FOOD ALLERGY AND SAFETY ASSESSMENT WORKSHOP

HESI ®

11-12 August 2014

Kenyatta International Convention Center
Nairobi, Kenya

Sponsor:

Protein Allergenicity Technical Committee
ILSI Health and Environmental Sciences Institute (HESI)

International Life Sciences Institute Code of Ethics and Organizational Standards of Conduct

Statement of Purpose

The goal of the International Life Sciences Institute's (ILSI) Code of Ethics and Organizational Standards of Conduct is to assure that ILSI members, scientific advisors, consultants, other key stakeholders in ILSI scientific activities, and users of ILSI's scientific work products are aware of the ethical principles guiding the organization's structure and the tenets behind the organization's adherence to rigorous, peer-reviewed scientific investigation and scientifically balanced, evidence-based work products. All scientists who work with ILSI shall be provided with a copy of this document.

Introduction

The International Life Sciences Institute is an international organization that seeks to promote [the] public health through the advancement of peer-reviewed scientific investigation and application of evidence-based decision-making in the areas of nutrition, food safety, toxicology, risk assessment, and the environment. ILSI accomplishes its mission through support of scientific research, publications, and workshops and conferences and other scientific activities. The principles listed below provide a framework to guide ethical decision-making. (Note: Reference below to policies applicable to "ILSI" includes ILSI, ILSI branches, and the ILSI Research Foundation.)

Principle 1. Scientific Integrity

All ILSI projects must have a primary public purpose and benefit, and must address issues of broad public health interest.

The ILSI, ILSI branches, and ILSI Research Foundation Boards of Trustees must be composed of at least 50 percent public sector members (primarily academic); the remaining trustees represent ILSI member companies. ILSI's trustees serve in a voluntary capacity; they are not paid for their time and are not personally eligible to receive grants from the ILSI entity on whose Board they sit.

ILSI shall only support animal and human subject research that has been approved by the appropriate bodies responsible for ensuring humane and ethical treatment of the animals or human subjects (e.g., Institutional Review Boards, Ethical Clearance Committees, Animal Care and Use Assurance Committee, etc.). All ILSI-supported research shall be conducted to meet the highest scientific standards as well as all applicable legal standards.

All ILSI sponsored research shall be conducted objectively and transparently so that the structure of the research is presented factually and without bias; be verifiable and reproducible.

ILSI encourages publication of all research results, regardless of outcome. ILSI entities shall not control the content of publications of research grantees or commissioned authors, but shall encourage academic freedom.

All ILSI research grantees must include language in their grant-related publications identifying the sponsor and providing appropriate sponsor contact information.

All ILSI committees and task forces must have scientific advisors from academia or government to ensure multi-sector input and balance, [and ILSI will only undertake activities for which there is broad interest and support.] All compensation (honoraria) provided to advisors must be disclosed by the advisors to the committee or task force overseeing the work.

Members of ILSI committees or task forces who are in attendance at meetings, symposia, or workshops must identify themselves on registration forms and materials by their primary affiliation (i.e., employer).

ILSI will be transparent in the disclosure of its funding sources.

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ILSI believes that ensuring balance of perspectives is the most appropriate way to ensure that the impact of any potential conflict of interest or bias is minimized and does not exert an undue influence on the scientific process.

To this end, ILSI operates with transparency, conducts activities objectively, and is accountable to all stakeholders.

ILSI trustees must declare any potential bias or interest, including but not restricted to financial interests, and may be asked to recuse themselves from voting on issues that might be construed as conflicts of interest.

With respect to publications, grant reviews, and expert panels, ILSI expects the scientists with whom it works to [disclose] declare any potential [conflicts of] financial interest. ILSI may ask scientists to excuse themselves from an activity based on such a declaration.

Scientists who work with ILSI are expected to act in accordance with their own institution's conflict of interest policies and with applicable laws, as well as comply with the conflict of interest policies of any journal or organization with which they may work, including ILSI.

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Advocacy of any kind is strictly limited to promotion of the use of evidence-based science as an aid in decision-making. ILSI does not conduct lobbying activities.

Principle 4. Transparency in Meetings and Publications

The purpose of and funding sources for all ILSI sponsored meetings, symposia, conferences, seminars, and workshops will be fully disclosed in meeting materials.

All invited presenters will provide declarations of financial interest to be disclosed if relevant at the time of the meeting (orally or in the meeting materials).

All ILSI publications must reflect the high standards of the organization. ILSI-sponsored manuscripts must undergo stringent peer-review by qualified reviewers. Editors and reviewers will treat manuscripts under review as confidential. Scientists are expected to recuse themselves as editors or reviewers of manuscripts if past or present connections with the author(s) preclude an objective evaluation of the work.

Authors of ILSI-sponsored publications shall make full, signed disclosures of financial and/or other interests (e.g., industry relationships, advisory relationships, or other conflicts of interest) that would reasonably appear to affect the contents of the article.

All ILSI publications, including proceedings from workshops or symposia sponsored by ILSI branches, the Research Foundation, or international committees will utilize appropriate attribution language to denote funding sources and sponsors, and ILSI entities shall provide contact information in all publications they produce for anyone interested in obtaining additional information about the organization or the specific sponsors of a particular project.

INTERNATIONAL LIFE SCIENCES INSTITUTE (ILSI)

ANTITRUST STATEMENT

The Branches and Institutes of ILSI, including their respective Boards of Trustees, Scientific Advisors, Scientific Directors, Members, Committees, Subcommittees, Task Forces, and Working Groups, meet to promote understanding and resolution of significant health, nutrition, and safety issues that confront the public, industry, and government. With this goal in mind, ILSI meetings should be occasions where members' representatives and other invited participants:

1. Discuss scientific solutions to problems affecting the health, nutrition, and safety of the public.

2. Develop means to contribute to proper analysis of public health, nutrition, and safety issues by regulatory bodies.

3. Review industrial activities and problems with implications for public health, nutrition, and safety, and review new scientific developments.

4. Support and promote research and educational programs to enhance public health, nutrition, and safety.

5. Develop objective and voluntary industry standards to promote health and safety and compliance with regulatory requirements.

ILSI meetings shall not be occasions where members' representatives and other invited participants:

1. Discuss prices or pricing policies, or any marketing policy with a direct or indirect effect on pricing or any other terms of sale.

2. Confer about division or allocation of sales territories or customers.

3. Establish blacklists or boycotts of suppliers, purchasers, or competitors.

4. Coerce members to implement particular programs or policies.

5. Resolve problems unique to a single member or a small, select group of members.

6. Exchange or disseminate information relating to costs of production, distribution, or marketing.

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FOOD ALLERGY AND SAFETY ASSESSMENT WORKSHOP

11-12 August 2014

Aberdares Room
Kenyatta International Convention Center
Nairobi Central Business District
Nairobi, Kenya

BACKGROUND AND OBJECTIVES

FOOD ALLERGY: Allergic diseases, including food allergy, have been on the rise for decades. This epidemic seems to be leveling off in some western societies. However, in rapidly developing economies in Asia, South America, and Africa, urbanization and industrialization, accompanied by adoption of a more westernized lifestyle and diet, has resulted in an increasing incidence of allergic diseases. Epidemiological studies on allergic asthma have been carried out all over the world, including in some countries in Africa. While the epidemiology of food allergy on the African continent is not yet studied in a coordinated fashion, ongoing studies focus on comparisons between urban and rural areas with higher and lower prevalence of (food) allergy, respectively, to identify environmental, microbial, lifestyle and dietary factors that are protective or represent risk factors. For a sound allergenicity assessment, basic knowledge on food allergy, its proper diagnosis, and its epidemiology are of great importance.

The aim of the first day of the workshop is to provide a state-of-the art overview of what food allergy is, how it is diagnosed, and why it is expected to be a growing problem in Africa in the decade(s) to come. After these introductory lectures, three sessions will provide an overview of allergy research in Eastern, Western, and Southern Africa, respectively.

AGRICULTURAL BIOTECHNOLOGY SAFETY ASSESSMENT: Evaluating safety is a cornerstone of registering genetically modified (GM) crops. A suite of global guidance directing the appropriate studies supports an assessment of potential effects on human and animal health from a food and feed use perspective. A thorough characterization of the inserted DNA and expressed novel proteins are the starting points that are then used to identify a protein's unique structure, function, and origin. Identifying risk for allergenicity, toxicity, or the presence of unintended adverse effects are key objectives. A global perspective on identifying allergy risk is outlined by the Codex Alimentarius Commission (Alinorm 03/34A) in the form of a weight-of-evidence approach, recognizing that no single endpoint is sufficiently predictive of allergenic potential. Toxicity assessments, including animal studies, support an evaluation of both the trait protein(s) and the crop in which it is included, although the predictive value of such toxicology data, particularly longer-term feeding studies, has not been clearly identified. The GM crop (grain) is also evaluated utilizing a comprehensive compositional analysis that establishes the level of similarity between the GM crop and appropriate comparators to establish the GM variety to be "as safe as" non-GM varieties.

A main objective of the second day of the workshop will be to tie together effective risk assessment processes and study designs that provide the basis for current GM registrations. Objectives also include discussing the framework for commercializing a GM crop and the global regulatory perspective on biotechnology-based foods. The protocols and advances in study methods for characterizing DNA, novel proteins, and GM crop products will be discussed. The workshop program includes time for interaction between the audience and the speakers to encourage information-sharing and an open discussion.

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Aberdares Room
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Nairobi, Kenya

PROGRAM

Workshop Co-Chairs:

- *Dr. Gregory Ladics* (DuPont Pioneer, USA; HESI PATC Co-Chair)
- *Dr. Scott McClain* (Syngenta Crop Protection, LLC, USA; HESI PATC Co-Chair)
- *Prof. Ronald van Ree* (Academic Medical Center / University of Amsterdam, The Netherlands; HESI PATC Co-Chair)

DAY ONE

Monday, 11 August 2014, 09:00 – 18:00

09:00 **Welcome**
About the HESI Protein Allergenicity Technical Committee (PATC)
Dr. Gregory Ladics (DuPont Pioneer, USA)

FOOD ALLERGY

09:30 **Introduction**
Prof. Ronald Van Ree (Academic Medical Center / University of Amsterdam, The Netherlands)

Session 1. Food Allergy: Mechanisms, Diagnosis and Epidemiology

Session 1 Chairs:

- *Prof. Ronald van Ree (Academic Medical Center / University of Amsterdam, The Netherlands; HESI PATC Co-Chair)*
- *Prof. Michael Levin (University of Cape Town School of Child & Adolescent Health, Red Cross Hospital, South Africa)*

09:40 **What is food allergy?**
Prof. Lars K. Poulsen (Copenhagen University Hospital at Gentofte, Denmark)

10:00 **How is food allergy diagnosed?**
Dr. Montserrat Fernández Rivas (Allergy Department, Hospital Clínico San Carlos, Spain)

10:20 **BREAK**

10:40 **Food allergy and different socio-economic backgrounds**
Prof. Maria Yazdanbakhsh (Department of Parasitology, Leiden University Medical Center, The Netherlands)

11:00 **Specific mammalian allergens and symptoms of allergic disease: Fel d 1 vs. alpha-gal**
Prof. Adnan Custovic (University of Manchester and University Hospital of South Manchester, United Kingdom)

11:20 **Q&A**

11:50 **LUNCH**

Session 2. Food and Respiratory Allergy in Eastern Africa

Session 2 Chair:
Prof. Peter Schmid-Grendelmeier (University Hospital, Switzerland)

13:00 **Asthma and allergy-related disease in Uganda**
Prof. Alison Elliott
Dr. Harriet Mpairwe
(Medical Research Council / Uganda Virus Research Institute, Uganda)

13:20 **Food and respiratory allergy in Kenya**
Dr. Evans Amukoye (Centre for Respiratory Diseases Research, Kenya Medical Research Institute, Kenya)

13:40 **Food and respiratory allergy in Tanzania**
Dr. Nohrasco Mang'ondi (Bugando Medical Centre/CUHAS, Tanzania)

14:00 **Q&A**

Session 3. Food and Respiratory Allergy in Western Africa

Session 3 Chairs:
- *Prof. Gabrielle Pauli (Strasbourg University, France)*

14:30 **Food and respiratory allergy in Ghana**
Ms. Abena Amoah (Noguchi Memorial Institute for Medical Research, University of Ghana, Ghana)

14:50 **Risk factors for food adverse reaction reporting in Lambaréné, Gabon**
Dr. Ayola Akim Adegnika (CERMEL, Hôpital Albert Schweitzer, Gabon)

15:10 **Q&A**

15:40 **BREAK**

Session 4. Food and Respiratory Allergy in Southern Africa

Session 4 Chair:
Harris Steinman, MBChB, UCT, DCh, SA, DAvMed (Food and Allergy Consulting and Testing Services (FACTS))

16:00 **Food and respiratory allergy in Zimbabwe**
Prof. Elopy Sibanda (Asthma, Allergy & Immune Dysfunction Clinic, Zimbabwe)

16:20 **Food allergy in South Africa**
Prof. Michael Levin (University of Cape Town School of Child & Adolescent Health, Red Cross Hospital, South Africa)

16:40 **Q&A**

Roundtable Discussion

17:10 ***Moderator:***
Prof. Ronald van Ree (Academic Medical Center / University of Amsterdam, The Netherlands; HESI PATC Co-Chair)

Panelists:
- *Dr. Emmanuel Addo-Yobo (Komfo Anokye Teaching Hospital, University of Science and Technology, Ghana)*
- *Prof. Adnan Custovic (University of Manchester and University Hospital of South Manchester, United Kingdom)*
- *Prof. Michael Levin (University of Cape Town School of Child & Adolescent Health, Red Cross Hospital, South Africa)*
- *Prof. Gabrielle Pauli (Strasbourg University, France)*
- *Prof. Peter Schmid-Grendelmeier (University Hospital, Switzerland)*

18:00 **Adjourn Day One**

DAY TWO

Tuesday, 12 August 2014, 08:30 – 15:30

AGRICULTURAL BIOTECHNOLOGY SAFETY ASSESSMENT

Chair:
Dr. Scott McClain (Syngenta Crop Protection, LLC, USA; HESI PATC Co-Chair)

08:30 **Introduction**
Dr. Scott McClain (Syngenta Crop Protection, LLC, USA)

08:45 **Agricultural biotechnology background in Africa**
Dr. Jacoba Adriana ('Kobie') de Ronde (Syngenta, South Africa)

09:15 **Safety assessment process in support of the regulatory approval of agricultural biotech products**
Dr. Laura Privalle (Bayer CropScience, USA)

09:45 **Crop composition as part of the GM crop safety assessment**
Dr. Philip Brune (Syngenta Crop Protection LLC, USA)

10:15 **BREAK**

10:45 **Molecular/protein characterization of GM products**
Dr. Scott McClain (Syngenta Crop Protection, LLC, USA)

11:15 **Assessment of potential allergenicity of GM crops**
Dr. Gregory Ladics (DuPont Pioneer, USA)

11:45 **Assessment of potential toxicity of GM crops**
Dr. Gregory Ladics (DuPont Pioneer, USA)

12:15 **LUNCH**

13:15 **Regulatory and safety assessment perspectives for GM food in Kenya**
Prof. Theophilus Mutui (National Biosafety Authority, Kenya)

13:45 **Regulatory and safety assessment perspectives: South Africa**
Dr. Liezel Michelle Gouws (Biosafety South Africa, South Africa)

Roundtable Discussion

14:15 ***Moderator:***
Dr. Scott McClain (Syngenta Crop Protection, LLC, USA)

Panelists:
- *Dr. Philip Brune (Syngenta Crop Protection LLC, USA)*
- *Dr. Kobie de Ronde (Syngenta, South Africa)*
- *Dr. Gregory Ladics (DuPont Pioneer, USA)*
- *Prof. Theophilus Mutui (National Biosafety Authority, Kenya)*
- *Dr. Liezel Gouws (Biosafety South Africa)*
- *Dr. Laura Privalle (Bayer CropScience, USA)*

15:15 **CLOSING REMARKS**
- *Prof. Ronald Van Ree (Academic Medical Center / University of Amsterdam, The Netherlands)*
- *Dr. Scott McClain (Syngenta Crop Protection, LLC, USA)*

15:30 **ADJOURN WORKSHOP**

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SPEAKER ABSTRACTS

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11-12 August 2014

Kenyatta International Convention Center
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HESI Protein Allergenicity Technical Committee

SPEAKER ABSTRACTS

FOOD ALLERGY

Sessions 1-4

Session 1. Food Allergy: Mechanisms, Diagnosis and Epidemiology

What is food allergy?

Lars K. Poulsen, PhD, Dr. Med.
Professor, Head of Research
Copenhagen University Hospital at Gentofte
Hellerup, Denmark

The symptomatology of food allergy is quite variable, and often symptoms originate from more than a single organ among: *the oral cavity*: oral allergy syndrome; *the skin:* urticaria and exacerbation of atopic eczema; the *respiratory system*: rhinitis and asthma; *the gastrointestinal system*: nausea, vomiting, abdominal pain, diarrhea; with additional symptoms being conjunctivitis, angioedema, and generalized anaphylaxis. It is generally believed that whole food allergen proteins either act on the mucosa in the intestinal tract or may be absorbed systemically in a bioactive form. Patients' reactivity to ingestion of allergic foods experienced in the community are extremely difficult to describe, but it is generally assumed that the threshold dosages that can be determined in clinical settings are the most reasonable approximation, even though many cofactors of real-life (infections, allergic co-morbidities, exercise, matrix in which the food is given, alcohol, drugs) may alter the patient's reactivity to challenges.

