Food allergy carries high importance and responsibility, affecting an estimated 220 million people worldwide. It is a frequent cause of food-induced anaphylaxis, a life-threatening condition requiring a toll of about one death per 50 million people a year worldwide. In order to help patients to identify all\-er\-genic foods and thus avoid anaphylactic reactions, 66 countries over the 5 continents require by law that allergenic ingredients must be declared when used in prepackaged foods. Unfortunately, the mandatory allergen list is not uniform, but varies among different countries. The widespread adoption of Precautionary Allergen Labeling (PAL) results in a proliferation of unregulated PALs with different informative statements. In this situation, the need of a scientific consensus on the definition of food allergy and the identification of a tolerable risk with routinely used detection assays, considering not only the eliciting dose but also the food source, is urgent. The aim of this manuscript is: 1) to draw a picture of the global situation in terms of PALs, and 2) to highlight new approaches that could aid in tackling the problem of regulating the labeling of allergens. These include the Voluntary Incidental Trace Allergen Labelling (VITAL) system, which intersects reference doses and labelling decisions, and a direct quantification of trace amounts of allergens at lower limit of detection (LOD) levels in the food itself through proteomics. We here highlight how, although with some limitations, the steady advances in proteomic approaches possess higher sensitivity than the recommended VITAL reference doses, allowing the identification of allergens at much lower LOD levels than VITAL. Considering that each assay used to detect allergen in food products carries method-specific issues, a more comprehensive and harmonized approach implementing both quantitative and qualitative methods could help overcoming the risk stratification approach and the overuse of PALs, offering promise as the field moves forward towards improving consumers’ quality of life.

Keywords: Food labeling, Allergies, Allergens, VITAL, Analytical methods

INTRODUCTION

In the World Allergy Organization (WAO) International Scientific Conference (WISC), streamed live on July 16–18, 2020, participants from 62 countries discussed the latest news in terms of allergic diseases. Attendees included international...
researchers from a wide range of disciplines including clinicians, physicians, and health professionals. In the session “Food Labeling Issues for Severe Food Allergic Patients”, the topic of Precautionary Allergen Labeling (PAL) was tackled in a multidisciplinary and translational approach, contextualizing how food allergen labeling is increasingly subject to legislative and regulatory scrutiny nationally and internationally, with regulations varying broadly across countries. Many efforts have been made by many international entities, and scientific organizations have tried to harmonize food regulations among countries using both quantitative and qualitative detection methods. The aim of this manuscript is to draw a picture of the global situation in terms of PALs, also highlighting new approaches that could aid in tackling the problem of regulating the labeling of allergens to help allergic consumers to safely enjoy the widest possible array of foods, improving their overall quality of life.

THE BURDEN OF FOOD ALLERGY

With an estimated 220 million people suffering worldwide from food allergies, food allergy carries high importance and responsibility. This condition, that affects 2%-10% of the world population, is a frequent cause of anaphylaxis, a life-threatening condition requiring a toll of about 1 death per 50 million people a year worldwide. Food allergy peaks in the pediatric age. Although children allergic to milk and egg may experience 1/2 reactions per year, older children and adolescents experience up to 1 reaction per month when suffering from severe and complex food allergies.

QUALITY OF LIFE IN PEOPLE WITH SEVERE FOOD ALLERGY

Living with severe food allergy can be described as an intricate pattern of “facts” and “feelings” interwoven into a child’s developmental pathway from the time of diagnosis. Prevalence is rising across the world, as are hospital admissions for anaphylaxis with a case fatality rate of up to 1% for medically coded food anaphylaxis, although this varies according to the definition used. Reliable identification of patients at increased risk of fatal food anaphylaxis is not currently possible, since the majority of symptom scores have been empirically created and data-driven instruments are scarce. It has been suggested, therefore, that health related quality of life (HRQL) should play a central role in driving treatment decisions for people with food allergy.

Compared to other allergies, such as seasonal allergies, in food allergy the risk is higher and constantly present. Questions such as “when”, “what”, “why”, “how much”, plague the sufferers’ life leading to uncertainty, fear, and anxiety. A decrease of HRQL is common among patients with food allergy and their caregivers. The Food Allergy Quality of Life Questionnaire (FAQLO) series of age-appropriate and disease specific measures have been used in general and treatment settings, cross-sectionally, and longitudinally. The measures consist of multidimensional items and subdomains, together with questions on demographics, symptoms, reaction history, diagnosis, prescription, and use of an epinephrine auto-injector (EAI). In FAQLO, severity is typically defined as having a prescription for an EAI, or self-reported previous episodes of anaphylaxis (ie, the symptoms “difficulty breathing”, “inability to stand”, collapse, and/or loss of consciousness). The Food Allergy Independent Measure (FAIM), used in concert with FAQLO, provides a measure of subjective perception of severity/chance of adverse outcome. A minimal clinical important difference (MCID) score of 0.45/0.5 has been reported for the questionnaires. The most significant impact of severe food allergy on FAQLO, across age groups, is the persistent fear of an adverse reaction, and the restrictions, vigilance, and planning that are necessary to minimize the risk. Environmental factors (clinician and general public awareness, industry policy and practices, including PAL) also play an important and dynamic role in impacting Food Allergy Quality of Life (FAQLO). Furthermore, disparities exist in the economic impact of food allergy based on socioeconomic status and anxiety may relate to the medical and nonmedical costs borne by families.

