bias should differentiate case reports of accidental reactions and

provocation tests. They differ regarding the accuracy of determining the amount of allergen ingested and in classifying the reaction as “life-threatening.” While case reports are very valuable, as they usually represent more accurately everyday life situations in which allergic reactions to food occur, the determination of the exact amount ingested allergen is difficult and additional cofactors like exercise, alcohol, or sleep deprivation may have influenced the manifestation or outcome of the reaction.³⁶ Furthermore, case reports depend partly on chance because the author has to decide if it was worth publishing. An underreporting is therefore possible but less likely for fatal cases.

For the second uncertainty, the amount of food ingested, there is a potential bias of patients tending to mention smaller amounts than truly eaten. In daily practice, a phenomenon often observed is that patients feel “guilty” and try to explain with statements such as “I hardly took a bite.” Still, as stated in the methods section, the overestimation of allergen amounts was chosen generously in case reports to avoid false low assumptions leading to inappropriate reassurances. Similarly, it should be mentioned that for any ingested nut or seed that was reported in the literature, in this review, we considered the amount of the nut or seed ingested which is definitely greater or equal to the amount digested, therefore once again having potentially a slight overestimation of the total allergen protein amount, this provides a greater safety margin.

Regarding classification accuracy, the courses of actions triggering the label “life-threatening” may be more reliable in the out-of-clinic setting. Particularly when looking at the injection of epinephrine, which in our methodology categorized the case as potentially fatal, there may be great differences between case reports and provocation studies. Many studies have shown that the psychological barrier of injecting adrenaline is very high in food allergic patients and their caretakers,³⁷⁻³⁹ resulting in a delay or an omission of intramuscular epinephrine administration.

On the other hand, handling epinephrine is routine in the clinical setting. Since those undergoing a provocation test are monitored closely, the first signs of an anaphylactic reaction will generally be noticed earlier and trigger counteractive measures, which will influence the natural course and disguise the severity of the allergic response. For example, epinephrine may be administered in cases where no life-threatening reaction would develop.

Despite the potential over-estimation in the severity of reactions in our study, categorizing all events in which epinephrine was administered as “life-threatening” increases safety, albeit at the expense of accuracy.

In accordance with the findings in this review, a cross-sectional study of food allergy prevalence in the population of Berlin by Zuberbier et al. revealed that in all open challenge tests, no adverse reaction occurred at the level of 5mg of protein.⁴⁰

However, a study by Ballmer-Weber et al., not included in the review as it did not meet all eligibility criteria, found estimated doses eliciting reactions in 10% of the study population (ED10), as low as 1.6 to 10.1 mg of protein for hazelnut, peanut, and celery.⁴¹ It should be noted that one limitation of this review is the defined search

criteria that may have excluded a few other publications that may contain further data regarding allergen tolerance thresholds.

This systematic review revealed that 0.5 mg/100 g as a threshold value for traces of allergens in processed food is generally a safe level for avoiding any allergic reaction to at least 6 of the 14 major allergens, even in the unlikely maximum portion size of 1 kg. Even for those allergens, a 0.5 mg/100 g threshold is highly likely to be a safe level below which fatal allergic reactions will not occur. Depending on the portion size, this level is also beneficial for the rare severely affected patients. For example, if a patient knows their personal threshold level is 2 mg they can still safely eat a portion of 100 g. However, the vast majority of all food allergic patients have a much higher threshold level for the elicitation of reactions. Very few individuals will experience symptoms below this level. Our finding of the level of 0.5 mg/100 g of food, 100 g of food being a common portion size, is in accordance with the FAO-WHO expert group recommendations on allergen thresholds, published on 20 August 2021.¹²⁰

Based on these results, 5 mg/100 g of food is a concentration that can be used in the food industry as the safety level for most food allergy sufferers. The advantage of 5 mg/100 g of food is that it can be readily detectable for all 14 food allergens with the currently existing technology. In addition, avoiding contamination at this level should be technically feasible for the food industry as the feasibility has been discussed at three different meetings with food technologists and analytical laboratories. Rare exceptions may occur if machinery is difficult to clean. For example, pieces of nut in chocolate may be a problem, as the allergen is not evenly distributed in the food matrix.