The most important single factor in food allergy is specific IgE directed against the food allergens. IgE is situated on mast cells, and by allergen cross-linking, mediators are released which form the basis of the acute symptoms. The diagnosis of food allergy is a response to two important questions: Does the patient have a food allergy? And if confirmatory: Which foods will elicit allergic symptoms?

Session 1. Food Allergy: Mechanisms, Diagnosis and Epidemiology

How is food allergy diagnosed?

Montserrat Fernández Rivas, MD, PhD
Allergy Department
Hospital Clínico San Carlos
Madrid, Spain

The diagnosis of IgE-mediated food allergy is based on a three-step approach. The first step comprises the collection of a medical history that allows the practitioner to establish the link between symptoms and food intake, identify the potential culprit food(s) and whether an immunological mechanism is involved, and guide the diagnostics tests to be performed and the evaluation of their results. The second step consists of the performance of IgE testing on the food(s) under investigation by means of skin prick tests (SPT) and/or serum determinations using whole foods extracts and individual allergens. The sensitivity of whole extracts is reduced when labile allergens are involved, something that may be overcome with individual component testing. Specificity of IgE testing is hampered by cross-reactivity among foods or between foods and inhalant allergens, and this can only be overcome with oral food challenges. Therefore, to establish the clinical relevance of the sensitization to the food, it is necessary to perform, as a third step, an oral food challenge. This test confirms or rules out the patient's reactivity to the food, although it has the inherent risk of inducing allergic reactions that may be severe and has a high cost.

Reference:

Muraro et al. 2014. EAACI Food Allergy and Anaphylaxis Guidelines: diagnosis and management of food allergy. *Allergy*. doi: 10.1111/all.12429. [Epub ahead of print].
Open access: http://onlinelibrary.wiley.com/doi/10.1111/all.12429/pdf

Session 1. Food Allergy: Mechanisms, Diagnosis and Epidemiology

Food allergy and different socio-economic backgrounds

Prof. dr. Maria Yazdanbakhsh
Head, Parasite Immunology Group
Leiden University Medical Center
Leiden, The Netherlands

Co-authors:
Abena Amoah[1,2], Elias Asuming Brempong[1,2], Firdaus Hamid[1,3], Sitti Wahyuni[3], Daniel Boakye[2], Taniawati Supali[4], Ronald van Ree[5]

[1] Department of Parasitology, Leiden University Medical Center, Leiden, The Netherlands
[2] Department of Parasitology, Noguchi Memorial Institute for Medical Research, Legon, Accra, Ghana
[3] Department of Parasitology and Microbiology, Hassanudin University, Makassar, Indonesia
[4] Department of Parasitology, University of Indonesia, Jakarta, Indonesia
[5] Department of Experimental Immunology and Otorhinolaryngology, Academic Medical Center, Amsterdam, The Netherlands

The prevalence of allergic disorders is often reported to be higher in urban compared to rural areas of developing countries. Within urban centres of countries undergoing economic transition, there is considerable variation in lifestyle and socioeconomic status and this appears to be an important predictor of allergy. The prevalence of allergies as defined by skin prick test positivity to allergens is higher in the urban rich than in urban poor. However, the IgE responses can show very different patterns. IgE responses to allergens are high in the rural compared to urban areas. However, IgE in urban poor is lower than in urban rich. Using both the ISAC biochip and glycan arrays, we have gained more insight into the molecular targets of the IgE from different geographical areas as well as from populations with different socioeconomic status and have suggestions for why IgE can at times not be directly associated with skin prick test positivity or clinical symptoms.

Session 1. Food Allergy: Mechanisms, Diagnosis and Epidemiology

Specific mammalian allergens and symptoms of allergic disease: Fel d 1 vs. alpha-gal

Adnan Custovic, DM, MD, PhD, FRCP
Professor of Allergy
Institute of Inflammation and Repair
University of Manchester
University Hospital of South Manchester
Manchester, United Kingdom

[abstract not available]

Session 2. Food and Respiratory Allergy in Eastern Africa

Asthma and allergy-related disease in Uganda

Prof. Alison Elliott
Harriet Mpairwe, MBChB, MSc, PhD
Research Unit on AIDS
Medical Research Council / Uganda Virus Research Institute
Entebbe, Uganda

Very little research has been conducted on asthma and allergy-related disease in Uganda. However, these conditions are increasingly recognised as important, especially among the region's rapidly expanding middle classes.

The combination of an environment in which exposure to infectious diseases, including helminths, is still common and the current, rapid transition to an urban lifestyle provide unique opportunities for research to understand the relationship between allergy-related conditions and the environment.

We will report upon recent clinical and epidemiological studies of asthma and atopy in Uganda, and upon the effects of early life infectious exposures on allergy-related outcomes in this setting.

Session 2. Food and Respiratory Allergy in Eastern Africa

Food and respiratory allergy in Kenya

Dr. Evans Inyangala Amukoye
Director
Centre for Respiratory Diseases Research
Kenya Medical Research Institute
Nairobi, Kenya

Food is an important cause of anaphylaxis, intolerance and allergies. Less than 6% of respiratory allergies are due to food. Studies done in Kenya in this area are few. Allergy to cow's milk, egg, wheat, soy, peanut, tree nuts, fish, and shellfish constitutes the majority of food allergy reactions worldwide, but reliable estimates of their prevalence are lacking. Allergies in general are common and, in the ISAAC studies done in the 1990s, Africa and Latin America had higher incidences of eczema. For the age group 13 to 14 years, and using data on 663,256 participants from 230 centers in 96 countries, Odhiambo et al. showed prevalence values ranging from 0.2% in China to 24.6% in Columbia, with the highest values in Africa and Latin America. 'Current eczema' in the same study was lower for boys than girls.

Asthma was a common occurrence in Nairobi, Kenya, recording 18% prevalence among the age group 13 to 14 years. Several studies have shown rural urban differences with higher rates reported in urban areas. This has been attributed to life style and pollution. This difference is now narrowing.

The role of helminthes and micronutrient such as Vitamin D will be discussed.

Session 2. Food and Respiratory Allergy in Eastern Africa

Food and respiratory allergy in Tanzania

Dr. Nohrasco Mang'ondi
Lecturer and Dermatovenereologist
Bugando Medical Centre
Catholic University of Health and Allied Sciences (CUHAS)
Mwanza, Tanzania

Tanzania is a large country in east Africa with a general population of 45 million and many different tribes with diverse cultural practices. Food and respiratory allergies are a common known problem, but definition and knowledge of allergic disease differ from one tribe to another and from rural to urban areas.

Food allergy is mostly suspected by many people when they have any chronic or recurrent skin problem which failed to be treated in Hospital, while any dry cough with recurrent nature is attributed to respiratory allergies.

No studies have been done so far to assess the magnitude of food or respiratory allergies, but a few studies have been done in special groups like children. Atopic dermatitis revealed a prevalence of food allergy ranging from 1.4% - 36.5% in some areas of the country. Respiratory allergy ranges from 1.2% - 18.6% in asthmatic and industrial worker populations.

Common food allergies are peanuts, cow's milk, hen egg, and fish, but currently no specific respiratory allergies have been studied.

Conclusion
Food and respiratory allergy are a common problem although may be differently interpreted by different communities. The burden of allergenic diseases in Tanzania is increasing due to urbanization and industrialization.

Session 3. Food and Respiratory Allergy in Western Africa

Food and respiratory allergy in Ghana

Ms. Abena Amoah
Department of Parasitology
Noguchi Memorial Institute for Medical Research
University of Ghana
Legon, Ghana

Over the past few decades, there has been a sharp global increase in the prevalence of allergic disorders, particularly among children. We conducted a cross-sectional study to investigate the prevalence of markers of aeroallergy and food allergy among urban and rural children in Southern Ghana. Of particular interest were sensitization to aeroallergens based on specific immunoglobulin E (IgE) levels and skin prick test reactivity, as well as reported symptoms of asthma and wheeze. In addition, food allergy was determined based on reported adverse reactions to food, as well as food sensitization to selected food allergens that included peanut. The effects of factors such as parasitic infections, body mass index, and area of residence on our allergy outcomes were also investigated.

We observed notable urban-rural differences in our allergy outcomes, as well as elevated levels of allergen-specific IgE that did translate into skin prick test positivity or reported symptoms. Further in-depth analysis demonstrated that helminth-induced IgE cross-reactivity may explain in part the lack of skin reactivity to allergens such as peanut in the face of elevated allergen-specific IgE. Overall, our investigation demonstrates the complexities underlying the rise in allergic diseases in rapidly developing countries such as Ghana.

Session 3. Food and Respiratory Allergy in Western Africa

Risk factors for food adverse reaction reporting in Lambaréné, Gabon

Ayola Akim Adegnika, MD, PhD
Co-Director and Group Leader
Immuno-Epidemiology of Parasitic Infections (IEPI)
Centre de Recherches Médicales de Lambaréné (CERMEL)
Hôpital Albert Schweitzer
Lambaréné, Republique of Gabon

Allergy disorders constitute a major public health problem in developed countries. In developing countries, data for allergy disorders are mainly available on inhalant allergy, while few data are available on food allergy disorders. In these countries, allergy disorders are negatively associated with poor hygiene and microbial infections, including helminths infections.

Lambaréné is a semi-urban city in Gabon which is endemic for parasitic infections including helminths parasites, and is composed of different socio-economic groups, geographic areas (rural, semi-urban and rural), and diverse food intake. Lambaréné was chosen to conduct a nested case-control study to assess factors associated with food adverse reaction reporting.

Data were collected on self-reported adverse food reactions in 2,679 participant at a cross-sectional level. The number of participants reporting the adverse food reaction was 353 (13.2%). From this cross-sectional cohort, 105 cases and 216 controls were selected for further assessment of factors associated with food adverse reaction, including parasitic infection, socio-economic status, and confirmatory tests including skin prick test as well as a measurement of specific IgG-E with reported food adverse reaction.

It was found that independent risk factors for food adverse reaction reporting included infection with schistosomiasis (OR (95%CI)) (0.44(0.22-0.55)) and living in the administrative area (OR (95%CI)) (4.15(1.63-11.16)). However there is no statistically significant correlation or association between specific IgE, as well as specific skin prick test positive, with food adverse reporting.

This population-based study reports for the first time food adverse concerns in Lambaréné and surrounding population, but fails to confirm so far a single true food allergy using existing and validated tools. Further investigations are needed to alleviate this discrepancy.

Session 4. Food and Respiratory Allergy in Southern Africa

Food and respiratory allergy in Zimbabwe

Professor Elopy Sibanda, MD
Asthma, Allergy & Immune Dysfunction Clinic
Harare, Zimbabwe

Diseases that result from allergic reactions are common worldwide. Their frequency and associated triggers are rarely documented in Africa. We have summarized the findings of an audit of laboratory test results of 981 patients referred to a specialist allergy clinic in Harare, Zimbabwe. The test panels included eleven inhalants (house dust mites, pollen, animal hair and molds) and twenty-two food allergen sources. The food allergen sources included egg, milk, grains, nuts, fruits and vegetables.

Serological reactivity to allergen sources was found in all age groups tested. The majority of the patients were children or young adults. A steep increase in the numbers of allergic patients was noted in individuals born in the last 20 years. The numbers of people with moderate to severe allergic diseases more than doubled with each decade from 1980 to 2010. The most significant inhalant allergen sources were house dust mites and pollen. House dust mite sensitization exceeded 50% in some age groups. Grass pollen was more frequently diagnosed than tree and weed pollen. Patients with grass pollen allergy reached 30% in certain age groups. The numbers of people with food allergen sensitization were lower than those with house dust mite or pollen allergy. The most prominent food allergen sources were potato and peanuts. Allergy to milk and seafood was infrequent. This study confirms the persistence of inhalant allergic diseases in Zimbabwe and reports the increasing prevalence of food allergy. The study also notes that in some cases (peanut, potato), sensitization does not always translate to clinical manifestations of disease.

Session 4. Food and Respiratory Allergy in Southern Africa

Food allergy in South Africa

Prof. Michael Levin
Head, Division of Asthma and Allergy
Department of Paediatrics
Red Cross Children's Hospital
Cape Town, South Africa

There is a paucity of information about food allergy in South Africa. Recent and ongoing studies are starting to cast light on the epidemiology of food allergy.

SAFFA STUDY

Primary researchers: Mike Levin, Maresa Botha, Wisdom Basera, Claudia Gray

Introduction: There are no data on the prevalence of food allergy (FA) in unselected South African children, a shortfall which this study addresses. The South African Food sensitisation and Food Allergy (SAFFA) study aims to determine the prevalence of IgE-mediated food sensitisation and food allergy in unselected 12-36 month old urban South African children.

Methods: This cross-sectional study recruited 12-36 month old toddlers from randomly selected registered crèches in Cape Town. Parents of eligible children in the crèche completed a questionnaire and the children had skin prick tests (SPT) for cow's milk, egg, soya, wheat, peanut, hazelnut and fish (cod). Participants with SPT test > 1mm, who were not tolerant to that food had an oral food challenge (OFC) to assess for IgE-mediated food allergy. Parents choosing not to participate completed a non-participant questionnaire to control for bias.

Results: Of 435 eligible participants, 281 responded (65% response rate) and 253 of 263 enrolled participants completed the study (96% completion rate). Of 10 children meeting the criteria for OFC, 7 completed challenges. Participants were black African (42.3%), Caucasian (13.0%), and Mixed Race (44.7%).

The prevalence for SPT ≥ 1mm to any food was 11.9% (95% CI: 7.9-15.9%), SPT ≥ 3mm 9.8% (95% CI: 6.2–13.6%), ≥ 7mm 4.0% (95% CI: 1.5-6.4%), and OFC confirmed food allergy 1.2% (95% CI: 0.2-3.4%) (3 food challenges remain to be done meaning that 1.2% is a minimum value for the prevalence of FA).

The most common sensitisation was to egg and then peanuts. Sensitisation ≥ 1mm to fresh egg was 8.3%, 7.5% ≥ 3mm, 4.0% ≥ 7mm with 2 (0.8%) positive OFCs. Sensitisation ≥ 1mm to peanut was 4.7%, 3.6 % ≥ 3mm, and 1.2% ≥ 7mm with 2 (0.8%) positive OFCs. Sensitisation ≥ 1mm for soya was 2.0%; wheat 1.6%; and for cow's milk, fish, and hazelnut 1.2% each. 4.7% of participants were poly-sensitised.

In general, sensitisation in Black African and Mixed Race children were slightly higher than in Caucasian participants, viz at SPT ≥ 1mm 12.8%, 11.6%, and 9.8%, respectively; SPT ≥ 3mm 11.9%, 8.0%, and 9.7%, respectively; and SPT ≥ 7mm 4.6%, 3.5%, and 3.2%.

Conclusion: This is the first food challenge proven prevalence of FA determined in unselected children in Africa and provides a basis for further monitoring of a population possibly only at the beginning of the food allergy epidemic.

Although not statistically significant, the higher sensitisation rates in Black African and Mixed Race children are similar to the high rates of aeroallergen sensitisation seen in unselected and allergic populations. Further expansion in the next phase of the study will compare the prevalence of sensitisation and food allergy between urban Caucasian, Mixed Race and Black African children and between rural and urban Black African Xhosa children, and will generate population-specific cut-off levels for SPT and Immunocaps with 95% positive predictive values.

RXH FOOD CHALLENGE AUDIT: OVERVIEW

Primary researchers: Talita Van Der Watt, Mike Levin

Introduction: The diagnosis and confirmation of food allergies can be challenging. The gold standard for diagnosing food allergy is the double-blind, placebo-controlled oral food challenge; however, open oral food challenges (OFC) are useful to exclude food allergies.

Methods: This is a retrospective, descriptive study of children who presented to Red Cross Children's Hospital's tertiary Allergy clinic with food allergies and subsequently had OFC during the 39 month period from February 2011 to April 2014.

Results: Two hundred and two OFCs were performed on 142 children (age 9 months to 14 years). Challenges were done to 18 different foods. Egg, peanut, baked egg, and cow's milk made up the largest number at 64, 37, 29, and 25 respectively.

Ninety four (66.2%) children had a single OFC, while 39 (27.5%) had 2 challenges and 9 children had more than 2 challenges.

Thirty eight (18.8%) challenges were positive with reactions varying from mild rash to wheeze. The rate of positive reactions increased significantly over the study period from 11.6% (n=5/43) in 2011 to 14.5% (n=10/69) in 2012, 21.5% (n=14/65) in 2013, and 36% (n=9/25) in 2014 (p=0.01). The most common reaction was urticaria in 23 (60.5%) and angioedema in 11 (28.9%). Three (7.9%) had wheezing.

Fourteen percent of egg challenges (n=9/64), 35.1% of peanut challenges (n=13/37), 17.2% of baked egg challenges (n=5/29) and 20% of cow's milk challenges (n=5/25) had a positive outcome. There is a significant difference between the median age at challenge (egg 53 months, peanut 67 months, baked egg 38 months and cow's milk 29 months) (p=0.01). Baked egg challenges with positive outcomes occurred in younger children than those with negative food challenges (13 vs 44 months) (p=0.04).

Co-morbidities were common in our population: atopic dermatitis was present in 73.9% (n=105/202), asthma in 37.3% (n=53/202), allergic rhinitis in 45.8% (n=65/202), and allergy to multiple foods in 62.7% (n=89/202). Co-morbidity prevalence was significantly different between groups with positive and negative OFC outcomes (p<0.01).

Conclusion: Oral food challenges are necessary to accurately diagnose children with food allergies. With increased utilization of OFCs, increased numbers of true food allergy diagnoses are made. The prevalence and age of food allergy varies with different foods tested. Peanut allergy was the most common food allergy diagnosed. The presence of other atopic diseases had a significant impact on the outcome of food challenges.