Due to the wide array of factors that may amplify the impact of severe Food Allergy (FA) and provide a barrier to self-management, a thorough assessment of FAQL, subjective perceptions of FA severity, and environmental factors is necessary.
when initiating treatment and other decision making with FA patients and caregivers. This is particularly important since the need for psychosocial support is largely unmet and there is insufficient number of mental health clinicians equipped to work with FA families.

INTERNATIONAL REQUIREMENTS FOR ALLERGENIC INGREDIENTS LABELLING

In order to help patients, identify allergenic foods and thus avoid anaphylactic reactions, 66 countries over the 5 continents require by law that allergenic ingredients have to be declared when used in prepackaged foods. Eight major food allergens (“The Big 8”) in addition to sulfites, have to be declared almost everywhere, namely eggs, milk, tree nuts, peanuts, fish, soy, wheat, and crustaceans shellfish, although some other countries such as Thailand, India, Philippines, and Hong Kong do not include specifically wheat but more generically cereals with gluten. Some other countries add cereals with gluten, molluscan shellfish, mustard, sesame (eg, Canada), plus lupin, and celery, (eg, Europe) to “The Big 8”. Korea has the most demanding legislation, adding to mandatory labeling buckwheat, molluscan shellfish, beef, chicken, peach, pork, and tomato. On the opposite, in Japan the food allergen labeling regulation has been in force for over 15 years and has been amended as needed, with currently fewer items on the mandatory allergens list (ie, crustacean shellfish, egg, milk, peanut, tree nuts, wheat, and buckwheat). In Australia and New Zealand, cereals with gluten, lupine, sesame, bee pollen/propolis, and Royal Jelly are added to the 8 main ones (Fig. 1). In South America, regulations on food allergen labeling range from "no show" (Belize, Antigua, Barbuda, Dominican Republic, Ecuador, Cuba, Jamaica) to a mandatory labeling (eg, Argentina, Brazil). Some countries adopt a “voluntary” food allergen labeling (eg, Mexico, Bolivia, and Peru). Other countries require a technical regulation on the labeling of prepackaged foods only (Nicaragua, Honduras, Guatemala, Panama, Costa Rica, Belize, El Salvador) (Table 1).

The legislation, implemented 15 years ago in Europe and the United States, is a precious instrument of protection of food allergy sufferers. It eliminates the possibility of “conscious” omissions of the presence of allergens (complex ingredients, unintelligible definitions, etc.); so is the latest Mexican amendment on food labelling, as it includes several new allergens and a new allergen declaration for possible direct and cross contamination.

Unfortunately, the mandatory listed allergens are not uniform, but vary, in some cases greatly,

Fig. 1 Selected examples of allergens subject to mandatory allergen labelling worldwide. In shades of blue are shown countries where the eight major allergens (“The Big 8”) must be declared if present. Country-specific allergens additionally subject to mandatory labeling are depicted with dedicated icons.
among different countries. Such allergens are also identified based on different criteria: for example, in countries with well-developed food allergen labeling requirements, they are chosen based on specific health-related concerns, while in other countries they are derived from already recognized international regulations.  

Although several countries have a regulation in place governing mandatory labeling, 81 still do not have any allergic labeling requirements. On the other hand, a shared clinical threshold allowing the individuation of a legal limit on an allergen-by-allergen basis is not yet presently defined. There are also few official analytical methods and limits of determination that are accepted as analytical reference in specific countries, such as in the case of polymerase chain reaction (PCR) methods for allergen detection in Germany and Japan. Overall, this poses a great risk for allergic people, as witnessed by the still observed reactions to food allergens, present even in countries with mandatory labeling.

