



Food labeling issues in patients with severe food allergies: solving a hamlet-like doubt

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Purpose of review

We review the laws on labeling in the international community, the difficulties they pose to the food manufacturers to prepare the food labels and the methodologies to determine the concentration of potential allergens in foods.

Recent findings

European Food Safety Authority and International Life Sciences Institute Europe are evaluating strategies to identify the threshold level of allergen that can trigger a reaction in individuals. The most used techniques to detect the presence of protein in food are Enzyme-linked immunosorbent assay, polymerase chain reaction and real time polymerase chain reaction. Researchers are now trying to apply proteomics to estimate the amount of protein within the food.

In order to protect the health of consumers, the Codex Alimentarius Commission updates constantly the list of allergens. In response to these regulations, some industries have also added some precautionary allergen labeling (PAL). It was generally agreed that PAL statements needed to be visible, simple, and safe. It was suggested that PAL be standardized, an action that would occur if the 'Voluntary Incidental Trace Allergen Labelling' process was made mandatory.

Summary

So far, no laboratory technique is able to reassure the consumers about the composition of foods found on the packaging. International authorities produced increasingly stringent laws, but more is still to do.

Keywords

food allergy, labeling, prevention

INTRODUCTION

Food allergy affects 2% to 10% of the population [1], and there is well-founded fear that the epidemic is in large increase [2]. A fraction of food-allergic patients is sensitive to minute amounts of foods [3]. This implies that every day people suffering from food allergies and parents of allergic children are facing a Hamlet-like question regarding food: 'Is this safe?' Answering this question entails at least some knowledge of labeling of fresh, processed, or prepackaged foods, as accidental ingestion of food allergens because of labeling ambiguities is a preventable risk.

Building on recent reports of reactions in severe food allergy, we review here various food labeling issues.

LAWS ON LABELLING IN FORCE IN THE INTERNATIONAL COMMUNITY

The Codex Alimentarius Commission, established in 1963 by Food and Agriculture Organization of the

United Nations and the World Health Organization in order to protect the health of consumers and to ensure the fairness of international trade, updates constantly the list of allergens encouraging government entities to produce efficient regulations of labeling [4]. The current laws in force in the various international communities (Fig. 1).

EUROPE

In the European Union, the labeling directive issued in September 2001 and the following Directives 2003/89/EC and 2006/142/EC require 12 food items

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Curr Opin Allergy Clin Immunol 2017, 17:204–211

DOI:10.1097/ACI.0000000000000362

KEY POINTS

- The Codex Alimentarius Commission in order to protect the health of consumers and ensuring the fairness of international trade, updates constantly the list of allergens encouraging government entities to produce efficient regulations of labeling.
- In response to these regulations, some industries have also spontaneously added some precautionary allergen labeling (PAL).
- Researchers are now trying to apply proteomics techniques to estimate the exact amount of protein within the food.

to appear on the label of prepackaged foods: cereals containing gluten, crustaceans, egg, fish, peanut, soy, milk (including lactose), nuts, mustard, sesame seeds, celery, and sulfites >10 mg/kg. These rules ensure that all consumers receive comprehensive ingredient listing information and make it easier for people with food allergies to identify ingredients they need to avoid. This legislation eliminated many of the problems with unlabeled hidden allergens in the prepackaged food supply. In particular, the risk that unfamiliar names can hide allergenic foods is now minimized, as for instance 'starch' has been replaced by 'corn starch' or 'wheat starch'; 'Lysozyme' has been replaced by 'lysozyme, containing egg,' and so on.

Following implementation of the Food Information for Consumers Regulation (EU) No. 1169/2011 [5], allergen-labeling rules changed in December 2014. The new regulation builds on allergen labeling provisions for prepacked foods and introduces a new requirement for allergen information to be provided for foods sold nonpacked or prepacked for direct sale. With the addition of lupin and mollusks, 14 recognized allergens must now be indicated. The food allergen must be highlighted through a typeset that clearly distinguishes it from the others, for instance with recognizable font, style, or background color. Thus, food sold in retail and catering outlets must now report the information on allergenic ingredients. In order to produce correct labels, traders can use online-dedicated software. This legislation is protective of the consumers, but some problems still exist with precautionary allergy labeling (*see infra*) [6].