RXH FOOD CHALLENGE AUDIT: SPECIFIC IgE ANALYSIS

Primary researchers: Talita Van Der Watt, Mike Levin

Introduction: Sampson determined 95% positive predictive values (95% PPVs) for food challenge outcome in children in a first world country. These values are used worldwide in decision making processes regarding oral food challenges and in the diagnosis of symptomatic food hypersensitivity. Predictive values for African children have not been determined. Decision points determined include IgE to egg of 7kU/l and 2kU/l for children above and below 2 years of age, IgE to cow's milk of 15kU/l and 5kU/l for those above and below 2 years of age, and IgE to peanut above 14kU/l. We aim to compare the applicability of international 95% PPVs for IgE levels in the African setting to determine whether significance of specific IgE levels differs from international standards and varies with ethnicity.

Methods: This is a retrospective, descriptive study of children who presented to Red Cross Children's Hospital's tertiary Allergy clinic with food allergies and subsequently had open oral food challenges (OFC) over the 39-month period from February 2011 to April 2014.

Results: Two hundred and two OFCs were done on 142 children between the ages of 9 months and 14 years. Egg, peanut, and cow's milk made up the largest number of challenges at 64, 37 and 25, respectively. Thirty-eight (18.8%) challenges had a positive outcome.

The majority of challenges were done in children of mixed race (84.1%), with black African and white children accounting for 12.9% and 3%, respectively. The rate of positive food challenges differed for children of different ethnicity.

Challenges had a positive outcome in 18.8% (n=32/170) of challenges in children of mixed race, 15.4% (n=4/26) of black African, and 33.3% (n=2/6) of those done in white children. Median age at challenge was 47 months for mixed race children, 42 months for black African and 117 months for white children. There was a significant difference in the median ages at challenge (p=0.007). Further analysis was not performed on white children as numbers are too small.

IgE levels for each food and each challenge outcome were compared to the published 95% PPVs. In challenges to egg, 36.1% (17/47) mixed race and 42.9% (3/7) black African had negative OFCs with IgE above the 95% PPV. In cow's milk challenges, 40.0% (6/15) mixed race and 80.0% (4/5) black African children had negative OFCs with IgE above the 95% PPV. For peanut challenges, 21.7% (5/23) mixed race children had negative OFC outcomes with IgE above the 95% PPV. Black African did not have negative OFCs with IgE above the 95% PPV (0/1).

Conclusion: In this setting, large numbers of patients have negative challenges despite IgE levels above the internationally derived 95% PPVs. A higher proportion of Black African children have negative egg and milk challenges despite IgE levels above the internationally derived 95% PPVs; however, the converse is true with regards to peanut challenges.

FOOD ALLERGY IN CHILDREN WITH ECZEMA

Primary researchers: Claudia Gray, George Du Toit, Mike Levin

Introduction
In 2009, South African infants with atopic dermatitis were shown to have frequent sensitisation to foods, most commonly egg white (47.1%), cow's milk (28.4%), and peanuts (26.8%). This study did not, however, explore clinical food allergy. In 2011, the South African food allergy-eczema study showed children attending a tertiary dermatology clinic for atopic dermatitis were shown to

have even higher sensitisation rates (66% to at least one food), most commonly to egg (54%), peanuts (43%), and cow's milk (27%). This latter study had stringent criteria for defining food allergy, with incremental oral food challenges where indicated, and found 40% of patients to have an IgE-mediated food allergy (25% were allergic to egg, 24% to peanut and 2% to cow's milk).

Age of onset of eczema below 6 months was a significant risk factor for food allergy, with much higher prevalence of food sensitisation (86%) and food allergy (66%) in children with eczema onset before 6 months compared to those with onset between 6-12 months or after 1 year. The study confirmed that in our local population, age of assessment affects allergy prevalence with 50% of patients under the age of 2 years at the time of study having a food allergy, compared with 25% of patients above the age of 4 years. Greater severity of eczema is also associated with higher risk of food allergy.

We then compared peanut sensitisation patterns, true peanut allergy, and peanut component patterns between South African children with atopic dermatitis (AD) of Black (Xhosa) origin and children of mixed race to determine whether there are ethnic differences in peanut sensitisation and peanut allergy patterns in South African children with AD.

Methods: 100 children (6 months to 10 years) with moderate to severe AD were randomly selected from a dermatology clinic at the Red Cross Children's Hospital in Cape Town. They underwent food allergy screening by questionnaire and skin prick tests, and allergen specific IgE was assessed with ISAC 103 component microarray testing. Those who were sensitised to peanut (n=43) had additional ImmunoCAP tests for components rArah 1,2,3,8 and 9. Patients with any uncertainty regarding clinical peanut allergy (n=25) underwent incremental open oral food challenges. Sensitisation was defined as SPT ≥ 3mm or ISAC > 0.3Units, and allergy as positive food challenge or convincing recent history of reaction with positive SPT/specific IgE above the "traditional" 95% positive predictive values for peanut allergy (8mm for SPT, 14kU/L for specific IgE).

Results: Overall, 43% of patients were peanut sensitised (53% mixed race and 37% Xhosa, p=0.1). Peanut allergy rates were high overall (24%), though significantly lower in the Xhosas (15%) compared with mixed race (38%, p=0.01), despite comparable baseline characteristics. Traditional 95% positive predictive values for SPT (≥8mm), peanut specific IgE (≥ 14 kU/L) and ImmunoCAP rArah2 (≥ 0.35 kU/L) fared well in the mixed race group (88%, 90%, and 93%, respectively), but poorly in the Xhosa group (80%, 57%, and 53%).

Component tests had a similar pattern in both ethnic groups with Arah2 being most strongly associated with peanut allergy in both ethnic groups. However, the likelihood of allergy with a positive rArah2 (≥ 0.35 kU/L) was significantly lower in Xhosa than mixed race patients (53% v 93%, p=0.01). Arah 3, 8, and 9 were more commonly positive in tolerant patients in both ethnic groups with Arah9 having the strongest association with tolerance of any single component.

Conclusion: In Xhosa patients, sensitisation to peanut (including Arah2) is significantly less likely to equate to true allergy than in mixed race patients. Traditional 95% PPV for peanut allergy perform poorly in Xhosa patients. The component Arah2 is the most valuable for differentiating sensitisation from allergy in both ethnic groups; Arah9 is associated with asymptomatic sensitisation.

EOSINOPHILIC OESOPHAGITIS IN CAPE TOWN, SOUTH AFRICA

Primary researchers: Mike Levin, Cassim Motala

Introduction: Eosinophilic oesophagitis has been described in patients from all ethnic backgrounds in studies originating in all continents apart from Africa.

Methods: This is a descriptive study of children who were diagnosed with eosinophilic oesophagitis at Red Cross Children's Hospital's tertiary Allergy clinic during 2009 to 2010.

Results: A cohort of 8 patients (3 boys, 5 girls) identified at Red Cross Hospital during 2009-2010 is described:
Average age: 7 years (1yr 11 months to 15 years 10 months)
Ethnicity: 2 Caucasian, 5 mixed, 1 Black African
Age of onset: mean 3 years, median 1 year 4 months
Age of diagnosis: mean 6 years 3 months; median 3 years 9 months
Time to diagnosis: mean 3 years 3 months, median 6 months, IQ range 5 months to 6 years.

Presenting symptoms in order of prevalence are reflux (7/8), long time to eat (6/8), difficult swallowing (6/8), growth failure (5/8), food refusal (5/8), and painful swallowing (4/8). Associated atopic diseases comprised immediate food allergy (6/8), eczema (6/8), rhinitis (6/8), asthma (3/8) and urticaria (2/8).

Total of 26 biopsy specimens; mean 3.25 per patient. Only 4/8 confirmed peak eosinophil count >15/hpf, 7/8 had minor features present. Food skin prick tests 152 (19 per patient). Positive skin tests ≥ 1mm 57 (13 per patient). The most commonly identified foods are peas, wheat, milk, egg white, banana, and egg yolk. Skin tests ≥ 3mm 32 (7 per patient). Most commonly identified foods by SPT > 3mm are egg yolk, egg white, peas, soya, rye, rice, carrot, and green beans. Patch tests 167 (21 per patient). 30 positive, average of 4.3 per patient. Most commonly identified foods are beef, peanut, lamb, chicken, soy and ham.

All commenced on initiation of short course of oral steroids. All put on targeted elimination diet. All had clinical improvement. 3 controlled and acceptable symptoms, 2 some symptoms and difficulties, 2 very symptomatic with poor control, 1 defaulted.

SPEAKER ABSTRACTS

AGRICULTURAL BIOTECHNOLOGY SAFETY ASSESSMENT

Agricultural Biotechnology Safety Assessment

Agricultural biotechnology background in Africa

Jacoba Adriana ('Kobie') de Ronde, PhD
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Agricultural productivity has a crucial role to play in ensuring food security in Africa. Because biotechnology holds great promise, African countries are increasingly considering genetically modified (GM) crops as a potential tool in the agricultural toolbox. The adoption of new and emerging technologies is, however, slow in most countries, mainly due to the status of biosafety regulatory frameworks, which include policies, laws and regulations. The development and implementation of a functional regulatory framework to move from research to commercialization of biotechnology crops varies greatly between countries. Africa accounts for about 3.5 million hectares of GM crops, planted only in Burkina Faso, Egypt, North Sudan and South Africa. Various countries are performing confined field trials or are involved in biotechnological research. I will provide a brief overview of the progress made in Africa regarding the adoption of regulatory frameworks and, consequently, the cultivation of biotechnology crops.

Agricultural Biotechnology Safety Assessment

Safety assessment process in support of the regulatory approval of agricultural biotech products

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Research Triangle Park, NC
USA

Crops produced through modern agricultural biotechnology are the most highly studied foods consumed. Even before identification of the elite event that is going to be taken commercial, the safety assessment begins. An evaluation using *in silico* techniques is undertaken to confirm that the gene of interest does not encode a protein that has similarity to known toxins or allergens. Once technical proof of concept in the crop is demonstrated, a preliminary evaluation of the digestive sensitivity is examined. After the commercial event is selected, an extensive safety assessment is conducted that includes studies on the safety of the newly expressed protein, molecular characterization of the insert, impact of the insert on plant performance and composition, environmental impact, and wholesomeness of the crop (Codex Alimentarius Commission, 2003). The registration dossiers are scrutinized by regulatory agencies around the world in both producing countries (those that will grow the crops) and in importing countries. Approval is granted only if the biotech crop has been demonstrated to be as safe as the conventional crop as food or feed and for the environment. This technology has been rapidly adopted by growers in all parts of the world and, in the almost twenty years since these crops have been grown and consumed, there have been no incidences of food safety attributed to them. Furthermore, the many benefits to the environment and for the grower have resulted in a very rapid adoption of this technology.

Agricultural Biotechnology Safety Assessment

Crop composition as part of the GM crop safety assessment

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The fastest adopted new crop technology to date is that of genetically modified (GM) crops because their use has led to reduced crop inputs, convenience and flexibility in crop management, and increased yield and quality. However, many countries require a safety assessment of novel GM crops before they can be grown within the country or before consumption of food and feed from the GM crop. Nutritional composition studies of GM crops are an important component of the overall safety assessment of novel GM crops. These studies compare the GM crop to an appropriate comparator in order to assess the nutritional status of food and feed originating from the novel GM crop, and to identify any possible unintended changes due to insertion of the transgene(s) or its products. If the levels of a nutritional component in the GM crop are not statistically significantly different than those in the comparator, then no further assessment is needed. If levels are statistically significantly different, then these changes are placed in the context of the natural variability within the traditional crop that is considered to be safe.

Agricultural Biotechnology Safety Assessment

Molecular/protein characterization of GM products

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The evaluation process for genetically modified (GM) crops begins with a molecular characterization of the DNA inserted into host plants which drives the expression of the GM trait(s) and selectable marker proteins. The process relies on asking key questions: 1) What DNA was put into the crop? 2) How many expressible genes were put into the crop? 3) What were the source organisms of the DNA? 4) Where in the host genome is the inserted DNA located? 5) Is expression of the gene(s) stable? Similarly, characterization of the trait proteins themselves relies on answering fundamental questions to support these products from a food and feed safety perspective: 1) Is the transgenic-expressed trait protein produced in the plant in a stable manner? 2) Are the biophysical properties of the protein consistent with a safe protein? 3) Is there a history of safe use of the protein or its homologues in other species? 4) Is the recombinant protein equivalent to the GM plant protein? 5) Is the purified trait protein suitable for human and environmental toxicity studies? 6) How much of the protein is expressed? Studies are designed that support these questions and the data are then used to assemble a risk assessment.

Agricultural Biotechnology Safety Assessment

Assessment of potential allergenicity of GM crops

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Unlike conventionally bred crops, a thorough safety assessment process exists for genetically modified (GM) crops. The goal of this process is to demonstrate that the GM crop is “as-safe-as” non-GM crops in the food supply. One of the issues for GM crops is the evaluation of the expressed novel protein for allergenic potential. The purpose of this assessment is (1) to protect allergic consumers from exposure to known allergenic or cross-reactive proteins, and (2) protect the general population from potential risks associated with the introduction of genes encoding proteins that are likely to become food allergens *de novo*. A food allergy is a reaction of the immune system to an otherwise harmless protein in food. Importantly, allergic reactions to food are relatively rare. The incidence of food allergy ranges from approximately 1 to 2% in adults and 6 to 8% in young children. Currently, no single endpoint or response is recognized as a predictor of protein allergenicity. Consequently, a weight-of-evidence approach, which takes into account a variety of factors for an overall assessment of allergenic potential, is conducted [Codex Alimentarius Commission, 2003). This assessment is based on what is known about allergens, including the history of exposure and safety of the gene(s) source (i.e., whether the gene source for the new protein is known to induce allergy); similarity to known allergens (*in silico* amino acid sequence identity comparisons to a database of allergens); stability to pepsin digestion *in vitro*; processing effects [heat stability]); and, when appropriate, specific IgE binding studies.

Agricultural Biotechnology Safety Assessment

Assessment of potential toxicity of GM crops

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An extensive safety assessment process exists for genetically modified (GM) crops. The goal of this process is to demonstrate that the GM crop is “as-safe-as” non-GM crops in the food supply. As part of the mammalian safety assessment, GM crops are evaluated for their toxicological potential. This is accomplished by employing a holistic approach where the host plant, gene, gene product (i.e., protein), and GM crop are evaluated. Some relevant questions initially asked include: 1) Does the host plant have inherent toxicity? and 2) Does the source of the gene(s) have a history of safe use (i.e., whether the gene source for the new protein is known to induce toxicity)? To evaluate the transgenic protein(s), a weight-of-evidence approach, which takes into account a variety of factors for an overall assessment of toxicological potential, is conducted [Codex Alimentarius Commission, 2003). This assessment is based on what is known about the transgenic protein and protein toxins, including similarity to known toxins (*in silico* amino acid sequence identity comparisons to protein databases); stability to pepsin digestion *in vitro*; processing effects [heat stability]); acute toxicity evaluation, mode of action and specificity; and expression level and dietary intake. The GM crop (i.e., the part consumed by humans [typically grain]) is further evaluated for unintended effects by conducting repeat-dose feeding studies in rodents where general health and food consumption, clinical chemistry, hematology, and histopathology are evaluated. When necessary, hypothesis-based toxicology studies may also be conducted.

Agricultural Biotechnology Safety Assessment

Regulatory and safety assessment perspectives for genetically modified food in Kenya

Prof. Theophilus M. Mutui, PhD
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Consumption of any food (conventional, genetically modified (GM), or organic) may present some risk of hazard due to the presence of proteins or other naturally occurring chemicals such as glycoalkaloids that might cause allergies or other harmful effects to humans. GM food safety assessment is the evaluation of known or potential adverse health effects resulting from human consuming GM foods. The safety evaluation of GM food is science-based, conducted on a case-by-case basis, and generally follows a comparative approach involving a step-wise process. The process is comprised of assessment of possible allergenicity (hypersensitive reaction initiated by immunologic mechanisms caused by allergens), toxicity, compositional analysis of key ingredients, food processing, and nutritional modification. Additional risk characterization may involve a toxicological assessment in a rodent model, depending on the outcomes of the previous risk evaluation steps. This paper describes the Kenyan regulatory and safety assessment process for GM food with a view to ensuring the safety of human health and providing adequate levels of protection of the environment.

Agricultural Biotechnology Safety Assessment

Regulatory and safety assessment perspectives: South Africa

Liezel Michelle Gouws, PhD
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The safety of foods derived from genetically modified (GM) crops has been a subject of significant interest and discussion between technology developers, consumers, and policy-makers. A number of national and international regulations govern the use of genetically modified organisms (GMOs). The primary aim of these regulations is to ensure that any activities with GMOs are assessed with regard to their potential risks to human health and the environment. In South Africa, GMOs are primarily governed by the GMO Act (Act 15 of 1997), which provides measures to promote the responsible development and use of GMOs. South Africa has a rigorous regulatory framework, which has been fully functional for more than 14 years. GM crops approved for commercial release in South Africa have undergone extensive safety assessments and have met all the stringent requirements set by the national and international regulatory framework.

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FACULTY OF SPEAKERS

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FOOD ALLERGY AND SAFETY ASSESSMENT WORKSHOP

11-12 August 2014

Kenyatta International Convention Center
Nairobi Central Business District
Nairobi, Kenya

HESI Protein Allergenicity Technical Committee

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Dr. Ayola Akim Adegnika is co-director and group leader of immuno-epidemiology of parasites infection at CERMEL, Hôpital Albert Schweitzer. Currently, he is a Principal Investigator of several studies. He is a research group leader at the Institute for Tropical Medicine, University of Tübingen, and associate researcher at the University of Leiden.