**PRECAUTIONARY ALLERGEN LABELLING**

In this situation, the need of a scientific consensus on the definition of food allergy and the identification of a tolerable risk with standardized detection assays, considering not only the eliciting dose but also the food source, is urgent. An attempt to help with ensuring that packaged foods were as safe as possible for allergic consumers, by informing them about the possible presence of allergen contaminations in primary ingredients, preparation and storage, has been made with the voluntary use of PAL, intended as an “information on the possible and unintentional presence in food of substances or products causing allergies or intolerances, provided voluntarily by the food business operator.” Despite the good intentions, the widespread adoption of PAL has resulted in a proliferation of unregulated PALs with different informative statements that have generated confusion, uncertainty, and stress amongst consumers with severe allergies, further reducing their possible food choices.

For these reasons, as also highlighted by other authors, PAL should be generally avoided or only used when a solid evidence-based risk management plan is present in place. Therefore, new approaches are required to tackle the problem of regulating the labeling of allergens to help allergic consumers to safely enjoy the widest possible array of foods. To this purpose, two possible solutions were brought up for discussion in the WISC in 2020.

**THE VOLUNTARY INCIDENTAL TRACE ALLERGEN LABELLING (VITAL) SYSTEM**

The VITAL system in intersecting reference doses and labelling decisions, allows thorough review of the allergen status of all the ingredients
and the processing conditions that contribute towards the allergen status of the finished product, avoiding the indiscriminate use of PALs.25 Pioneers in this field have been the Australians, whose Allergen Bureau developed a two-grade approach intended to orient the choices of the industry in terms of labelling. According to the VITAL indications, food industry may choose to adopt in a label action level one (no precautionary statement) or two (.... may be present). Every specific recommendation is based on reference doses for the specific food allergen, taken from the results of diagnostic Oral Food Challenges (OFCs). The labeling outcomes of the latest version of VITAL (ie, 3.0) are based on both reference doses and reference amounts of foods that, taken together, establish an action level underlying a cross-contact amount.27 Action level one is suggested when the food contains up to the eliciting dose 1% or 5% – depending on the food allergen. This is the dose expected to elicit objective symptoms in 1% or 5% of food allergy sufferers in OFCs. VITAL is not universally adopted but remains voluntary. Such an approach may provide a consistent risk assessment and labeling across the food industry, by guiding the review and management of allergen risk, providing a consistent and systematic framework to assess allergens and cross-contact allergens present in ingredients or generated during manufacturing processes. In addition, it could be of assistance demonstrating supply chain due diligence and reducing time and cost in responding to consumer complaints and product recall. However, the VITAL approach, by definition, is applicable only when the unintended allergen is distributed homogenously in the product; therefore, in situations where allergens are present in particulate forms, other approaches need to be identified to avoid PALs.16

Food and Agriculture Organization [FAO] or Codex Alimentarius Commission Committee on Food Labelling [Codex]), above regional regulators and Governments, would take the lead in trying to implement the VITAL system globally.

THE PROTEOMIC MASS SPECTROMETRY BASED APPROACH

A potentially alternative approach to PAL is the direct quantification of micro amounts of allergens in the food itself, to overcome the risk stratification approach. In this regard, a good sensitivity is demanded to the analytical method under development to be able to detect allergen traces in processed food products.28 Sensitivity of the method should comply with the reference doses recommended depending on the specific country. These values are often used as minimal target values for setting suitable Limit of Detection (LOD) and/or Limit of Quantification (LOQ) during development of a method for allergen quantification.

Targeted liquid chromatography-mass spectrometry (LC-MS/MS) methods have been proposed in alternative to enzyme-linked immunosorbent assay (ELISA) and DNA-based methods, thanks to the high accuracy and reliability offered as the case of milk and egg detection in cookies.29 Mass spectrometry (MS) proved to offer many advantages over the immunoassays, such as i) unambiguous identification of the allergen through the detection of signature peptides for each allergen, ii) multi-target analysis through detection of multiple peptide-markers in one run, and iii) allergen quantification through the quantification of the produced signature peptides.30 On the other hand, it should also be highlighted that MS approach suffers from some limitations being considered in general: (i) not a rapid method to be used along the food production lines for analytical verification of established sanitation procedures, allowing to minimize cross-contact and thus to minimize the use of PAL, (ii) expensive for the sophisticated instruments requiring specialized operators to run MS method, and (iii) subject to matrix issues. Other methods, such as
ELISA and quantitative polymerase chain reaction (qPCR), while covering some of the above-mentioned limitations also carry method-specific issues, as illustrated by Holzhauser et al.\textsuperscript{21} Efforts have been directed at the European level to overcome issues encountered in food allergen analysis. The establishment of reference doses and the necessity for sensitive and harmonized analytical methods along with the production of allergen Reference Materials have been the key objectives of the past Integrated Approaches to Food Allergen and Allergy Management (IFAAM) project, are part of the objectives of the International Association for Monitoring and Quality Assurance in the Total Food Supply Chain (MoniQA), and are part of the current European Food Safety Authority (EFSA) funded Detection and Quantification of Allergens in Food and Minimum Eliciting Doses in Food Allergic Individuals (ThRAll) project. This latter is based on the application of a dual risk-based approach to food-allergen management.\textsuperscript{31} The first aims at developing a reference quantitative MS-based prototype reference method for the detection of multiple food allergens in complex standardized incurred food models by targeting 6 allergens including milk, egg, peanuts, hazelnuts, almond, and soy. Once stable and reliable markers have been identified in hard to analyze matrices, the method can be optimized and in-house validated.\textsuperscript{32} At last, an inter-laboratory comparison needs to be carried out to allow comparability of results among laboratories. Proteomic evaluations may in general offer a higher sensitivity than the recommended VITAL reference doses, allowing the identification of milk and egg allergens at a LOD levels 40 and 13 times lower than VITAL action level 1, respectively.\textsuperscript{29}