UNITED STATES OF AMERICA

In the United States, the Food Allergen Labelling and Consumer Protection Act of 2004 [7] defined a major food allergen 'one of eight foods or food groups' and 'any ingredient that contains protein from one of these foods or food groups': milk, egg, fish, crustacean shellfish, tree nuts, peanuts, wheat, and soybeans. Food that contains an undeclared major food allergen is misbranded under the U.S. Food, Drug, and Cosmetic Act and is subject to

Allergens	Europe	Australia - New Zealand	United States	Canada	South America	China	Japan	South Korea	South Africa
Crustaceans	x	x	x	x	x	x	x	x	x
Egg	x	x	x	x	x	x	x	x	x
Fish	x	x	x	x	x	x		x	x
Milk	x	x	x	x	x	x	x	x	x
Peanut	x	x	x	x	x	x	x	x	x
Soy	x	x	x	x	x	x		x	x
Tree Nuts	x	x	x	x	x	x			x
Wheat	x	x	x	x	x	x	x	x	x
Cereals with gluten	x	x		x	x	x			
Buckwheat						x	x	x	
Celery	x								
Lupin	x								
Shellfish	x	x		x		x			x
Mustard	x			x					
Sesame	x	x		x					
Sulfites	x	x	x	x	x				
Propolis		x							
Royal jelly		x							
Peach								x	
Pork								x	
Tomato								x	

FIGURE 1. Labeling requirements for food allergens in Countries.

recall. Food allergen labeling problems are the most common cause of recalls for US FDA-regulated food products. To help understand why food allergen recalls continue to occur at a high rate, information on each food allergen recall that occurred in fiscal years 2007–2012 was obtained from the FDA recall database. This information was analyzed to identify the food, allergen, root cause, and mode of discovery for each food allergen recall [8]. Bakery products were the most frequently recalled food type, and milk was the most frequently undeclared major food allergen. Use of the wrong package or label was the most frequent problem leading to food allergen recalls. These data are the first reported that indicate the importance of label and package controls as public health measures.

SOUTH AMERICA

In South America, the South American Common Market, known as Mercosur, represents Brazil, Argentina, Uruguay, Paraguay, and Venezuela. While these nations do have their own regulatory systems in place, many of their food standards are gradually being replaced by official Mercosur standards as they are developed. In Argentina and Brazil, food additives are regulated under Mercosur standards (GMC 11/06, 34/10 and 35/10). For new food additives, applicants must submit to the Comisión Nacional de Alimentos or Agência Nacional de Vigilância Sanitária (for Argentina and Brazil, respectively), which will subsequently forward the application to Mercosur's Sub Work Group #3. In a scenario of demand of society, after public actions by consumers, the Brazilian national agency of sanitary surveillance (Agência Nacional de Vigilância Sanitária) published in 2015 the resolution of the Collegiate Board (DRC) no. 26/2015, reporting the requirements for compulsory labeling of the main foods that cause food allergy. Wheat, rye, barley, oats, and their hybridized strains; crustaceans; eggs; fish; peanuts; soybeans; milk of all species of mammals; almond, hazelnut, chestnut-of-cashews, Brazil nuts, macadamia nuts, Brazil nuts, Pecans, pistachios, pine nuts, chestnuts, and natural latex are listed [9].

AUSTRALIA AND NEW ZEALAND

Australia New Zealand Food Standards Code requires that, if the products contain any of the nine key allergens or allergen groups (peanuts; tree nuts; soy; milk; egg; cereals; crustacean, fish (including shellfish); and sesame), or derivatives of them, allergens must be declared on label.

Food allergen information is included in the ingredient list in common language consumers will understand, for example, 'milk' rather than 'sodium caseinate.' Some food labels say 'may contain' certain allergens, such as 'may contain nuts.' These are voluntary statements made by a food manufacturer and are not regulated by the Food Standards Code. The Allergen Bureau has produced guidance for the food industry in respect to 'may contain' statements and the management of allergen cross-contamination. Australia is the first country to set an industry standard around precautionary allergen labeling (PAL) in an attempt to standardize assessment and communication of risk to allergic consumers [10].

JAPAN

Handbook for agricultural and fishery products: 2009 Import Regulations (Handbook for Agricultural and Fishery Products Import Regulations 2009) contains specific provisions for the labeling of food in Japan [11].

Foods containing wheat, buckwheat, eggs, milk, peanuts, shrimp, and crabs are subject to regulated labeling.

It must be compulsorily reported the presence among the ingredients

Foods containing soy, chicken, pork, beef, mushrooms, apple, peach, orange, banana, potato, Actinidia (kiwi), walnut, gelatin, mollusks (squid, abalone), salmon eggs, and fish (salmon, mackerel)

- (1) are considered less risky.
- (2) are subject to further scientific insights.
- (3) are not subject to the obligation of reporting among the ingredients.

It is not allowed to show on the label the possible presence of allergens

Cross-contamination, so they are prohibited phrases like 'May contain Traces' (Foods may Contain), and so on.