Dr. Adegnika has significant experience in field work activities of basic research studies and epidemiology of helminthiasis in relationship with allergy diseases and malaria infection. As PI and/or investigator, he has conducted several clinical trials of new anti-malarial agents and evaluated efficacy of the existing anti-malarial drugs. In addition, he has excellent international cooperation with European universities, including the University of Tübingen in Germany and the Leiden Medical University Center in The Netherlands.

Dr. Adegnika has received a number of grants, including TDR-WHO, several EU grans (FP6, FP7), and German fellowships (DAAD, DFG-Grant). He is the author and co-author of numerous published papers.

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Abena Amoah is a researcher in the Parasitology Department at the Noguchi Memorial Institute for Medical Research (NMIMR) in Accra, Ghana. Since 2002, she has been involved in multi-centre collaborative projects that focus on parasitic infections and allergic diseases among Ghanaian children. Prior to working at NMIMR, Ms. Amoah was a clinical research assistant at Rockefeller University in New York City for two years.

Ms. Amoah holds a bachelor's degree in Biological Sciences from Mount Holyoke College and a master's degree in Epidemiology from the London School of Hygiene and Tropical Medicine. In September 2014, she will defend her PhD thesis at Leiden University on the complex dynamics between parasitic worm infections and allergy disease among Ghanaian children. Her doctoral research was supervised by Professor Maria Yazdanbakhsh of the Department of Parasitology at Leiden University Medical Center and Professor Daniel Boakye of the Parasitology Department at NMIMR.

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Dr. Philip Brune currently holds the position of Technical Expert for Compositional Analysis, Product Safety, for Syngenta Crop Protection, LLC, in Research Triangle Park, NC, USA. He has been in this position since 2009. Dr. Brune received a BA degree in Biology from Wittenberg University (Springfield, OH), and a MS degree in Plant Pathology from The Ohio State University. He then went on to obtain a PhD degree in Plant Pathology from North Carolina State University. From 1995 to 1997, Dr. Brune held an assistant professorship in the Math and Science Department at St. Mary's College (Raleigh, NC). In 1997, he accepted a position with Syngenta Crop Protection, where he has held positions as a research scientist (conducting field research on disease control of most major field, fruit, and vegetable crops), in data management (data capture, analysis, and mining; experimental design), and as team lead for Compositional Analysis of genetically modified crops. Dr. Brune was Co-Chair of the International Life Sciences Institute (ILSI) Crop Composition Task Force, and was one of the organizers of the ILSI International Food Biotechnology Committee (IFBiC) Crop Composition Workshop, held in Washington, DC, in September 2012. He has spoken about crop compositional analysis at workshops sponsored by ILSI (November 2012, Brasilia, Brazil), the Organisation for Economic Co-operation and Development (November 2013, Paris, France) and EuropaBio (February 2014, Brussels, Belgium).

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Prof. Custovic's major academic contributions have been in fields of genuine unmet clinical need, especially prevention of childhood asthma and food allergy. He has published more than 200 papers in peer-reviewed journals. His research output has been highly cited over the last decade. He is an Associate Editor of *Thorax* and a member of the Editorial board of several major international specialty journals.

Prof. Custovic served as a Secretary of the British Society of Allergy and Clinical Immunology (BSACI) in two terms, represented allergy on the Specialist Advisory Committee of the Royal College of Physicians, is President of the Asthma section of the European Academy of Allergy and Clinical Immunology, and is a member of several World Allergy Organisation Special Committees.

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Prof. Alison Elliott became interested in Tropical Medicine as an undergraduate as a result of a course on parasitology and immunology at Cambridge, and this interest was encouraged further, as a medical student, by an elective with the MRC Unit in The Gambia. After completing medical training, she joined the London School of Hygiene and Tropical Medicine and, during the late '80s and early '90s, undertook studies on the interaction between tuberculosis and HIV infection in Zambia. An infectious diseases fellowship in Denver, Colorado, provided an opportunity to learn about management of MDR-TB and laboratory immunology. This enabled Prof. Elliott to plan and conduct subsequent clinical-immuno-epidemiological studies. Since 1997, she has been based in Uganda at the Uganda Virus Research Institute. Current interests focus on the effects interactions between co-infections, the effects of helminth infection on immune responses to vaccines, infectious and allergic disease incidence in children in Uganda, and research capacity building in Africa.

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Prof Levin has a special interest in epidemiology of allergy in Africa, severe allergies and anaphylaxis, as well as patient support and education.

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Currently, Prof. Mutui is the Chief Biosafety Officer responsible for Compliance and Enforcement. He represents the National Biosafety Authority in the National Food Safety Coordination Committee (NFSCC) and Technical Committee on Biotechnology at the Kenya Bureau of Standards. He has been (2007-2013) the National Coordinator for the European Union (EU) Executive Agency for Health and Consumer's (EAHC) Hazard Analysis & Critical Control Point (HACCP) Training Program. Previously, Prof. Mutui was a faculty member in the Department of Horticulture, School of Agriculture and Biotechnology, University of Eldoret, Kenya. Consequently, he has many years of experience in research, consultancy, and teaching. Prof. Mutui is a member of many local and international professional societies, including the International Society of Horticultural Sciences (ISHS), Horticultural Association of Kenya (HAK), and the Kenya DAAD Scholars Association (KDSA). He has widely published in international refereed journals and he is regularly invited as a guest speaker at scientific conferences. Prof. Mutui is a strong believer in ensuring accessibility of safe and affordable food in adequate quantities to the Kenyan citizenry.

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Prof. Gabrielle Pauli studied medicine at the Faculty of Medicine of Strasbourg University. She qualified as a doctor in 1967 and was appointed assistant at the Department of Chest Diseases. As soon as 1968, she specialized in asthma and allergy at the Faculty of Medicine of Marseilles. Back in Strasbourg, she developed a specific consultation for respiratory allergic diseases. Her research was aimed at the role of mites in allergic asthma, and she performed the first bronchial challenge tests with mite allergens; she also demonstrated the plurality of allergens in house dust using in vivo and in vitro tests.

Prof. Pauli carried on her clinical research, initiating immunotherapy with mite extracts and testing eviction methods. She validated a mite detection test (by dosing guanine concentration in house dust samples) and initiated the employment of an environmental counsellor. Her work won her the *Environment and Health Prize* delivered by the French Academy of Medicine in 1993 and the 9th Gold Medal of the Foundation for Research in Allergy in 1995.

As a pneumologist, she took a thirty-year long interest in occupational asthma and trained a team of practitioners, nurses and technicians which made her department a pole of reference.

Several new etiologies of occupational asthma were described by her team. She co-founded the occupational asthma registry in France and, with two colleagues, issued the first book on occupational asthma published in French (first edition 1999, second 2012).

From 1995 onward, her research has been aimed at molecular allergens and, thanks to exceptional collaborations with European researchers in the same field, she was one of the first clinicians to test recombinant molecules in patients. Together with two other groups, she initiated the first trial of immunotherapy with a recombinant allergen showing that the concept led to satisfactory results.

In 2011 the European Academy of Allergy and Clinical Immunology gave her the Clemens von Pirquet Award for her research, which found expression in more than 300 publications, general reviews, and book chapters.

Gabrielle Pauli is professor emeritus, former Head of the Pneumology Department of the Strasbourg University Hospital, former President of the French Society of Allergology, former President of the French Society of Pneumology, and a member of the Collegium internationale allergologicum.

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Prof. Ronald van Ree was originally educated in history but switched to biochemistry and immunology, the field in which he defended his thesis at the University of Amsterdam in 1994 on the topic of grass pollen allergens and their interaction with the immune system. From 1994 until 2005, he headed the Allergy Research Laboratory at Sanquin Blood Supply Foundation in Amsterdam. In July 2005, he moved to the Academic Medical Center in Amsterdam where he was appointed as Associate Professor at the Department of Experimental Immunology. There he is head of the Laboratory for Allergy Research. In June 2009, Prof. van Ree was appointed as Full Professor of Molecular and Translational Allergology. In 2010, he began work as a consultant for one day a week at HAL Allergy BV in Leiden, where he continues to advise the management of the R&D program. During 2011, he *ad interim* headed the Department of Experimental Immunology.

Prof. van Ree has participated in many European Union (EU) Framework Programme projects, including as vice-coordinator in the Integrated Project on Food Allergy, EuroPrevall, the GLOFAL project aimed at integrating food allergy research in developing countries into the EU framework programme, and most recently as co-ordinator of the ongoing project on immunotherapy for food allergy (2008-2015). He is a Member-at-Large of the Executive Committee of the European Academy of Allergy and Clinical Immunology (EAACI), and is a Co-Chair of the ILSI Health and Environmental Sciences Institute's (HESI) Protein Allergenicity Technical Committee. He is on the editorial board of several leading journals in the field of allergology, and is associate editor of International Archives of Allergy and Immunology. Prof. van Ree has published over 200 papers in peer-reviewed journals, as well as several book chapters.

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RESOURCES

FOOD ALLERGY AND SAFETY ASSESSMENT WORKSHOP

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HESI Protein Allergenicity Technical Committee

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY

Allergy

POSITION PAPER

EAACI Food Allergy and Anaphylaxis Guidelines: diagnosis and management of food allergy

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Abbreviations

APT, atopy patch test; BAT, basophil activation test; CRD, component-resolved diagnosis; DBPCFC, double-blind, placebo-controlled food challenge; EAACI, European Academy of Allergy and Clinical Immunology; EoE, eosinophilic esophagitis; FA, food allergy; FPIES, food protein-induced enterocolitis syndrome; GERD, gastroesophageal reflux disease; GRADE, Grading of Recommendations Assessment, Development and Evaluation; IgE, immunoglobulin E; IgG4, immunoglobulin G4; LR, likelihood ratio; LTP, lipid-transfer proteins; NIAID, National Institute of Allergy and Infectious Diseases; NPV, negative predictive value; NSAID, nonsteroidal anti-inflammatory drugs; OFC, oral food challenge; PPV, positive predictive value; RCTs, randomized controlled trials; sIgE, specific IgE; SLIT, sublingual immunotherapy; SPT, skin prick test; US, United States.

Keywords
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Abstract

Food allergy can result in considerable morbidity, impact negatively on quality of life, and prove costly in terms of medical care. These guidelines have been prepared by the European Academy of Allergy and Clinical Immunology's (EAACI) *Guidelines for Food Allergy and Anaphylaxis Group,* building on previous EAACI position papers on adverse reaction to foods and three recent systematic reviews on the epidemiology, diagnosis, and management of food allergy, and provide evidence-based recommendations for the diagnosis and management of food allergy. While the primary audience is allergists, this document is relevant for all other healthcare professionals, including primary care physicians, and pediatric and adult specialists, dieticians, pharmacists and paramedics. Our current understanding of the manifestations of food allergy, the role of diagnostic tests, and the effective management of patients of all ages with food allergy is presented. The acute management of non-life-threatening reactions is covered in these guidelines, but for guidance on the emergency management of anaphylaxis, readers are referred to the related EAACI Anaphylaxis Guidelines.

Food allergy has been defined as adverse reactions to food in which 'immunologic mechanisms have been demonstrated' (1, 2); this term therefore encompasses both immunoglobulin E (IgE)-mediated and non-IgE-mediated food allergies (Tables 1 and 2). Food allergy can result in considerable morbidity and in some instances results in life-threatening

Table 1 Key terms (85)

Allergen	Any substance stimulating the production of immunoglobulin IgE or a cellular immune response, usually a protein
Atopic eczema/dermatitis	Chronic inflammatory skin disease characterized by typical age-related lesions with pruritus and personal or family history of atopic disease
Cofactors	Patient-related external circumstances that are associated with more severe allergic reactions. They are known also as augmentation factors
Eosinophilic esophagitis	A chronic, immune/antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation
Food	Any substance, whether processed, semi-processed, or raw, which is intended for human consumption, and includes drink, chewing gum, and any substance which has been used in the manufacture, preparation, or treatment of 'food' but does not include cosmetics or tobacco or substances used only as drugs (Codex Alimentarius)
Food allergy	An adverse reaction to food mediated by an immunologic mechanism, involving specific IgE (IgE-mediated), cell-mediated mechanisms (non-IgE-mediated) or both IgE- and cell-mediated mechanisms (mixed IgE- and non-IgE-mediated)
Food desensitization	Induction of short-term tolerance that may disappear after withdrawal of the treatment
Oral tolerance	A state of local and systemic immune unresponsiveness induced by oral administration of innocuous antigens/allergens
Oligo-allergenic diet	An empirical elimination diet with minimal content of major food allergens for the given population
Oral tolerance induction	A state of local and systemic permanent immune unresponsiveness induced by following oral administration consumption of innocuous antigens such as food proteins, does not disappear after withdrawal of the antigens
Prebiotic	Nondigestible substances that provide a beneficial physiological effect for the host by selectively stimulating the favorable growth or activity of a limited number of indigenous bacteria
Probiotic	Live microorganisms which, when administered in adequate amounts, confer a health benefit on the host
Sensitization	Presence of specific IgE to an allergen
Symbiotics	A mixture of probiotics and prebiotics

Table 2 Food-induced allergic disorders (classified based on the underlying immunopathology)

Immunopathology	Disorder	Clinical features	Typical age group	Prognosis
IgE mediated	Pollen food allergy syndrome	Pruritus, mild edema confined to oral cavity	Onset after pollen allergy established (adult > young child)	May be persistent and may vary by season
	Urticaria/angioedema	Triggered by ingestion or direct contact	Children > adults	Depends on food
	Rhinoconjunctivitis/asthma	Accompanies food-induced allergic reaction but rarely isolated symptoms May be triggered by the inhalation of aerosolized food protein	Infant/child > adult, except for occupational disease	Depends on food
	Gastrointestinal symptoms	Symptoms such as nausea, emesis, abdominal pain, and diarrhea triggered by food ingestion	Any age	Depends on food
	Anaphylaxis	Rapid progressive, multisystem reaction	Any age	Depends on food
	Food-dependent, exercise-induced anaphylaxis	Food triggers anaphylaxis only if ingestion is followed temporally by exercise	Onset in late childhood/adulthood	Presumed persistent
Mixed IgE and cell mediated	Atopic eczema/dermatitis	Associated with food in 30–40% of children with moderate/severe eczema	Infant > child > adult	Usually resolves
	Eosinophilic gastrointestinal disorders	Symptoms vary depending on the site of the intestinal tract involved and degree of eosinophilic inflammation	Any age	Likely persistent
Cell mediated	Dietary protein-induced proctitis/proctocolitis	Mucus-laden, bloody stools in infants	Infancy	Usually resolves
	Food protein-induced enterocolitis syndrome	Chronic exposure: emesis, diarrhea, poor growth, lethargy Re-exposure after restriction: emesis, diarrhea, hypotension a couple of hour after ingestion	Infancy	Usually resolves

Modified from Sicherer and Sampson (86) with permission.

anaphylaxis. These guidelines aim to provide evidence-based recommendations for the diagnosis and management of patients of any age with suspected or confirmed food allergy. Development of the guidelines has been based on three systematic reviews of the epidemiology, diagnosis, and management of food allergy (3–5) with weaker forms of evidence being used where there were insufficient data from more robust studies or where high-level evidence is practically or ethically unobtainable. These guidelines build on the previous EAACI position paper on adverse reaction to foods (6) and are complementary to the other current food allergy guidelines, including the United States (US) National Institute of Allergy and Infectious Diseases (NIAID) Guidelines (7). Distinctive features include a European focus and the placing of particular emphasis on the practical issues associated with diagnosis and long-term management of food allergy. Details on the production of these guidelines, the approaches used, and the involvement of experts and stakeholders are summarized in the Data S1 and Table S1 (Box 1).

Box 1: Key questions addressed in the supporting systematic reviews: diagnosis and management (3–5)

- What is the epidemiology (i.e., frequency, risk factors, and outcomes) of food allergy in Europe and how does this vary by time, place, and person?
- What is the diagnostic accuracy of tests aimed at supporting the clinical diagnosis of food allergy?
- What is the effectiveness of pharmacological and nonpharmacological interventions for the management of acute, non-life-threatening food-allergic reactions?
- What is the effectiveness of pharmacological and nonpharmacological interventions for the longer-term management of food allergy?

Epidemiology

To estimate the incidence and prevalence, time trends, and potential risk and prognostic factors for food allergy in Europe, we conducted a systematic review of recent (i.e., 2000–2012) European studies (3). One hundred and nine articles were assessed for eligibility, and 75 (comprising 56 primary studies) were included in a narrative synthesis and 30 studies in a meta-analysis. Most of the studies were graded as at moderate risk of bias.