There has also been a lot of discussion with different patient organizations which would prefer to have legally binding legislation regarding the declaration of food allergen contaminants as it remains an unmet need. However, we view the voluntary declaration as a positive direction that would benefit food allergy sufferers and their families.

Such a declaration would not only help all food allergic patients who have a known threshold above 5 mg, but it would be also helpful to the family of those patients who have anaphylaxis against allergens at levels of <1 mg, to purchase processed foods for the household, as they would be informed that the food allergic family member would not be endangered if products with possibly such low concentrations of contaminants would be used within the household. The current situation is that often the whole family of severely food allergic patients is afraid to buy any processed food at all.

In addition, physicians, dietitians, and nutritionists could better advise patients about their risk level in daily practice. This of course is mandatory for the exceedingly rare patients described in the literature who react below 5 mg protein. They should be counseled about which processed food, in general, they should avoid.

We propose as a voluntary labeling for the European Union that no traces of the 14 main food allergens in a given processed food are above 0.5 mg/100 g, together with a warning that traces below this level can occur but are likely not harmful. This message can improve the situation where manufacturers often state on the packages that

traces can be contained without stating the amount of the trace, that the product has been processed in a facility which also processed, for example, peanut products. Both kinds of information are more for the sake of the producer to keep away from liability issues than for the true benefit of the consuming patient who wants to know the exact levels. The 0.5 mg/100 g level, as a clear statement on packages, would cover the vast majority of food allergic patients.

Finally, this proposal has been discussed with the food industry authorities and a statement that it is regarded as positive has been received, found in Appendix 2.

5 | LIMITATIONS

There are limitations that should be noted in the interpretation of the present work. First, due to the defined literature search query, there may be some available literature that was not identified in this review, and therefore, the data were not taken into consideration. An example would be publications on immunotherapy trials where low doses of allergen caused reactions, but they were not reported as life-threatening or fatal. Due to the large volume of hits obtained from the first round of literature screening, the publications were screened based on their title and abstract; therefore, it is possible that some data included only in the text were overseen. Also, large number of studies which were found by our search strategy did not report direct relation of the amount of allergen ingested to the observed reaction, therefore, a lot of data addressing food anaphylaxis could not be included in our analysis. It should also be taken into account that we relate to the amount of allergenic protein ingested. If the information was not reported by the investigators, it was calculated based on the usual protein content of the food product used in the provocation test or reported in the case report. Despite the careful evaluation and supervision of a professional dietitian, it cannot be ruled out that the amounts given differ from actual amount of protein ingested. It should also be mentioned that the screening of the data was done by the reviewers separately, data of uncertain relevance however was discussed by all three reviewers. Lastly, the summary of case reports may give the impression that in most cases the dose amount is unknown, suggesting that the information is incomplete and insufficient. As case reports are a valuable data source of real-life situations, it is an unmet need to standardize the investigation and tracking of fatality in food allergy.

6 | CONCLUSIONS

No fatal reactions have been reported below 5 mg of protein exposure in food allergic patients. The individual eliciting threshold differs considerably between patients, but the vast majority of patients do not react at levels below 5 mg of protein. For these patients, it would be helpful to know that contamination with allergens in processed food does not exceed this level. Looking at a further safety margin, it is therefore proposed that 5mg/kg of contaminating

allergen in processed food is not exceeded acknowledging that the usual portion size is far lower than 1 kg.

The labeling could read as follows: "this product contains the named allergens in the list of ingredients, it may contain traces of other contaminants (to be named, e.g. nut) at concentrations less than 0.5 mg per 100g of this product" for a voluntary declaration on processed food packages.

We further see this only as a first step as legally binding thresholds would be preferred. The authors however feel that realistically it would take a long time before this will be implemented on a global scale, and in the meantime, the more precise the labeling is the better.

Furthermore, we conclude that also this review is only a first step in research concentrating on a threshold to avoid fatal reactions, more research is needed to identify thresholds for milder symptoms of food allergy.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Additional supporting information may be found in the online version of the article at the publisher's website.

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