When they contained as main products expensive ingredients such as salmon eggs or fungi, it is not possible to emphasize its presence.

POPULAR REPUBLIC OF CHINA

Two government rules for food labeling active in China: the China National Standard GB7718–2011 General Rule for the Labelling of Prepacked Foods (GB 7718–2011), active from 20 April 2012, and the China National Standard GB28050–2011 General Rule for Nutrition labeling of Prepacked foods (GB 28050–2011) who entered into force on 1 January 2013.

Vinegar, salt, sugar, and monosodium glutamate may be exempted from the presentation of the information of the quality guarantee period, together with alcoholic beverages that contain more than 10% by volume of alcohol (1.2% in Europe). When the maximum label area is less than 10 cm², only the name of the food are requested, its net quantity, the name and address of the manufacturer (or distributor). In Europe, the law requires in such case designation, allergens, net quantity, date of minimum durability and the expiration date [12].

PRECAUTIONARY ALLERGEN LABEL

In response to these regulations, some industries have also spontaneously added indications that may appear on the labels aiming to increase the consumers' safety and put the manufacturing company away from possible legal problems. The endorsement may be different: for example in the United Kingdom, the term is 'must not be used in people allergic to ... (allergen)'; Canada 'may contain ... (allergen).' In Europe and the United States, there are three main variants:

- (1) may contain ... (allergen).
- (2) product or plant in which it is used ... (allergen).
- (3) product or not separate food chains, which is also on trial ... (allergen).
- (4) contains trace of ... (allergen).

The use of 'traces' terminology in PAL is counterproductive: either allergic consumers consider themselves to be less allergic (or better, react to a higher threshold than that in a 'trace') and so ignore PAL, or consider themselves to be so allergic that 'even a trace' could cause a potentially life-threatening allergic reaction. The reality is that fatal allergic reactions occur following exposure to significant quantities of allergen and not 'traces.' Both extremes are unhelpful, reducing self-efficacy and confidence in managing an appropriate level of dietary avoidance [13].

Precautionary labeling has become widespread. However, such warnings are applied in an inconsistent manner and are not always reflective of either the likelihood of allergen contamination or a clinical reaction. As a result, consumers with food allergy are confused about ingredients contained in commercial food products [14]. Many of them consider information to be unclear or insufficient, leading to personal stress and feelings of insecurity and potential risk taking. In addition, there is confusion about interpretation of precautionary labels among health professionals who provide allergic consumers with advice on how to manage their condition. For

instance, up to 40% of consumers believe that PAL depends by law [15]. To discipline it, some countries are attempting to issue specific regulations (Table 1).

Further confusion may be added by the practice of overlabeling. As an example, the requirement of labeling lactose as allergenic for cow's milk allergic individuals contradicts the fact that this sugar has never been reported to determine allergic reactions after ingestion among children with cow milk allergy [31]. In the case of mustard, it should be the only member of the *Brassicaceae* family to be labeled both in European Union and in Canada. Yet, in the explanatory documents, Health Canada warns consumers with mustard allergy to avoid consuming other members of the *Brassicaceae* family such as broccoli, cauliflower, cabbage, Brussel sprouts, turnip and rapeseed 'as these have the potential to trigger an adverse reaction' [32]. In addition, in its Scientific Opinion on the safety of 'rapeseed protein isolate' as a novel food ingredient, the European Food Safety Authority reassured on the toxicological aspects, but stated, '...the risk of sensitization to rapeseed cannot be excluded and it is likely that rapeseed can trigger allergic reactions in mustard allergic subjects' [33]. Should this kind of over-precautionary labeling be implemented, the quality of life of food-allergic patients would be heavily affected [34].

In a recent Australian consensus, it was agreed that PAL statements needed to be clearly visible, simple to understand, reliable and safe [35]. Importantly, they needed to clearly indicate identified risk levels. A motion was raised to incorporate into the labeling an element that would identify safe foods for allergy affected individuals. It was suggested that PAL be standardized, an action that would occur if the 'Voluntary Incidental Trace Allergen Labelling process was made mandatory. This is an important step as there is evidence to suggest that current labeling is resulting in consumers taking unnecessary risks when purchasing foods or unnecessarily limiting their diets.

The diversity of the ethnic background, education, and literacy levels of the food-allergic consumer adds to the challenge of this process. One of the other major challenges of Voluntary Incidental Trace Allergen Labelling and PAL (in its current form in Australia) is that foods that have been through a risk assessment process are not labeled as such. Therefore, the consumer has no way of knowing whether a food that does not bear a PAL statement has been tested and deemed safe or whether it has been through a risk assessment process at all [35]. Studies on thresholds in populations of food allergy sufferers, and case reports, may be useful to get a precise idea of the minimum possible eliciting dose.