A summary of the key findings is presented in Table 3. The point prevalence of self-reported food allergy was approximately six times higher than the point prevalence of challenge-proven food allergy. The prevalence of food allergy

Table 3 Summary of the pooled prevalence of food allergy (FA) in Europe, by age and region: studies published January 1, 2000–September 30, 2012*

	Self-reported food allergy		Sensitization to at least one food allergen (point prevalence)		Symptoms + sensitization to at least one food allergen (point prevalence)		Convincing clinical history or positive food challenge† (point prevalence)	Positive open food challenge or DBPCFC† (point prevalence)
	Life time prevalence	Point prevalence	Positive specific IgE	Positive skin prick test	Symptoms + positive specific IgE	Symptoms + positive skin prick		
All	17.3 (17.0–17.6)	5.9 (5.7–6.1)	10.7 (9.4–10.8)	3.0 (2.7–3.3)	2.7 (1.7–3.7)	1.5 (1.3–1.7)	2.6 (2.1–3.1)	0.9 (0.8–1.1)
Age								
Children (0–17 years)	17.4 (16.9–18.0)	6.9 (6.6–7.2)	12.2 (11.4–13.1)	3.0 (2.7–3.3)	3.6 (2.8–4.4)	1.5 (1.3–1.7)	2.6 (2.1–3.1)	1.0 (0.8–1.2)
Adults (≥18 years)	17.2 (16.0–17.6)	5.1 (4.8–5.3)	4.1 (3.2–5.1)	–‡	2.2 (0.8–3.7)	–‡	–‡	0.9 (0.8–1.0)
Region§								
Western Europe	23.8 (22.9–24.7)	3.3 (3.1–3.5)	11.7 (9.8–13.6)	1.8 (1.5–2.1)	2.6 (1.3–3.8)	1.4 (1.1–1.7)	–‡	3.1 (2.6–3.7)
Eastern Europe	41.6 (39.5–43.7)	3.3 (1.2–5.4)	–‡	–‡	–‡	–‡	–‡	–‡
Southern Europe¶	8.6 (8.2–9.0)	3.5 (2.5–4.5)	–‡	4.2 (2.2–6.3)	–‡	1.8 (1.3–2.3)	–‡	0.2 (0.1–0.3)
Northern Europe	30.3 (28.7–31.9)	14.5 (13.9–15.2)	9.8 (9.0–10.5)	5.4 (4.6–6.1)	3.0 (2.1–3.9)	1.6 (0.9–2.3)	2.6 (2.1–3.1)	1.1 (0.9–1.3)
Europe**	19.2 (18.6–19.8)	5.0 (4.6–5.5)	–‡	–‡	–‡	–‡	–‡	–‡

DBPCFC, double-blind, placebo-controlled food challenge.

Figures are percentages (95% CI).

*The pooled prevalence of FA was based on random-effects meta-analysis for 30 clinically and methodologically comparable studies.

†Where a study reported estimates for both open food challenges and DBPCFC, the DBPCFC estimates were always used; otherwise open food challenges estimates were used if DBPCFC was not carried out in the study.

‡No study undertaken for this group for this particular outcome.

§European regions were classified based on the United Nations classification (http://unstats.un.org/unsd/methods/m49/m49regin.htm#europe, accessed on December 28, 2012).

¶We further added studies from Turkey into southern Europe.

**For studies that included several European countries and gave overall estimate for all the countries and in which it was not possible to calculate the frequency for each country studied.

was generally higher in children than in adults. While the prevalence of primary food allergy appeared to be stable over time, the prevalence of secondary food allergy caused by cross-reactions of food allergens with inhalant allergens appears to be increasing. There were no consistent risk or prognostic factors for the development or resolution of food allergy. However, sex, age, country of residence, familial atopic history, and the presence of other allergic diseases may play an important role in its etiology.

Few studies employed double-blind, placebo-controlled food challenge (DBPCFC) in a population-based sample; further studies are therefore required to establish the actual prevalence of objectively confirmed food allergy in the general population. Further studies are also needed to investigate the long-term prognosis of food allergy.

Diagnosis

Patient's clinical history and examination

The clinical presentation of food allergy involves a large spectrum of symptoms ranging from skin (urticaria, angioedema, atopic eczema/dermatitis), gastrointestinal (i.e., vomiting, colic, abdominal pain, diarrhea, constipation), respiratory (rhinorrhea, sneezing, cough, dyspnea) to circulatory (cardiovascular collapse; see Table 2). Attention should be paid to the fact that reactions can be triggered by food ingestion, inhalation, and skin contact. A careful dietary history is fundamental to the diagnosis of food allergy (see Data S2). It can establish the likelihood of the diagnosis, suggest whether an IgE or non-IgE mechanism is involved, and identify the potential food triggers. A small amount of literature indicates that the predictive value of the clinical history for immediate symptoms, either alone or in combination with skin prick tests (SPT) or serum-specific IgE (sIgE) blood tests, ranges from 50% to 100% (8–10). The clinical evaluation should include a thorough examination of nutritional status and growth, especially in children, as well as associated atopic diseases such as atopic eczema/dermatitis, allergic rhinitis, and asthma.

See *Recommendations Box* 2*A,B*.

Diagnostic tests for food allergy

In vivo SPT and sIgE for food allergens are the first-line tests to assess IgE sensitization. However, like the patient history, these tests cannot always accurately diagnose food allergy. Elimination diet for diagnostic purposes and oral food

Box 2: EAACI recommendation on the diagnosis of food allergy

Recommendations	Evidence level	Grade	Key references
(A) Patient's clinical history			
Detailed clinical history is essential for the diagnosis of food allergy	IV	D	Expert opinion
When taking a clinical history eliciting allergens, timing and chronicity, symptoms, severity and signs, reproducibility, known risk (co)factors, family history, coexisting medical problems including other allergic diseases should be addressed	V	D	Expert opinion
The use of structured questions on symptoms, foods, and other background information is recommended	V	D	Expert opinion
(B) Determination of sensitization to food			
Where available, standardized tests and procedures should be used	IV	D	Expert opinion
IgE sensitization does not always predict clinically relevant food allergy, so specific allergy testing should be directed by case history	IV	C	(4)
Either SPT or sIgE can be the test of choice for sensitization depending on local availability and absolute and relative contraindications to SPT	IV	C	(4)
Evidence of IgE sensitization to common food and appropriate aeroallergens can support a diagnosis of food allergy in conjunction with clinical history and/or food challenge	I–III*	A–C	(4)
In the presence of a suggestive history, a negative SPT or sIgE needs to be interpreted with caution particularly as these are expected in non-IgE-mediated food allergy	IV	C	(4)
Where SPT and sIgE tests are inconclusive, component-resolved diagnostic test (if available) may provide additional diagnostic information	I–IV*	A–C*	(4, 22–24)
If clinical history with SPT and/or sIgE results is not *highly predictive* (see figure 1), an OFC is required	IV	D	Expert opinion
Determination of total IgE is particularly useful in patients with severe eczema; a very high total IgE level suggests that positive sIgE results should be interpreted with care as they may represent asymptomatic sensitization	IV	D	Expert opinion
(C) Elimination diets for diagnostic purposes			
Determining which foods to be avoided should be based on the allergy-focused diet history, clinical history, and allergy testing (SPTs and/or sIgE)	V	D	Expert opinion

Box 2: (Continued)

Recommendations	Evidence level	Grade	Key references
For each individually avoided food, the results of the diagnostic elimination diet should be carefully monitored and evaluated over 2–4 weeks of avoidance	V	D	Expert opinion
Where the elimination diet leads to a significant relief of symptoms, it should be continued until the provocation test is performed	V	D	Expert opinion
Where the elimination diet does not lead to a significant relief of symptoms, food allergy to the eliminated foods is highly unlikely	V	D	Expert opinion
(D) Oral food challenge (OFC)			
The OFC (particularly the double-blind placebo-controlled food challenge) is the gold standard investigation for the objective diagnosis of IgE- and non-IgE-mediated food allergy	IV	D	Expert opinion
OFCs should be used to demonstrate allergy or tolerance and in so doing facilitate safe dietary expansion or appropriate allergen avoidance	IV	D	Expert opinion
The DBPCFC should be performed when symptoms are subjective, with delayed or atypical symptoms, where patients and/or caregivers are anxious, and considered in all research settings	IV	D	(18, 20)
A negative DBPCFC should end with an open or cumulative ingestion of the food based on a normal age-appropriate portion to confirm oral tolerance	IV	D	Expert opinion
OFC must be performed in a specialist setting with emergency support immediately available; where there is a moderate-to-high risk of a severe reaction, intensive care support must be immediately available	IV	D	Expert opinion
(E) Diagnosis of EoE			
Every patient with EoE should be referred to an allergist/immunologist for workup	IV	D	(41)
EoE is diagnosed by an upper endoscopy with 2–4 biopsies from both the proximal and distal esophageal biopsies (43). Biopsies should be performed when the patient has been treated for at least 6 weeks with double-dose proton-pump inhibitors to rule out esophageal eosinophilia caused by gastroesophageal reflux disease and to exclude proton-pump inhibitor-responsive esophageal eosinophilia	IV	D	(41, 42)
The clinical utility of measuring serum food sIgE and SPT results to generate a successful elimination diet needs further investigation. Future studies should clearly document a clinical and histologic benefit from dietary interventions guided by results from serum IgE levels, skin prick testing, or atopy patch testing	IV	D	(41)
(F) Unconventional tests, including specific IgG testing			
There are no unconventional tests which can be recommended as an alternative or complementary diagnostic tool in the workup of suspected food allergy, and their use should be discouraged	III	C	(48)

DBPCFC, double-blind, placebo-controlled food challenge; SPT, skin prick test; OFC, oral food challenge; EoE, eosinophilic esophagitis; sIgE, specific IgE.

*For consistency with the EAACI Guidelines on Anaphylaxis, level III-1 to level III-3 for establishing diagnostic test accuracy are summarised as level III in this document.

challenges are still required for both IgE- and non-IgE-mediated food allergy in order to define the clinical relevance of the initial investigations. For some clinical manifestations such as food-induced enteropathies, endoscopy and biopsy are often required to establish the diagnosis. The diagnostic workup of food allergy is summarized in Fig. 1.

Specific IgE: in vitro and skin tests

The determination of sensitization to suspected food allergens includes the assessment of co- and cross-sensitization to related food or aeroallergens. To avoid identifying food allergens where sensitization is seen without clinical relevance, only food and aeroallergens related to the clinical presentation, age, geographic location, and ethnic dietary habits of the patient should be investigated.

Specific IgE and SPT are scientifically valid tests although not all are standardized. Currently, single recombinant protein solutions for SPT are not approved in the EU. However, in some countries, purified natural date profilin and Pru p 3 are available for SPT. Determination of total IgE levels can be helpful in the interpretation of results as very high IgE levels can be associated with multiple positive SPTs or sIgE results that are not clinically relevant.

Skin prick test can be undertaken in patients of any age although reactivity may be lower in infants and possibly the elderly (11). The choice of tests should be guided by the

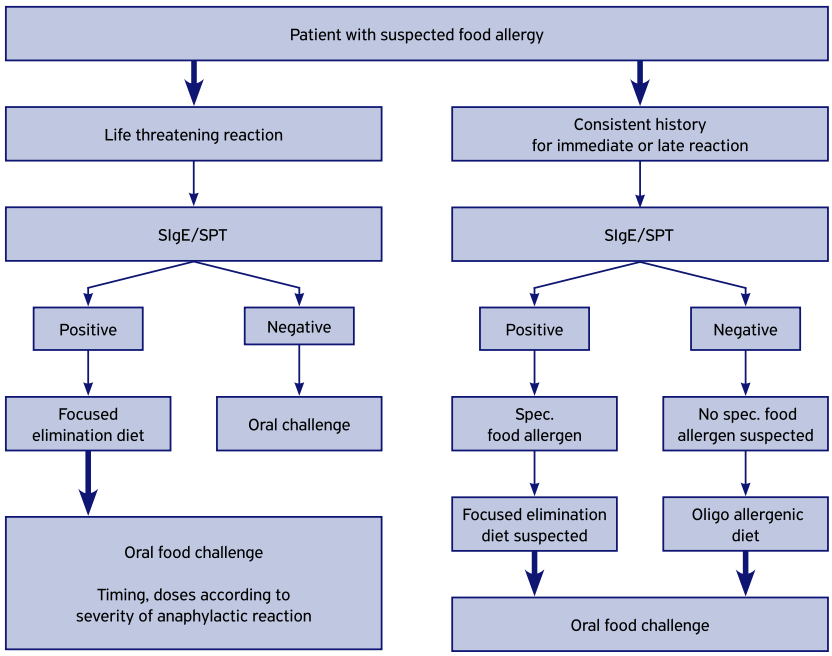

Figure 1 Algorithm for the diagnosis of food allergy.

detailed clinical history. The use of good-quality food allergen extracts, characterized by the demonstration of clinical efficacy and the presence of relevant allergens, is strongly recommended when available. Due to a possible under-representation of minor allergens or instability of the allergenic proteins, false-negative reactions can occur. Whenever these types of extracts are not available and/or minor or instable allergens are relevant for the sensitization (i.e., most fruits and vegetables), fresh foods should be used. Only trained healthcare professionals, able to interpret results and manage possible adverse reactions, should perform SPTs. These tests are performed on the forearm or upper back. Negative (saline 0.9%) and positive (histamine 10 mg/ml) controls are required and the maximum wheal diameter is reported with an arbitrary positive cut-off diameter ≥3 mm after 15 min (12, 13). There are numerous variables to be considered when performing and interpreting SPT including lancet type, recording of wheal diameter, timing, age, sex, and site of testing (12, 14). In addition, it should be considered that European parameters may differ from North American ones. For food allergy, intradermal skin testing is not recommended because of its low specificity, high potential for irritant reactions, and risk for systemic reactions, except in particular situations, for example alpha-gal allergy (15).

In our systematic review, we found reasonable sensitivity (70–100%), although less for most plant food allergies, but moderate specificity (40–70%) both for sIgE and for SPT using the DBPCFC as a reference test (4). Sensitivity and specificity of serum IgE testing and SPT varied depending on the food being tested and due to the heterogeneity of studies with respect to inclusion criteria for patients, their geographic background, and their age and ethnicity, as well as recruitment processes. High-quality performance of these tests is observed for allergens such as peanut, egg, milk, hazelnut, fish, and shrimp, but less so for soy and wheat (4). For other plant-derived (carrot, celery, kiwi, lupine, maize, and melon) or animal-derived foods (chicken and pork), only single studies were included in the recent systematic analysis.

Specific IgE and SPT tests are good to confirm or rule out the involvement of IgE in (self-)reported food hypersensitivity. Interpretation is improved when presenting features and the magnitude of results are taken into account (see Data S2). However, they are often unable to differentiate between clinically relevant allergy and tolerance and oral challenges are therefore required.

Atopy patch test

Due to the lack of standardized test substances and the lack of studies showing advantages of atopy patch test (APT) over SPT or sIgE, APTs are not recommended for routine diagnosis of food allergy (16, 17).

See *Recommendations Box 2B*.

Elimination diet

An elimination diet for diagnostic purposes consists of the avoidance of the food(s) suspected of triggering allergic reactions based on the clinical history, allergy-focused diet history, and adjunct allergy testing such as SPT and sIgE. The duration of the avoidance should be no longer than necessary to achieve a significant relief of symptoms, usually 2–4 weeks for IgE-mediated symptoms and longer for non-IgE ones [e.g., up to 6 weeks for eosinophilic esophagitis (EoE)]. The diet should be thoroughly monitored and results evaluated to establish or refute the diagnosis to prevent unnecessary food restrictions. If the effect of the avoidance is limited, the diet needs to be carefully re-evaluated in case potential food allergens have been overlooked. Cofactors may also be impli-

cated. For cow's milk allergy, extensively hydrolyzed formula may not be effective in achieving remission, and an amino acid-based formula may be required. When a properly performed elimination diet does not ameliorate the symptoms, food allergy to the eliminated foods is highly unlikely. The avoidance phase should be followed by a planned reintroduction of the eliminated food(s). Where there is no risk of a severe reaction, reintroduction may occur at home. A reported clinical reaction should be confirmed by oral food challenge (OFC) under medical supervision.

See *Recommendations Box 2C*.

Oral food challenges

Oral food challenges are usually required to confirm the diagnosis of food allergy, to monitor food allergy, or to prove oral tolerance to a given food (Table 3). There are guidelines, including one from the EAACI (18, 19) and a recent PRACTALL consensus (20), that describe procedures of OFCs in detail. These recommendations deal with the many variables involved in designing a patient-specific challenge (Table 5). These include patient selection, safety criteria, type and quantity of the food allergen to be administered, timings between doses, outcome criteria, observation periods, and recipes to be used. Some of the key recommendations are summarized in Table 4.

Oral food challenges can be performed in an open or blinded manner. Blinded challenges can be single- or double-blinded. In many cases, an open OFC with an objective unequivocal reaction is sufficient for the diagnosis of food allergy. The DBPCFC is considered the gold standard diagnostic test for the diagnosis of food allergy. However, a negative open challenge of a regular age-appropriate serving or the negative outcome of the administration of a cumulative dose of the previous challenge on another day (21) is required for confirming the result of a negative DBPCFC (Fig. 2). Double-blind, placebo-controlled food challenge is time-consuming and resource-intensive to undertake. A negative OFC may be useful as a first step in ruling out food allergy. In patients with atopic eczema subjective or suspected psychological symptoms, the DBPCFC is superior to an OFC. The food should be blinded for taste, smell, texture, and appearance (consistency, color, and shape). The placebo and the active food should be sensory indistinguishable from each other.

In order to avoid severe reactions, patients receive the food in titrated doses often with half-logarithmic dose increments, at set intervals. For many foods such as cow's milk, hen's egg, peanut, or tree nuts, dose ranges from 3 mg to 3 g of food protein seem sufficient in clinical practice (see Data S2).

Food allergy challenges are usually stopped if objective clinical reactions are observed or the last dose is consumed without clinical symptoms. Immediate reactions usually appear within 2 h after the last food intake, atopic eczema may worsen several hours or days following an oral challenge. Urticaria and angioedema are the most common objective signs, and gastrointestinal, respiratory or cardiovascular system involvement is also common.

To optimize safety, vital signs should be closely monitored during OFC and equipment and appropriately trained staff should be in place to deal with allergic reactions – including anaphylaxis.

For patients with non-IgE-mediated reactions, challenges tailored on the individual modalities of reactions should be designed.

See *Recommendations Box 2D*.