The second objective of ThRAll aims at gathering and curating data derived by oral food challenge tests, to define thresholds and minimum eliciting doses for several allergens.\textsuperscript{31} The accomplishment of these objectives, using a more comprehensive and harmonized approach that implements both quantitative and qualitative methods, may pave the way to fill the current gaps in the food allergen field and help with tackling the problem of the risk stratification approach and the overuse of PALs.

CONCLUSIONS

Potential new approaches could help address the current food labeling issues for severe food allergic patients. Indeed, current gaps in the evidence include, among others, a need for harmonization in labelling activities, certified reference materials and standardized detection assays, a definition of acceptable risk level in food allergy, and best practices to support the food allergic consumer.\textsuperscript{16} A scientific consensus on the definition of food allergy that considers both the eliciting dose and the food source is therefore needed, and WAO is taking steps in that direction.\textsuperscript{33} In this context, measures of quality of life and economic burden of food allergy are essential. In the framework of the new WAO definition,\textsuperscript{34} we are currently in the preliminary stages of developing an integrative and intuitive website for all food allergy measures. Researchers, clinicians, and healthcare professionals (HCPs) will be able to download the FAQL and other questionnaires or use them online, and also access norms data, advice on use and scoring, papers and reports, and simple calculators. This will promote adherence to quality measures, consistency in quality measure reporting, and comparative and longitudinal research, with benefits for patients and families living with severe food allergy. Furthermore, the development of a dedicated website can help to create an on-line community, allowing for discussion of potential and ongoing projects in an interactive forum.

A more precise harmonization and regulation of the labeling of food allergens, together with a combination of both quantitative and qualitative methods of detection, will help to improve consumers’ quality of life. Although with some limitations, the steady advances in proteomic approaches have been shown to possess higher sensitivity than the recommended VITAL reference doses, allowing the identification of allergens at much lower LOD levels than the VITAL and potentially helping to tackle the problem of the risk stratification approach and the overuse of PALs. All in all, a tight collaboration among international organizations, regulators, and food industries should work towards implementing, as a first step, mandatory requirements for labelling of allergen
in food products in all countries in a more coherent way, detected through harmonized laboratory assays and reference materials. On the opposite, PAL should only be applied with a solid technical rationale to avoid creating unnecessary confusion, uncertainty, and stress amongst consumers with severe allergies.

**Abbreviations**

EAI - epinephrine auto-injector; EFSA - European Food Safety Agency; FAIM - Food Allergy Independent Measure; FA - Food Allergy; FAQL - Food Allergy Quality of Life; FAQLO - Food Allergy Quality of Life Questionnaire; HCP - Healthcare Professionals; HRQL - Health Related Quality of Life; IFAAM - Integrated Approaches to Food Allergen and Allergy Management; LC-MS - Liquid chromatography-mass spectrometry; MCID - Minimal Clinical Important Difference; MoniQA - Monitoring and Quality Assurance in the Total Food Supply Chain; MS - Mass Spectrometry; PAL - Precautionary Allergen Labelling WAO - World Allergy Organization.

**Authors’ consent for publication**

All authors of this paper have read and approved the final version submitted.

**Author contributions**

Conceptualization: AF, DR; data curation: AF, DR, LM, AD, SGD; project administration: AF; writing-original draft: AF, DR; writing-review & editing: AF, DR, AD, SGD, LM, VF, IJA; validation: AF, DR, AD, SGD, LM, VF, IJA; figures and tables: AF, DR; supervision: AF.

**Availability of data and materials/Ethics approval**

Being our work a review paper of the present literature, these two sections are not applicable.

**Declaration of competing interest**

Davide Risso is a full-time employee of Soremartec Italia Srl, Alba (CN, Italy).

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