Table 1. Presence and regulation of additional/precautionary labeling on prepacked foods

	Precautionary labeling			'Contains...' labeling permitted	'Legislation on allergen disclosure implemented since...
	In use?	Is use regulated?	Risk-based approach, using thresholds?		
Argentina [17]	No	Use is prohibited	No	Yes and may be used as an alternative to precautionary labeling to indicate potential cross-contamination	2010
Australia/New Zealand [10]	✓	No	Voluntary. Thresholds vary with allergen	✓	2002
Canada [18]	✓ (specific phrasing recommended)	No	No	✓	1994
Chile [19]	✓	No	No	Yes and can be used to indicate risk from cross-contamination. NB free-from labels prohibited	2010
China [20]	✓	No	No	✓	2012
European Union [21]	✓	No	No	No longer permitted from December 2014	2003
Hong Kong [22]	✓	No	No	✓	2004
Japan [23]	NO	Use is prohibited	>10 ppm requires mandatory disclosure for all allergens	Yes, only for allergen present in >10 ppm	2002
Kuwait/Gulf [24]	✓	No	No	✓	2008
Malaysia [25]	✓	No	No	✓	2009
Mexico [26]	✓	No	No	✓	2010
Singapore [27]	✓	No	No	✓	2011
South Africa [28]	✓	Yes ^a	No	✓	2012
South Korea [29]	✓	No	No		2004
Switzerland [30]	✓	Precautionary statements can only be used for noningredients above 1 g/kg	Any allergen (whether 'ingredient' or not) above 1000 ppm requires disclosure	✓	2002
USA [7]	✓	No	No	✓	2006

^aLegislation requires use of precautionary labeling to be substantiated by a documented risk assessment demonstrating adherence to GMP. Reproduced with permission from [16].

CLINICAL REPORTS OF REACTIONS IN SEVERE FOOD ALLERGY

Food-induced anaphylaxis is responsible of fatalities among allergy sufferers [36], and avoiding the offending food is the main way for the management of this risk. However, even those who are very careful could experience a food-induced reaction.

A 30-year-old European woman, allergic to lupin, developed anaphylaxis after eating a pepper and lemon chocolate. The labeled ingredients were cocoa, soy lecithin, milk, egg, sugar, sorbitol, honey, lemon essence, cayenne pepper, and unspecific flour. The manufacturer denied the use of lupin in both the pepper and lemon chocolate and other

foods processed nearby. The immunological study revealed full cross-reactivity of the patient's serum with both lupin and chocolate extracts. As the patient had experienced the reaction after the ingestion of an 'unconventional' chocolate, and had previously developed mild self-limited urticaria, clinical reactivity to lupin, and its potential severity where evaluated at double-blind placebo-controlled food challenge. The dose that elicited the reaction during the challenge was within the range previously reported for lupin. In this case, lupin behaved as a hidden allergen. As Lupin is among the 14 food allergens subject to obligatory food allergen labeling in Europe, this

report reveals that – despite current regulation – some manufacturers do not report the presence of it as an ingredient. It emphasizes the need for adequate control of food production, manipulation, and labeling processes [37].

Masked allergens in processed foods are sometimes responsible for ‘idiopathic’ anaphylaxis because of the lack of full ingredient labeling. Patients, even if they are aware of a specific hypersensitivity, may be unaware of trace amounts of the offending allergen(s) that are present in these products. A 2-year-old milk-allergic experienced multiple generalized reactions after ingestion of ‘pareve’-labeled raspberry sorbet. It was discovered that milk was incorporated into the sorbet when equipment used to package ice cream had been used to package the sorbet. The milk allergen level in three independently purchased containers of sorbet ranged from 2% to undetectable. The presence of milk in three of four of the sorbets was confirmed by immunoblotting studies, by quantitation of milk proteins by polyacrylamide gel electrophoresis, and by quantitation of lactose by gas chromatography [38]. A 38-year-old woman experienced an anaphylactic reaction 20 min after eating ‘chicken dips’ in a fast food restaurant. Again, an undeclared food allergen (mustard) was masked in ‘chicken dips’ [39].

A 10-year-old Japanese boy, allergic to apple, developed anaphylaxis after eating rose-flavored soft-serve ice cream. He tested negative for rose essence and Food Red No. 2, the ingredients declared in the recipe. However, it was found that red rose syrup contained apple juice. A prick-prick test for apple returned strongly positive to apple, thus identified as the cause of anaphylaxis [40].