Table 4 Indications for oral challenge tests

Indication	Rationale
Demonstrate allergy	Uncertain diagnostic outcome despite the use of detailed clinical history and IgE sensitization testing
	Suspected food-allergic reaction for which the cause is uncertain despite allergy testing (e.g., composite meal eaten)
	Determine threshold dose of causative allergen
Demonstrate tolerance	When allergy tests suggest tolerance but food has never been eaten and patients and/or parents too cautious to introduce at home
	Nonclinically relevant cross-reactivity suspected, for example a patient with a low positive IgE result to hazelnut but high positive birch pollen sensitization
	When the diet is restricted due to a suspicion that one or more foods are resulting in delayed allergic symptoms (e.g., eczema)
	Allergy suspected to have been outgrown
Monitor therapy for food allergy	To monitor response to immunomodulatory treatment in research setting

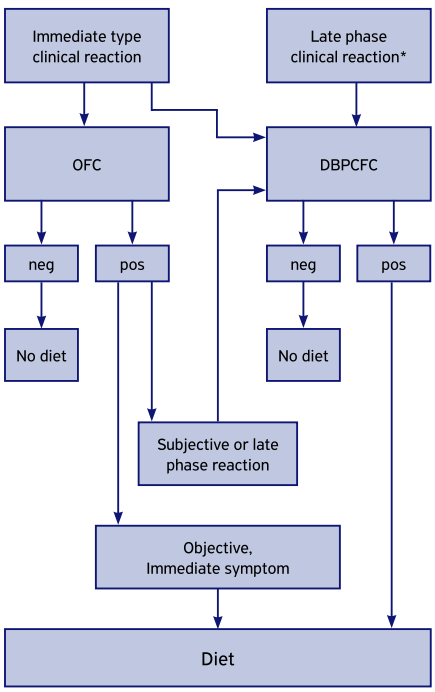

Figure 2 Algorithm for oral food challenge. *Atopic dermatitis, gastrointestinal symptoms.

Table 5 Variables associated with oral food challenges

Variable	
Design	May be open (cumulative or incremental) or blinded (single- or double-blinded). Design selected according to the indication and purpose for which the challenge is being performed
Form of challenge food	The challenge food should closely replicate the usual edible form of the food or form of the food implicated in allergic reaction
	Food processing can significantly influence allergenicity of the food (e.g., baked *vs* raw egg)
	For oral food challenges performed to diagnose the pollen food syndrome, fresh fruit and vegetables should be used, as the responsible proteins are commonly heat labile
Choice of food matrix	Strictly avoid use of allergenic ingredients for individual patient
	Minimize the number of ingredients used
	Provide adequate allergen protein in a manageable portion size
	For placebo foods, sensory qualities should closely replicate those of active challenge food
Doses	
Number of doses	In most cases, half-logarithmic dose increments are indicated. If a negative outcome is anticipated, and there are no safety concerns, a single cumulative dose is appropriate
Initial dose	In clinical settings, 3 mg of food protein seems adequate for most common food allergens such as cow's milk, hen's egg, peanuts, and tree nuts. Lower doses are used for threshold studies in research setting or for patients at high risk of a severe reaction
Top dose	Equivalent to an 'age-appropriate' portion, 3 g of food protein seems adequate for the most common food allergens such as cow's milk, hen's egg, peanuts, and tree nuts
Time intervals between doses	15–30 min, but may be adjusted to the patient's history
Total challenge duration	Usually completed within 8 h (immediate symptoms) and 1–4 weeks (delayed symptoms)

Promising novel diagnostic approaches

In molecular or component-resolved diagnostic tests (CRD), sIgE antibodies are measured against individual allergenic molecules from foods with the potential to improve the specificity of serum IgE testing and the specificity for selected food. This can be performed either in single test formats or in a microarray, testing a range of purified allergens simultaneously. For peanut allergy, determination of sIgE for the major allergen, Ara h 2, showed sensitivity of 100% and specificity of 70–80% in two recent studies (22, 23). The determination of omega-5-gliadin proved to be of high diagnostic relevance in exercise-induced food allergy to wheat in a number of recent case reports and cohort studies (24) as well as the determination of rGly m 4 for allergy to soy milk in birch-sensitized patients (25). For certain fruits (i.e., apple, peach, kiwi, and melon), vegetables (i.e., carrot and celery), tree nuts and peanut, soy, fish, and shrimp, CRD are also available and provide better insight into sensitization patterns (23). The technique of CRD is promising and broadly studied, and some important clinical results are summarized in Data S2. Evidence from well-designed randomized controlled studies on the diagnostic test accuracy of CRD is still required to properly assess its diagnostic value (see Box 2B).

Basophil activation tests (BATs) have been applied in the diagnosis of cow's milk, egg, and peanut allergy (22, 26, 27) as well as in the diagnosis of pollen food syndromes in small clinical studies (28, 29). Basophil activation test has shown higher specificity and negative predictive value than SPT and sIgE, without losing sensitivity or positive predictive value. However, BAT requires a specialized laboratory setting and large clinical studies on its diagnostic performance are lacking. Thus, the use of this promising test is still limited to research purposes on food allergy.

Another promising research area is the determination of IgE antibodies against overlapping synthetic linear peptides of food allergens, as it has been performed for milk (30–32), peanut (33, 34), egg (35), and shrimp (36, 37).

See *Recommendations Box 2B*.

Diagnostic workup of gastrointestinal non-IgE-mediated symptoms

Infants in the first year of life may present with gastrointestinal food-related clinical manifestations such food protein-induced enterocolitis syndrome (FPIES), proctocolitis, and enteropathy (38). Usually, patients have negative food sIgE testing (see Table 2). The diagnosis is based on symptoms, clinical history, elimination diet for up to 3 weeks, and specifically designed OFCs (39). Endoscopy with biopsies might be helpful in confirming bowel inflammation. Currently, there is scarce evidence that APT is helpful in diagnosing food allergy in such types of food allergy (40).

Eosinophilic esophagitis is defined as a chronic, immune-/antigen-mediated esophageal disease, characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation. All age groups can be affected and the current estimated prevalence is around one in 24 000 adults (41). Adult patients mostly present with dysphagia, less frequently with retrosternal pain and food bolus impaction, whereas the symptom presentation in children is much more variable and includes failure to thrive, vomiting, regurgitation, thoracic and abdominal pain. Eosinophilic esophagitis is diagnosed by an upper endoscopy and biopsies (42). Biopsies should be performed when the patient has been treated for at least 6 weeks with double the standard dose proton-pump inhibitors to rule out esophageal eosinophilia caused by gastroesophageal reflux disease (GERD) and to exclude proton-pump inhibitor-responsive

esophageal eosinophilia. Other disorders associated with esophageal eosinophilia such as Crohn's disease, celiac disease, achalasia, or eosinophilic gastroenteritis should be ruled out. Approximately 15–43% EoE patients are diagnosed with food allergies and sensitization rate to aeroallergens is up to 80% (43). A close collaboration between gastroenterologists and allergists is essential to optimize management of patients with EoE (41).

See *Recommendations Box* 2*E*.

Unconventional tests including specific IgG testing

A number of expensive diagnostic alternative approaches are sometimes promoted to physicians and often used by complementary and alternative medicine practitioners in cases of suspected food allergy. Examples are bioresonance, kinesiology, iridology, hair analysis, cytotoxic test, and IgG and IgG4 determination. These tests are not currently validated and cannot be recommended in diagnosing food allergy (43–47). For example, IgG measurements cannot be correlated with any clinical symptoms or disease. Food-specific IgG4 levels indicate that the atopic individual has been repeatedly exposed to high doses of food components, which are recognized as foreign proteins by the immune system. Therefore, EAACI gave a clear recommendation not to use these tests (48).

See *Recommendations Box* 2*F*.

Barriers and facilitators to implementation of recommendations and gaps and research needs for food allergy diagnosis are summarized in Tables S2 and S3, respectively.

Management of food allergy

The clinical management of food allergy includes short-term interventions to manage acute reactions and long-term strategies to minimize the risk of further reactions. The latter aim is primarily achieved through dietary modification, education, and behavioral approaches to avoid allergens and pharmacological and nonpharmacological management strategies for further reactions. There is growing interest in the effectiveness of potential immunomodulatory treatment approaches, including sublingual and oral immunotherapy to induce tolerance (49).

Management of acute reactions

Most foods contain proteins which may be allergenic and cause food allergy and, in some cases, anaphylaxis. Recently, severe reactions have been attributed to carbohydrate [e.g., alpha-gal (15)]. Assessment of the risk of severe reactions is crucial in successfully managing patients with food allergy. The risks vary in different patient subgroups; for example, patients with previous anaphylaxis or severe asthma have a higher risk than other patients; known cofactors include nonsteroidal anti-inflammatory drugs (NSAID), exercise, infections, and mastocytosis. For detailed guidance on the emergency management of anaphylaxis, readers are referred to the EAACI Anaphylaxis Guideline Chapter (50).

In our systematic review, we found weak evidence to support the benefits of H1 antihistamines for children and adults with acute non-life-threatening symptoms from food allergy in three randomized trials and two nonrandomized comparisons (5). Importantly, there is no evidence for efficacy of antihistamines in the treatment of more severe symptoms. The prophylactic administration of antihistamines can mask early symptoms of anaphylaxis and lead to delayed treatment of dangerous reactions with adrenaline (epinephrine).

See *Recommendations Box* 3*A*.

Long-term management strategies

Elimination diet and dietary interventions

Dietary avoidance is the key intervention in the management of food allergy resulting in complete or almost complete resolution of symptoms. Little research has been published about dietary eliminations due to the difficultly to perform randomized controlled trials (RCTs) in subjects for ethical issues. The findings from the few studies available (51–54) are mixed, and all had a high risk of potential bias. The lack of evidence does not mean that elimination diets are not effective, just that any recommendations made about elimination diets may need to rely on expert opinion and experience rather than a high-quality research base.

Dietary restrictions should eliminate the culprit food allergen(s) and be tailored to the individual's specific allergic and nutritional needs. This will cover a wide spectrum of issues such as the nutritional needs of food-allergic infants who are currently being introduced to solid foods, which are very different, form the nutritional needs of adults with primary or secondary fruit and vegetable allergies. Extensive and long-term avoidance should be carefully monitored as it can result in nutritional compromises and impair the quality of life. Ideally, the patient should receive proper counseling by a dietician with specific competence in food allergy. This is particularly important in infants and children. In addition, it is crucial to take into account that individual tolerance levels to the allergenic food may differ and change overtime, especially in children, and may affect the stringency of avoidance advice. In breast-fed infants suffering symptoms due to maternal intake of food allergens, the mother should eliminate the foods in question and following a dietetic review, receive a calcium supplement following a dietetic review if cow's milk, cow's milk substitutes, and derivatives are eliminated.

Education is the key pillar of an effective long-term elimination diet. Patients, their families, close relatives, and caregivers should be aware of risk situations and should be instructed in reading labels and how to avoid the relevant food allergens both in and outside the home (e.g., at restaurants). They should know that European Union (EU) directives ask for the declaration of allergenic ingredients in foods and be informed about precautionary labeled foods. They should also be provided with information on possible substitute products for most food allergens.

Patients should be re-evaluated at regular intervals to assess whether they have developed tolerance to avoid inappropriate or unnecessarily lengthy dietary elimination. This is discussed below.

Box 3: EAACI recommendation on the management of food allergy

Recommendations	Evidence level	Grade	Key references
(A) Acute management			
The patient at risk of severe reactions should be properly and timely identified	IV	D	Expert opinion
Antihistamines and mast cell stabilizers			
There is evidence to support the benefits of antihistamines for children and adults with acute non-life-threatening symptoms from food allergy	III	C	(5)
The prophylactic application of antihistamines is not recommended	V	D	Expert opinion
Mast cell stabilizers are not recommended for the prophylactic treatment of food allergy	III	C	(5)
(B) Long-term management strategies			
(B1) Elimination diet			
A sufficient elimination diet should be based on a formal allergy diagnosis identifying the food allergen(s) responsible of the patient's symptoms/reactions. The indications should be re-evaluated at appropriate intervals	IV	D	(51, 52, 54)
Appropriate dietary avoidance is the key treatment in the management of food allergy	IV	D	Expert opinion
Patients with food allergy who are on long-term elimination diets should have access to appropriate dietetic counseling, ideally by a dietitian with competencies in food allergy, and regular monitoring of growth (in children)	IV	D	Expert opinion
Extensively hydrolyzed cow's milk formulas with documented hypoallergenicity can be recommended as first choice for the treatment of cow's milk allergy, especially in infants and young children. Amino acid formulas can also be recommended especially for the subgroup of patients with more severe symptoms	I	A	(55, 57, 59, 84)
Soy formulas should not be recommended before 6 months of age and at any age in the presence of gastrointestinal symptoms. From 6 to 12 months, it can be considered on a case-by-case basis	I	B	(5)
Currently, probiotic supplements cannot be recommended for the management of food allergy	I	D	(5, 69)
(B2) Education and risk assessment			
Patients and caregivers need to be informed about the foods that should be avoided and practical advice given on avoidance measures, how to recognize a further reaction and the self-management of these reactions	V	D	Expert opinion
The diagnosis of food allergy should, with permission, be communicated to all relevant caregivers	V	D	Expert opinion
Patients/carers should be encouraged to join an appropriate patient support organization	V	D	Expert opinion
All patients with food allergy require a management plan with appropriate education for the patient, caregiver including school	V	D	Expert opinion
Education should cover allergen avoidance, symptom recognition, and indication for specific treatment and administration of specific mediation	V	D	Expert opinion
Absolute indications with adrenaline autoinjector include previous anaphylaxis to any food, food allergy associated with persistent or severe asthma, and exercise-induced food-dependent anaphylaxis	IV	D	Expert opinion, refer to the Anaphylaxis Guidelines Chapter
Relative indications for adrenaline autoinjector with food allergy include (i) food allergies that are likely to be persistent; (ii) mild-to-moderate allergic reaction to peanut and/or tree nut; (iii) mild-to-moderate reaction to very small amounts of food; and (iv) specific high-risk groups, e.g., adolescents, young adult males, poor access to medical care	IV–V*	C–D*	Expert opinion, refer to the Anaphylaxis Guidelines Chapter
Adrenaline should be immediately administered for cardiovascular symptoms and/or respiratory symptoms such as altered voice, stridor, or bronchospasm that are thought to be induced by food allergy	IV	C	Refer to the Anaphylaxis Guidelines Chapter
Short-acting beta agonists should be included in the management plan for all patients with coexisting asthma and should be administered for bronchospasm after adrenaline has been administered	V	D	Expert opinion, refer to the Anaphylaxis Guidelines Chapter
Patient held glucocorticosteroids may be given with reactions to possibly prevent late-phase respiratory symptoms (self-administered if traveling far from medical care, otherwise in emergency center)	V	D	Expert opinion, refer to the Anaphylaxis Guidelines Chapter

Box 3: Continued

Recommendations	Evidence level	Grade	Key references
Any patient who has received adrenaline should be reviewed in an emergency department	IV	D	Expert opinion, refer to the Anaphylaxis Guidelines Chapter
(B3) Specific immunotherapy			
Food allergen-specific immunotherapy for primary food allergy is a promising immunomodulatory treatment approach (I), but it is associated with risk of adverse reactions, including anaphylaxis (I); it is therefore not currently recommended for routine clinical use	III	C	(5)
For patients with respiratory or other allergy symptoms to inhalant allergens that may also cause cross-reactive food allergy, specific immunotherapy is only recommended for the treatment of the respiratory symptoms, not for cross-reactive food allergy	IV	D	Expert opinion
(B4) Anti-IgE			
The use of anti-IgE alone or in combination with specific immunotherapy is currently not recommended for the treatment of food allergy although it represents a promising treatment modality	IV	D	(5)
(B5) Challenges at regular intervals to assess achievements of tolerance			
Oral food challenge should be performed at regularly at intervals, as appropriate for the specific food and patient's history, in order to assess achievement of tolerance	V	D	Expert opinion
Specific IgE testing (*in vitro* and skin prick test) has limited value in guiding adequately the timing of oral food challenges for the development of tolerance	V	D	Expert opinion
(B6) Cofactors			
In food allergy reactions, the potential augmenting role of cofactors (e.g., exercise, NSAID, omeprazole, alcohol intake) should be assessed in a structured history	III–IV**	D	Expert opinion
In allergic reactions occurring after exercise, NSAID or alcohol intake, an underlying allergy to foods consumed in the previous hours should be assessed (especially gliadin sensitization or lipid-transfer proteins in southern Europe)	IV	D	(24, 72, 73)

NSAID, nonsteroidal anti-inflammatory drugs.
*Range of levels of evidence and grades are due to range of indications.
**Range of levels of evidence and grades are due to range of different cofactors.

Cow's milk substitutes

In children with cow's milk allergy, several substitutes are available. In infants and young children, these products are especially necessary to ensure a diet that is adequate for growth and development. In infants younger than 6 months, such formulas have to fulfill the general requirements for full nutrition until the introduction of complementary foods. In addition, these substitutes may also be required in older children to ensure a satisfactory caloric intake. There is some moderate-level evidence about some alternatives to cow's milk. However, most of the research is of low quality and there are a relatively small number of studies about each type of alternative formula. There is some evidence to suggest that extensively hydrolyzed formula, amino acid-based formula, and soy-based formula may all be useful long-term management strategies. Extensively hydrolyzed cow's milk formulas are the first choice as an alternative to cow's milk. However, amino acid-based formulas are the only completely nonallergenic formula and they can be effective in patients not responding to extensively hydrolyzed formulas and in subgroups of children. These include infants with severe growth faltering (55–57), those with cow's milk protein allergy with severe symptoms and non-IgE-mediated syndromes such as food protein-induced enterocolitis and enteropathies, eosinophilic gastroenteropathies. Soy formulas may be useful provided that nutritional evaluation regarding the phytate and phyto-oestrogens content is considered, and they cannot be recommended before 6 months of age. Rice hydrolyzed formulas have been recently introduced to the market in some European countries, and further research is needed to compare these formulas with extensively hydrolyzed formula and soy formulas. The substitutes for cow's milk should fulfill the criteria for documented hypoallergenicity and for nutritional adequacy (58, 59). To achieve these requirements, the formula should be investigated in consecutive patients with both IgE- and non-IgE-mediated cow's milk protein allergy (60). Some extensively hydrolyzed formulas have been investigated and fulfill these criteria (56, 61–63). In addition, attention should be paid to taste and price as reimbursement policies for these types of formulas differ across the EU.

Based on several reports, partially hydrolyzed cow's milk-based formulas are not regarded as safe for patients with

cow's milk allergy (64, 65). There is less evidence regarding other mammalian milk. Goat milk and sheep's milk are very similar to the proteins in cow's milk and therefore should not be recommended for patients with cow's milk allergy (66). Camel, donkey, or mare's milk has been shown to be less cross-reactive than goat's milk, although evidence for recommendations is lacking as well as for chicken-based formula (67) or meat-based formula (68). In summary, it is recommended that the choice of an appropriate cow's milk substitute should be assessed carefully balancing the following factors: age, type of food allergy (IgE/non-IgE), coexistence of gastrointestinal symptoms, history of life-threatening reactions, and nutritional requirements as well as cost-effectiveness.

Probiotics and prebiotics

Probiotics have been investigated as another option for the management of patients with food allergy, particularly cow's milk allergy, either added to formulas or given as a supplement. Evidence that probiotic supplements have preventative or therapeutic activity for food allergy is lacking (5), and further research is needed to make recommendations in this area (69).

See *Recommendations Box* 3*B1*.

Pharmacological treatment

Studies on the prophylaxis of food allergy with mast cell stabilizers have led to different clinical results (5). Four randomized trials and two nonrandomized comparisons found that mast cell stabilizers reduced symptoms of food allergy, but three randomized trials found no benefits. Overall, the evidence is not sufficient to recommend mast cell stabilizers for the prophylactic treatment of food allergy.

Education and risk assessment

Education and training are a fundamental part of managing food allergies and should be combined with a risk assessment of those patients at risk of severe reactions (70). A personalized management plan, including an emergency plan, should be issued as part of the overall educational package offered to patients (family and caregivers; see also Anaphylaxis Guidelines). The plan should be personalized to take into account the many variables that may influence the identification and treatment of allergic reactions: age of the patient, literacy of patient and family, type and range of food allergy, concomitant disease, geographic location, and access to medical support. Training should cover patient-specific avoidance strategies at home and in the wider environment, interpretation of warning signals, when and how to treat reactions including use of self-injectable adrenaline if appropriate (6). All professionals, including family doctors, school nurses, dieticians, school teachers, and nursery staff, should be trained. There is some evidence that a multidisciplinary clinical approach (5) and the provision of educational printed and online materials for food allergy (71) improve knowledge, correct use of adrenaline autoinjectors, and reduce reactions (see Anaphylaxis Guidelines).

See *Recommendations Box* 3*B2*.

Cofactors

Several augmentation factors are known to increase the severity of some food-allergic reactions. Sometimes these factors are even obligatory to elicit symptoms of food allergy. Among the best characterized factors are physical exercise and NSAID, and others include alcohol, fever, and acute infection. One example is wheat-dependent exercise-induced anaphylaxis due to omega-5-gliadin sensitization (24); other allergens such as lipid-transfer proteins (LTP) seem to be relevant in certain geographic areas (72, 73). Potential cofactors should be assessed in any case of food allergy.

See *Recommendations Box* 3*B6*.

Immunomodulation

Specific immunotherapy of food allergy

For the treatment of food allergy, specific immunotherapy with food allergens using the subcutaneous, oral, or sublingual route has been assessed (5). Most controlled studies have been performed with peanuts, hazelnut, hen's egg, or cow's milk. For pollen-associated food allergy, immunotherapy has been performed with subcutaneous or sublingual pollen allergens and the oral or sublingual food allergen.

Two low-quality controlled cross-over studies suggest that subcutaneous immunotherapy with food allergens is effective. For pollen-associated food allergy, three very low-quality RCTs (74, 75) and two nonrandomized studies showed conflicting efficacy for the injection treatment with pollen allergen.

Four randomized trials found that sublingual immunotherapy (SLIT) with food allergens was associated with improved tolerance and reduced symptoms for those with peanut, hazelnut, and peach allergies (76, 77). One trial with birch pollen allergen found no benefit in subjects with apple allergy (78).

For oral immunotherapy, two systematic reviews, eight randomized trials, and three nonrandomized comparisons found that oral immunotherapy with food allergens was associated with improved tolerance and reduced symptoms for children and adults with various food allergies (5). However, around 90% of participants have side-effects although these were usually not severe. Oral immunotherapy was more efficacious for desensitization to cow's milk than SLIT but was accompanied by more systemic side-effects in one study (79). One randomized trial found no benefit (80). The two systematic reviews found mixed evidence and suggested that oral immunotherapy should not currently be recommended as routine treatment (81, 82). In light of its potential benefit, it should be performed only in highly specialized centers, with expert staff and adequate equipment, and in accordance with clinical protocols approved by local ethics committees.

The evidence from these studies supports the need for further exploration of immunotherapy with food allergens (5), although especially in subcutaneous and oral immunotherapy the treatment seems to be associated with significant adverse effects. In regard to pollen-associated food allergy, there is conflicting evidence on efficacy of subcutaneous and SLIT with pollen allergens; these therapeutic interventions should only be used for the pollen allergy symptoms.

See *Recommendations Box* 3*B3*.

Anti-IgE treatment

Omalizumab is a humanized monoclonal anti-IgE antibody, which is licensed for the treatment of allergic asthma. The impact of omalizumab and another anti-IgE antibody (TNX-901) on food allergy has been investigated (5). Increased thresholds of tolerance to food allergens were found in a subgroup of participants. Studies suggest that the clinical benefits of omalizumab are achieved after just a few doses of omalizumab. Moreover, it has been demonstrated that more rapid up-dosing and higher doses of milk protein could be administered when omalizumab was used as an adjunct therapy (83).

See *Recommendations Box* 3*B4*.

Challenges at regular intervals to assess development of tolerance

As tolerance can be acquired spontaneously for some food allergens, particularly in children, or can develop with pollen sensitization. There is therefore a need to regularly re-evaluate patients to prevent inappropriate or unnecessarily lengthy dietary eliminations that may impair the quality of life, affect normal growth, and incur unnecessary healthcare costs. Repeated IgE testing can be helpful to determine whether sensitization is decreasing (common in egg and milk allergy) and helpful to identify associated allergies [e.g., peanut, associated with tree nut, sesame (14)].

Currently, OFCs are the only tests that can predict with adequate certainty the achievement of tolerance although it has been shown that low food allergen sIgE levels at diagnosis and a decrease over time both correlate with clinical tolerance. It is therefore recommended that OFC should be performed at regular intervals in order to avoid unnecessary dietary restrictions. The eliciting food may influence this process as, for example, in cow's milk and hen's egg allergy the majority of children will become tolerant within a few years, while most patients with peanut or tree nut allergy remain allergic throughout their life. In cow's milk or hen's egg allergy, intervals for re-evaluation might be every 6–12 months, while for peanut and tree nut allergy OFC every 2 years in the absence of an accidental reaction would be more appropriate.

See *Recommendations Box* 3*B5*.

Management of EoE

Symptomatic EoE patients should be treated not only for quality of life reasons but also to reduce the risk for the occurrence of the potentially dangerous food bolus impactions. Untreated eosinophil-predominant inflammation leads to esophageal remodeling with narrowing of the esophageal caliper and a loss of function. Treatment modalities include drugs, diets, and esophageal dilation. Swallowed topical corticosteroids (budesonide or fluticasone) and diets have shown to reduce symptoms and eosinophilic infiltration. The following diet types are available: amino acid-based formula diet (necessitates often feeding tube), targeted elimination diet (according to allergy workup), and empiric elimination diet. Esophageal dilation of strictures can increase esophageal diameter and improve symptoms; however, it does not influence the underlying inflammation. The long-term treatment strategies are not yet defined. Close collaboration between allergists/immunologists and gastroenterologists is advised (41).

See *Recommendations Box* 3*B6*.

Barriers and facilitators to implementation of recommendations, gaps, and research needs for the management of food allergy are summarized in Tables S4 and S5, respectively.

Conclusions and future perspectives

Food allergy appears to be an increasing burden, which needs to be properly addressed in a structured diagnostic and management approach. The overall body of evidence indicates that patients' clinical history, through the use of structured questions on symptoms, food, and background information, should guide the allergy testing as IgE sensitization does not always equate with clinically relevant food allergy. Skin prick test and sIgE (and probably CRD) offer high sensitivity in relation to a range of allergens implicated in IgE-mediated food allergy. Direct comparisons among the tests are difficult given the limited body of evidence in which these tests have been compared in the same population. There is greater variation in the specificity of these tests, because they indicate sensitization that may not be of clinical relevance, with sIgE tending to have a higher rate of false-positive results. There is limited evidence for the value of APT in diagnosis. The comparability of the local population and the relative availability, safety, and costs of the tests will influence local protocols for diagnostic evaluation.

An elimination diet based on an allergy-focused clinical history and allergy testing should be followed until a significant relief of symptoms is achieved. Careful consideration should be given to the nutritional completeness of patients' diet. Given the limitation of other tests, OFC (ideally DBPCFC) is still the gold standard in IgE- and non-IgE-mediated food allergy in order to establish a firm diagnosis, to determine threshold reactivity, to assess tolerance and the response to immunomodulation. Facilities for OFC are lacking and reimbursement policies vary across national European countries. Efforts should be provided to adequate diagnostic facilities and capabilities to all food-allergic patients in Europe.

The optimal management of food allergy consists of a multidisciplinary and multifaceted approach, which encompasses the treatment of acute episodes of the disease, identification of patients at risk of severe reactions, and long-term management strategies in order to minimize recurrences of reactions and improve quality of life.

Although there are several management strategies available, evidence of effectiveness is very limited in this context. The data on pharmacologic treatment are limited with only H1 antihistamines considered to alleviating acute symptoms but only non-life-threatening ones. Dietary avoidance of properly identified culprit food(s) is the cornerstone of management. There is some evidence to recommend extensively hydrolyzed formulas with documented hypoallergenicity or amino acids formulas as alternatives to cow's milk formula. However, few extensively hydrolyzed formulas have been investigated for hypoallergenicity in properly designed studies, particularly in children with newly documented cow's milk protein allergy. There is currently no evidence for

recommending probiotics and prebiotics with the aim to induce tolerance, although there might be new findings in this field in the near future. Patients at risk of anaphylaxis should have access to self-injectable adrenaline for treating future severe reactions. Facilitated access to allergy consultations, counseling by dietitians with competencies in food allergy, psychological interventions as well as coordination among the several healthcare professionals dealing with the various clinical manifestations of the disease should all be ideally put in place for the effective treatment of these patients.

More proactive treatment for food allergy is urgently needed to address the associated health risk and social burden. Findings suggest that immunotherapy for food allergy through several routes (subcutaneous, sublingual, oral, epicutaneous) may help to increase tolerance with accidental exposure although the expected improvement may be small. Oral immunotherapy may be useful for IgE-mediated food allergy but is associated with a significant risk of local and systemic reactions. Overall, specific immunotherapy is not yet suitable for use in routine clinical care and should be performed in specialized clinical settings under supervision by an allergist with expertise in the field. As a long-term strategy, further research is required into whether immunotherapy could be offered in daily clinical practice.

Education is a key feature in the management of food allergy and should be heavily promoted to patients, families, and caregivers as well as to healthcare professionals. Developing and validating educational tools will further the establishment of vertical and horizontal networks between Centres of Excellence, allergy specialists, and primary care practitioners. Implementation at the community level should be in partnership with the patient organizations (see Community Guidelines Chapter). Adequate reimbursement from national healthcare systems and insurance bodies for diagnostic procedures and the management strategies, including education, should be available.

Expert panel

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Author contributions

Antonella Muraro, Chair of the EAACI Food Allergy and Anaphylaxis Guidelines Initiative, has steered and coordinated the publication. Thomas Werfel, Karin Hoffman-Sommergruber, and Graham Roberts facilitated and edited these guidelines. Susanne Halken, Berber Vlieg Boestra, Kirsten Beyer, Carsten Bindslev-Jensen, George du Toit, and Margitta Worm contributed to the subsections discussion. Karla Soares-Weiser, Debra de Silva, Bridget Nwaru, and Sukhmeet Panesar undertook the supporting systematic reviews under the supervision of Aziz Sheikh. All authors participated in the discussion of the systematic review, the evidence table, recommendations, gaps, and specific sections and approved the final version.

Conflict of interest

Antonella Muraro has provided scientific advice for Meda. Graham Roberts has provided scientific advice for Danone and ALK-Abelló; Thomas Werfel has provided scientific advice for Meda and Novartis. Caroline Nilsson and Susanne Halken have provided scientific advice for ALK-Abelló. Barbara Ballmer-Weber has provided scientific advice for Thermo Fisher Scientific. Thermo Fisher and ALK-Abelló have provided consumables for his research activities. Tony DuBois has provided scientific advice for ALK-Abelló and received funding from ALK-Abelló to support his research activities. Margitta Worm has provided scientific advice for ALK-Abelló, Meda, Novartis, and Stallergenes. Montserrat Fernández Rivas has provided scientific advice to GSK and has received funding from the European Union, the Spanish Ministry of Science, and ALK-Abelló. Carsten Bindslev-Jensen has received funding from Thermo Fisher, HAL, Stallergenes and Anergis, ALK, Novartis, MSD, Schering-Plough for his research activities. Victoria Cardona has provided scientific advice for ALK-Abelló. Philippe Eigenmann has provided scientific advice for Danone, Novartis, ALK-Abelló, DBV technologies, and Stallergenes; he has received funding for research activities from LETI, Nestlé, and Thermo Fisher. Carina Venter has produced educational material for Danone, Mead Johnson, and Nestlé and has received research funding from

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Assigning levels of evidence and recommendations according to new grading system.

Table S2. Food allergy diagnosis: barriers and facilitators to implementation of recommendations.

Table S3. Diagnosis of food allergy: gaps and research needs in the diagnosis of food allergy.

Table S4. Management of food allergy: barriers and facilitators to implementation of recommendations.

Table S5. Gaps and research needs for the management of food allergy.

Data S1. Methodology used for the production of these guidelines.

Data S2. Tools to support implementation of diagnosis of food allergy.

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WEBSITES

http://www.allergenonline.org
FARRP Protein AllergenOnline Database, version 14. Food Allergy Research and Resource Program, University of Nebraska, Lincoln, Nebraska, USA.

https://www.cropcomposition.org/query/index.html
ILSI Crop Composition Database
Ridley WP, Shillito RD, Coats I, Steiner H-Y, Shawgo M, Phillips A, Dussold P, Kurtyka L. 2004. Development of the International Life Sciences Institute Crop Composition Database. J Food Comp Anal 17, 423-438.

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International Service for the Acquisition of Agri-Biotech Applications (ISAAA)

http://gmoanswers.com
GMO Answers is an initiative committed to responding to questions about how food is grown. Its goal is to make information about GMOs in food and agriculture easier to access and understand. GMO Answers is funded by the members of The Council for Biotechnology Information, which includes BASF, Bayer CropScience, Dow AgroSciences, DuPont, Monsanto Company and Syngenta. Members are dedicated to the responsible development and application of plant biotechnology.

http://cera-gmc.org/GMCropDatabase
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PROTEIN ALLERGENICITY TECHNICAL COMMITTEE

MISSION

The mission of the HESI Protein Allergenicity Technical Committee (PATC) is to advance the scientific understanding of the relevant parameters defining allergenic proteins, as well as encourage the development of reliable and accurate methodologies for characterizing the allergenic potential of novel proteins.

OBJECTIVES

- Promote understanding of what makes a protein allergenic.
- Establish processes useful in a weight-of-evidence approach to the evaluation of novel proteins expressed in biotech products.
- Develop scientific uniformity for these evaluations.
- Communicate findings to the academic, industry, and regulatory communities.

STRATEGY

- Convene focused workshops and symposia with experts from government, academia, and industry.
- Support and direct basic research to evaluate utility of *in vivo* methods.
- Harmonize the development of common approaches for *in vitro* assessments.
- Report research and perspectives in peer-reviewed, scientific publications.
- Conduct outreach activities to update and communicate the state-of-the-art in allergy science and the role played by new information in regulatory safety assessment of food and feeds.

SCOPE

The PATC's well-established reputation for unbiased scientific consensus-building has provided an excellent forum for government, academic, and industry scientists to work collaboratively to improve the science associated with conducting comprehensive allergenicity evaluations of novel proteins. PATC participants are experts in the fields of biochemistry, allergy, and toxicology and have an extensive professional network that helps support its workshops, basic research, and outreach on a global scale. This PATC represents the only HESI committee that is devoted exclusively to science issues associated with agricultural biotechnology and food safety.

An important component of the safety assessment of biotechnology products is making a determination of the allergenic potential of newly expressed proteins. The PATC engages in activities to advance the science related to predicting the risk of human allergy from exposure to novel proteins and genetically modified organisms (GMOs). These activities have largely focused on the various components of a weight-of-evidence approach for evaluating the

allergenicity of novel proteins, as described in the FAO/WHO Codex Alimentarius 2003 and 2009 guidelines for Novel Food and Feed Safety.