THRESHOLDS OF FOOD REACTIONS IN ALLERGIC POPULATIONS

A threshold is ‘the level that must be reached for an effect to be produced.’ Definitions of thresholds have crucial importance to make the right choices in food avoidance practices. Reviewing the data on threshold levels for food allergic reactions, a strong interindividual variability appears immediately. The calculated dose of fatal anaphylaxis to peanut (one of the most frequent event) varies from few milligrams to several tens of grams [41]. The interindividual threshold levels differ substantially and it is difficult to reach general recommendations for allergic subjects [42].

The European Food Safety Authority and other scientific organizations (International Life Sciences Institute Europe) are evaluating strategies in order to identify the minimum dose or threshold level can

trigger a reaction in the most sensitive individuals, and enable the industry to give correct information. One of the first studies exploring this problem concluded that even a low dose of 100 µg could induce a reaction [43]. To search the eliciting dose of the specific food, confounding factors like geographic areas, subject recruitment requirements and dosing protocols, have to be taken in account. In 2002, a consensus of experts drawn up a protocol to try to minimize this bias. Applying this protocol author could estimate threshold doses for allergenic foods, and found that even the highly sensitive patients develop a mild reaction to the minimum dose [44]. Later on, it was a higher accuracy in determining the eliciting dose was reached increasing the number of food allergic patients in the studies [45]. Specifically designed protocols, using prolonged intervals of 2 h between incremental doses, found that >70% of subjects had objective eliciting doses occurring in median 50 min after challenge. Until the studies applied shorter time intervals, 30 min, so it was possible that ED was two or threefold lower than reported [46]. The Australian Voluntary Incidental Trace Allergen Labelling and International Life Sciences Institute Europe Food Allergy Task Force reviewed retrospectively data from challenges, particularly focusing on low-dose reactors to different allergenic food. This probabilistic risk assessment approach [47,48] shown that the eliciting dose for an allergic reaction in 1% of the population estimated were: 0.2 mg of protein for peanut, 0.1 mg for cow’s milk, 0.03 mg for egg, and 0.1 mg for hazelnut [49].

These studies were conducted on the whole population of food allergic subjects. A novel approach tried to identify the most highly sensitive patients within any given food-allergic population. In 2013, the Peanut Allergen Threshold Study predicted for peanut an eliciting dose for 5% of the study population, the most sensitive, of 1.5 mg protein [50]. In 2017, using a single dose protocol, it was found that the single administration of 1.5 mg peanut protein elicited reactions in fewer than the predicted 5% of peanut-allergic subjects [51]. Walnut protein eliciting doses have been also evaluated, founding that the eliciting dose for 5, 10 and 50% in the walnut allergic population ranged from 3.1 to 4.1 mg for the ED05, from 10.6 to 14.6 mg for the ED10, and from 590 to 625 mg for the ED50 [52].

IDENTIFICATION OF FOOD ALLERGEN TRACES IN FOODS

If a minimum threshold in the population can be identified, than foods containing less than that dose could be labeled as safe for food allergic consumers.

For this reason, techniques for the quantification of the food allergen amount in foods are needed. Starting in the 90's the first technique used to detect the presence of allergen protein in food was antibodies-based assay, with or without protein sequence technique, the IgE immunoblotting. Currently, the mainly used are: Enzyme-linked immunosorbent assay, polymerase chain reaction, and the real time polymerase chain reaction, but, the latter two are able to detect DNA and not proteins.

All techniques have a series of limitations:

- (1) Complexity of food matrix,
- (2) Presence of allergenic contaminants,
- (3) The variable specificity of the antibodies in commercial kit, and
- (4) The absence of animal and plant genome databases prevented the possibility of molecular studies for allergen protein in food characterization together with The IgE epitope [53].

The use of -omics sciences, with mass spectrometry and updated genomic databases, could help to overcome these limitations. Proteomics techniques may evaluate the exact amount of protein within the food, and their sensitivity could be pushed up to dose tiny amount of proteins, lower than those that can theoretically determine an allergic reaction.

CONCLUSION

In the era of molecular diagnosis of food allergy, laboratory techniques allow precise diagnoses, identifying with precision the protein that triggers allergic reactions [54]. This does not yet go hand in hand with information about the composition of foods found on the packaging. International communities have done a lot enacting increasingly stringent laws, but more is still to do. The inability to correctly read the labels is a problem felt worldwide [15,55]. These concerns are not only experienced by consumers but also by food-related employees on security [56]. The main goal for the future is to fill this gap to allow an increasing the quality of life of patients with food allergy.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

The authors have no conflicts of interest to declare.

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- of special interest
- of outstanding interest

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