Research and workshop activities are focused on areas where scientific understanding of protein allergenicity assessment has been or remains ambiguous or unavailable. Projects, education, and outreach are accomplished through international workshops, symposia and roundtable discussions with recognized experts. These activities result in publications in the scientific, peer-reviewed literature. The goal is to better understand the basic science and/or technological needs for developing improved allergen assessment methodologies, and to register safe products through global regulatory product development and safety review processes. To collaboratively assess the current state of the science, identify gaps, and assist in the development of a plan to improve allergenicity assessments, the PATC engages experts from the public sector on the committee and maintains ongoing partnerships with international experts.

Since its formation in 1997, the PATC has addressed the following specific areas:

- Biochemical parameters associated with allergenic proteins
- Sequence homology / bioinformatics evaluations
- Animal models for predicting human food allergy
- Sera bank development
- Detection methods to support endogenous allergen assessments
- Development of a common *in vitro* digestive stability (SGF) protocol
- Impact of food processing on allergenicity
- Sensitizing properties of proteins

PARTICIPATION

Co-Chair: Dr. Gregory Ladics (DuPont Pioneer)
Co-Chair: Dr. Scott McClain (Syngenta USA)
Co-Chair: Prof. Ronald van Ree (Academic Medical Center, University of Amsterdam)
Staff: Nancy G. Doerrer, MS (HESI)
Brianna A. Farr (HESI)

Public Sector:

- Academic Medical Center, University of Amsterdam, The Netherlands
- Copenhagen University Hospital at Gentofte, Denmark
- Guangzhou Medical University, China
- US Environmental Protection Agency
- US Food and Drug Administration

Private Sector:

- BASF Plant Science
- Bayer SAS / Bayer CropScience
- DuPont Pioneer
- Monsanto Company
- Dow AgroSciences
- Syngenta Crop Protection, LLC

RECENT AND ONGOING FOCUS

- Increasing global regulatory requests for highly technical evaluations of endogenous soybean allergens.
  - Open collaboration among industry members.
  - Two workshops bringing together technical experts who perform 2-D gels, serology, and other proteomic approaches.
  - Basic research into the technical capabilities of quantitatively determining soybean allergen content.
  - Extensive discussions with EU regulators.
  - Multiple publications in support of quantitative mass spectrometry methods for soybean allergens.

- Novel protein digestibility
  - Pepsin enzyme digestibility remains a cornerstone of novel protein safety assessments.
  - 2004 PATC initiative: Evaluated a standardized in vitro protocol to support the Simulated Gastric Fluid (SGF) methodology. Successfully completed a general protocol built on the ring-trial concept. 2004 publication.
  - 2013-2014 PATC initiative: Due to impending changes in European Commission regulatory guidance, the PATC is sponsoring an intra- and inter-laboratory evaluation of a more physiologically-based SGF assay.

- 2D-DIGE phase 2 validation: analysis of rice proteins with different cultivars
  - Inter-laboratory validation of 2D-DIGE method (two-dimensional difference in gel electrophoresis) to quantify rice allergens in four different non-transgenic rice cultivar seeds.
  - Five laboratories (two in Japan and three in the US) quantified rice allergens using 2D-DIGE analysis to determine the reproducibility of the method when performed using a common protocol.
  - In parallel, two different laboratories quantified the same rice allergens using coomassie-blue stained 2D-gel electrophoresis.
  - Final analysis of results is underway, and a manuscript will be prepared for publication.

- Protein toxins
  - Investigate approaches for identifying protein toxins.
  - Focus on bioinformatics approaches to characterize existing protein toxins.
  - Discuss modes of action and likely exposure scenarios for known protein toxins.
  - Identify the appropriate search tools (BLAST, FASTA, etc.) and homology criteria (e.g., E-score, % identity, 3-D structural information, clustering and classification of protein families and superfamilies) for comparison purposes.
  - Suggest specific guidelines to identify new protein toxins.

PUBLICATIONS

Doerrer N, Ladics G, McClain S, Herouet-Guicheney C, Poulsen L, Privalle L, Stagg N. 2010. Evaluating biological variation in non-transgenic crops: executive summary from the ILSI Health and Environmental Sciences Institute workshop, November 16-17, 2009, Paris, France. *Regul Toxicol Pharmacol* 58, S2-S7.

Houston NL, Lee DG, Stevenson SE, Ladics GS, Bannon GA, McClain S, Privalle L, Stagg N, Herouet-Guicheney C, MacIntosh SC, Thelen JJ. 2011. Quantitation of soybean allergens using tandem mass spectrometry. *J Proteome Res* 10, 763-773. *[research supported by the HESI PATC]*

Ladics GS, Fry J, Goodman R, Herouet-Guicheney C, Hoffmann-Sommergruber K, Madsen CB, Penninks A, Pomés A, Roggen EL, Smit J, Wal J-M. 2014. Allergic sensitization: screening methods. *Clin Transl Allergy* 4, 13.

Lee D-G, Houston NL, Stevenson SE, Ladics GS, McClain S, Privalle L, Thelen JJ. 2010. Mass spectrometry analysis of soybean seed proteins: optimization of gel-free quantitative workflow. *Anal Methods* 2, 1577-1583. *[research supported by the HESI PATC]*

McClain S, Bowman C, Fernández-Rivas M, Ladics GS, van Ree R. 2014. Allergic sensitization: food- and protein-related factors. *Clin Transl Allergy* 4, 11.

McClain S, Jones W, He X, Ladics G, Bartholomaeus A, Raybould A, Lutter P, Xu H, Wang X, Jia X, Chen J. 2014. Agricultural biotechnology safety assessment. *Chi J Prev Med. Submitted*.

Poulsen LK, Ladics GS, McClain S, Doerrer NG, van Ree R. 2014. Sensitizing properties of proteins: executive summary. *Clin Transl Allergy* 4, 10.

Thomas K, Aalbers M, Bannon GA, Bartels M, Dearman RJ, Esdaile DJ, Fu TJ, Glatt CM, Hadfield N, Hatzos C, Hefle SL, Heylings JR, Goodman RE, Henry B, Herouet C, Holsapple M, Ladics GS, Landry TD, MacIntosh SC, Rice EA, Privalle LS, Steiner HY, Teshima R, Van Ree R, Woolhiser M, Zawodny J. 2004. A multi-laboratory evaluation of a common *in vitro* pepsin digestion assay protocol used in assessing the safety of novel proteins. *Regul Toxicol Pharmacol* 39, 87-98.

Thomas K, Bannon G, Hefle S, Herouet C, Holsapple M, Ladics G, MacIntosh S, Privalle, L. 2005a. In silico methods for evaluating human allergenicity to novel proteins: International Bioinformatics Workshop meeting report, February 23–24, 2005, *Toxicol Sci* 82, 307-310.

Thomas K, Bannon G, Herouet-Guicheney C, Ladics G, Lee L, Lee S, Privalle L, Ballmer-Weber B, Vieths S. 2007a. The utility of an international sera bank for use in evaluating the potential human allergenicity of novel proteins: workshop report. *Toxicol Sci* 97, 27-31.

Thomas K, Herouet C, Bannon GA, Ladics GS, MacIntosh S, Privalle L, Woolhiser M. 2005b. Evaluation of mouse models for assessing the allergenic potential of proteins. *Toxicologist* 84 (S-1), 1307. (Abstract)

Thomas K, Herouet-Guicheney C, Ladics G, Bannon G, Cockburn A, Crevel R, Fitzpatrick J, Mills C, Privalle L, Vieths S. 2007b. Evaluating the effects of food processing on the potential human allergenicity of novel proteins: international workshop report. *Food Chem Toxicol* 45, 1116-1122.

Thomas K, Herouet-Guicheney C, Ladics G, McClain S, MacIntosh S, Privalle L, Woolhiser M. 2008. Current and future methods for evaluating the allergenic potential of proteins: international workshop report, 23-25 October 2007. *Food Chem Toxicol* 46, 3219-3225.

Thomas K, MacIntosh S, Bannon G, Herouet-Guicheney C, Holsapple M, Ladics G, McClain S, Vieths S, Woolhiser M, Privalle L. 2009. Scientific advancement of novel protein allergenicity evaluation: an overview of work from the HESI Protein Allergenicity Technical Committee (2000-2008). *Food Chem Toxicol* 47, 1041-1050.

van Ree R, Hummelshøj L, Plantinga M, Poulsen LK, Swindle E. 2014. Allergic sensitization: host-immune factors. *Clin Transl Allergy* 4, 12.

van Ree R, Poulsen LK, Wong GWK, Ballmer-Weber BK, Gao Z-S, Jia X, Chen J. 2014. Food allergy: definitions, prevalence, diagnosis and therapy. *Chi J Prev Med*. *Submitted*.

CONFERENCES, SYMPOSIA AND JOINT WORKSHOPS

Events sponsored or co-sponsored by the PATC between 2001 and 2014:

- August 2014 Food Allergy and Safety Assessment Workshop, with the Kenya National Biosafety Authority, Kenya, Africa

- August 2014 GM Food / Feed Safety Assessment: Training Workshop for Regulators, with the Kenya National Biosafety Authority, Kenya, Africa

- January 2014 Meeting on the Genetic Basis of Unintended Effects in Modified Plants with the Canadian Food Inspection Agency, the ILSI International Food Biotechnology Committee (IFBiC), the ILSI Research Foundation, and CropLife International, Ottawa, Ontario, Canada http://www.hesiglobal.org/i4a/pages/index.cfm?pageID=3654

- September 2013 Scientific Workshop on Biotech Safety Assessment with ILSI India, the ILSI International Food Biotechnology Committee (IFBiC), and the Ministry of Science and Technology of the Government of India, New Delhi, India

- September 2013 Food Allergy Session at the IUNS 20th International Congress of Nutrition (ICN), with ILSI Europe, ILSI North America, Granada, Spain

- June 2013 International Meeting on Comparative Approaches to Safety Assessment of GM Plant Materials, with ILSI Argentina, the ILSI International Food Biotechnology Committee (IFBiC), and SENASA, Buenos Aires, Argentina

- May 2013 joint NAFTA Biotechnology Update Symposium with the ILSI International Food Biotechnology Committee (IFBiC), Arlington, VA http://www.hesiglobal.org/i4a/pages/index.cfm?pageID=3619

- April 2013 joint Food Allergy and Safety Assessment Workshop with the ILSI Focal Point in China, the ILSI International Food Biotechnology Committee (IFBiC), the China National Centre for Food Safety Risk Assessment, and the China Key Laboratory on Food Safety Risk Assessment, Beijing, China http://www.hesiglobal.org/i4a/pages/index.cfm?pageID=3618

- November 2012 joint Workshop on Food Safety Evaluation & Environmental Risk Assessment of GM Plants with ILSI Brasil, the ILSI Center for Environmental Risk Assessment, and the ILSI International Food Biotechnology Committee (IFBiC), Brasilia, Brazil

- November 2012 International Seminar on Protein Allergenicity hosted by ILSI Argentina, Buenos Aires, Argentina

- September 2012 joint poster at 12th International Symposium on Biosafety of Genetically Modified Organisms (ISBGMO12), with the ILSI International Food Biotechnology Committee (IFBiC), the ILSI Research Foundation, and the ILSI Center for Environmental Risk Assessment, St. Louis, MO

- June 2012 posters at European Academy of Allergy and Clinical Immunology (EAACI) Congress, Geneva, Switzerland (2D-DIGE phase 2 validation; absolute quantitation of seed allergens from three varieties of soy from eight geographical locations)

- April 2012 Symposium on Sensitizing Properties of Proteins, Prague, Czech Republic http://www.hesiglobal.org/i4a/pages/index.cfm?pageid=3595

- November 2011 joint Workshop on Safety Assessment of Novel Proteins and GM Crops with the ILSI Focal Point in China, the Chinese Centre for Disease Control and Prevention, and the ILSI International Food Biotechnology Committee (IFBiC), Beijing, China

- May 2011 joint Biotechnology Workshop 2011 with the ILSI International Food Biotechnology Committee (IFBiC) for the OECD Working Group on the Harmonization of Regulatory Oversight in Biotechnology (WGHROB) and the OECD Task Force on the Safety of Novel Foods and Feeds (TFSNFF), Paris, France

- May 2011 joint Biotechnology Update Workshop with the ILSI International Food Biotechnology Committee (IFBiC) for the Canadian Food Inspection Agency (CFIA), Ottawa, Canada

- October 2010 joint symposium with ILSI Europe, EuroPrevall, UK Food Standards Agency, and FAARP on Frontiers in Food Allergen Risk Assessment, Nice, France.

- September 2010 joint NAFTA Biotechnology Update Symposium with the ILSI International Food Biotechnology Committee (IFBiC), Washington, DC.

- November 2009 workshop on Evaluating Biological Variation in Non-transgenic Crops, Paris, France.

- October 2008 host of symposium on Efforts to Improve Techniques for Identifying and Evaluating Food Allergens, as part of the 45th Eurotox Annual Meeting, Rhodes, Greece.

- September 2008 joint symposium with ILSI SEA and the Thai National Science and Technology Development Agency (NSTDA), Bangkok, Thailand.

- September 2008 joint symposium with ILSI SEA on Biotechnology and Nutritionally Enhanced Food and Crops, Cebu, Philippines.

- April 2008 joint meeting with IFBiC, ILSI Research Foundation on ILSI Activities Related to Biotechnology, Washington, DC.

- February 2008 joint workshop with ILSI Japan and Japanese regulators on Sequence Homology and Bioinformatic Assessments, Tokyo, Japan.

- February 2008 joint workshop with the Biotechnology Coalition of the Philippines, ILSI Southeast Asia (SEA), Department of Agriculture (Philippines), and the International Service for the Acquisition of AgriBiotech Applications on Novel Protein Safety Evaluation, Manila, Philippines.

- October 2007 PATC workshop on New Methods for Allergenicity Assessments, Nice, France.

- November 2006 seminar with ILSI Argentina and Food and Feed Safety Authority of Argentina (SENASA), International Course on Food Risk Analysis, Buenos Aires, Argentina.

- November 2006 joint workshop with ILSI Brazil on Conducting a Comprehensive Allergenicity Evaluation of Novel Proteins, Sao Paula, Brazil.

- June 2006 International Effects of Food Processing on Allergenicity Workshop, hosted in partnership with ILSI Europe, ILSI International Food Biotechnology Committee (IFBiC), and ILSI Research Foundation, Estoril, Portugal.

- April 2006 International Sera Bank Development Workshop, Seoul, Korea.

- March 2005 poster at the American Academy of Asthma, Allergy, and Immunology (AAAI) meeting, San Antonio, TX.

- March 2005 poster at the Society of Toxicology (SOT) Annual Meeting, New Orleans, LA.

- February 2005 International Sequence Homology / Bioinformatics Workshop, Mallorca, Spain.
- July 2004 Symposium at International Congress of Toxicology Meeting (ICTX), Tampere, Finland.
- September 2003 poster at the Eurotox Annual Meeting, Florence, Italy.
- September 2003 joint workshop with ILSI Japan to present committee activities to scientists at National Institute of Health Sciences, Tokyo, Japan.
- March 2002, Committee-led ILSI delegation at CODEX Ad Hoc Task Force on Food Derived from Biotechnology Meeting, Yokohama, Japan.
- September 2001, Committee-led ILSI delegation at CODEX Ad Hoc Open-Ended Working Group on Allergenicity Meeting, Vancouver, Canada.

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***The Health and Environmental Sciences Institute (HESI)
is a nonprofit institution whose mission is to engage scientists
from academia, government, industry, research institutes, and
NGOs to identify and resolve global health and environmental issues.***

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HESI, a non-profit charitable organization, provides the framework for scientists from the public and private sectors to meaningfully collaborate in developing science for a safer, more sustainable world.

MISSION:
Engage scientists from academia, government, industry, research institutes, and NGOs to identify and resolve global health and environmental issues.

VISION:
Create science-based solutions for a sustainable, healthier world.

PHILOSOPHY:
HESI's technical programs bring together scientists from around the world from academia, government, industry, research institutes, and NGOs to address and reach consensus on scientific questions that have the potential to be resolved through creative application of intellectual and financial resources. This ***tripartite approach*** forms the core of every HESI scientific endeavor. As a non-profit organization, HESI provides a unique, objective forum for initiating dialogue among scientists with different perspectives and expertise. Industry sponsors provide primary financial support for HESI programs, but HESI also receives financial and in-kind support from a variety of US and international government agencies.

HESI improves public health by generating quality science to support the following:

- Safe and effective medicines
- Environmental quality and sustainability
- Accurate and resource-efficient risk assessment
- Food safety

HISTORY:
HESI was established in 1989 as a global branch of the International Life Sciences Institute (ILSI) (www.ilsi.org) to provide an international forum to advance the understanding of scientific issues related to human health, toxicology, risk assessment, and the environment. In 2002, HESI was recognized by the United States government as a publicly supported, tax-exempt organization, independently chartered from ILSI.

PARTICIPATING ORGANIZATIONS:
Over 200 academic institutions, medical centers, foundations and NGOs, government agencies, and private sector companies provide intellectual contributions to HESI's scientific programs. This diverse partner base allows for identification of high priority cross-cutting issues, ensures balance, drives effective solutions, and establishes critical networks to facilitate the uptake of new science.

Insights from participating researchers in Asia, Europe, South America, and North America help make HESI's scientific programs and outputs meaningful across borders and cultures and applicable at regional, national, and international levels.

In addition to our core scientific committees, HESI has also developed formal partnerships with key governmental and non-governmental bodies in shared support for quality safety science.

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FOOD ALLERGY
AND
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WORKSHOP

11-12 August 2014

Kenyatta International
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Nairobi, Kenya

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