Finding a Path to Safety in Food Allergy

Assessment of the Global Burden, Causes, Prevention, Management, and Public Policy

Committee on Food Allergies: Global Burden, Causes, Treatment, Prevention, and Public Policy

Food and Nutrition Board

Health and Medicine Division

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A Report of

The National Academies of

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This activity was supported by federal sponsors: the Food and Drug Administration (Contract No. HHSP233201400020B/HHSP23337025), the Food and Nutrition Service of the U.S. Department of Agriculture (Grant # FS_NAS_IOM_FY2015_01), and the National Institute of Allergy and Infectious Diseases; and nonfederal sponsors: the Asthma and Allergy Foundation of America, the Egg Nutrition Center, Food Allergy Research and Education, the International Life Sciences Institute North America, the International Tree Nut Council Nutrition Research & Education Foundation, the National Dairy Council, the National Peanut Board, and the Seafood Industry Research Fund. Any opinions, findings, conclusions, or recommendations expressed in this publication do not necessarily reflect the views of any organization or agency that provided support for the project.

Library of Congress Cataloging-in-Publication Data

Names: National Academies of Sciences, Engineering, and Medicine (U.S.). Committee on Food Allergies: Global Burden, Causes, Treatment, Prevention, and Public Policy, author. | Stallings, Virginia A., editor. | Oria, Maria, editor. | National Academies of Sciences, Engineering, and Medicine (U.S.), issuing body.
Title: Finding a path to safety in food allergy : assessment of the global burden, causes, prevention, management, and public policy / Committee on Food Allergies: Global Burden, Causes, Treatment, Prevention, and Public Policy, Food and Nutrition Board, Health and Medicine Division ; Virginia A. Stallings and Maria Oria, editors.
Description: Washington, DC : The National Academies Press, [2016] | Includes bibliographical references.
Identifiers: LCCN 2016052811| ISBN 9780309450317 (pbk.) | ISBN 0309450314 (pbk.) | ISBN 9780309450324 (pdf)
Subjects: | MESH: Food Hypersensitivity—prevention & control | Food Hypersensitivity—etiology | Food Hypersensitivity—epidemiology | Health Policy
Classification: LCC RC596 | NLM WD 310 | DDC 616.97/5—dc23 LC record available at https://lccn.loc.gov/2016052811
Digital Object Identifier: 10.17226/23658

Additional copies of this publication are available for sale from the National Academies Press, 500 Fifth Street, NW, Keck 360, Washington, DC 20001; (800) 624-6242 or (202) 334-3313; http://www.nap.edu.

Printed in the United States of America

Suggested Citation: National Academies of Sciences, Engineering, and Medicine. 2017. *Finding a path to safety in food allergy: Assessment of the global burden, causes, prevention, management, and public policy.* Washington, DC: The National Academies Press. doi: 10.17226/23658.

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COMMITTEE ON FOOD ALLERGIES: GLOBAL BURDEN, CAUSES, TREATMENT, PREVENTION, AND PUBLIC POLICY

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This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

David B. Allison, University of Alabama at Birmingham
Dianne E Campbell, The University of Sydney
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Anita Kozyrskyj, University of Alberta
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Carina Venter, Cincinnati Children's Hospital
Robert Wood, The Johns Hopkins Hospital

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by **Robert S. Lawrence,** Johns Hopkins Bloomberg School of Public Health, and **Huda Akil,** University of Michigan. They were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

Preface

As pediatricians in training, we learned about life-threatening anaphylaxis and that prompt, appropriate treatment with a simple drug, epinephrine, saves lives. We mostly worried about anaphylaxis triggered by an undiagnosed drug allergy, or maybe by multiple bee stings. Food allergy was not well appreciated and was confused in our minds and those of parents with food intolerance, food sensitivity, and family reports of food reactions. Prevention of severe allergic reactions from peanut exposure in schools and airplanes was not discussed.

Food allergy is a complicated, multifactorial disease whose causes, mechanisms, and effects are not yet fully understood. The evidence on the true prevalence of food allergy is obscured by insufficient or inconsistent data and variable methodology. Despite these obstacles, public concern has grown in response to the apparent rising global prevalence of food allergies, and many health care experts who provide care to patients agree that any real increase in food allergies that has occurred is unlikely to be due simply to an increase in awareness. Numerous stakeholders are concerned about this rise in food allergies, including the general public, policy makers, regulatory agencies, the food industry, scientists, clinicians, and especially families of children and young people suffering from food-related allergies.

This consensus study is the result of a planning meeting that was held by the National Academies of Sciences, Engineering, and Medicine in response to broad public interest in the health aspects of food allergy, the relevance to public health, health care, and society, and the current lack of solutions both for preventing and managing food allergies. The goal of this consensus study is to review the science and management practices of food

allergies. Our committee intends that this report will clarify the nature of the disease, its causes, and its current management; highlight gaps in knowledge; encourage the implementation of food allergy management tools at many levels and among many stakeholders; and delineate a roadmap to safety for those who have, or are at risk of developing, food allergies, as well as for others in society who are responsible for public health.

This committee had the unique opportunity to hear directly from an advisory panel made up of nine parents of children with food allergies and one individual with food allergy. Members of the advisory panel were invaluable to the committee as meaningful examples of the sentiments and struggles of living with food allergies. We heard about the anxiety they feel in restaurants, schools, airplanes, and other settings where they are fearful about unintentional exposure to a food that can cause a life-threatening allergic reaction. The advisory panel asked for clear and consistent guidelines for diagnosing and managing food allergies and for treating reactions. We also heard their desire for more clarity in food labeling, appropriate training for emergency personnel, and greater access to epinephrine. And we heard their plea for a roadmap to safety so that people with food allergy and their family and friends can participate fully in the world without the fear of a severe or fatal food allergy reaction.

Drawing on insights from the advisory panel, as well as expert testimony, comprehensive literature reviews, committee expertise and deliberations, the committee recognized that preventing and treating food allergy and creating a roadmap to safety is a multifaceted undertaking that must take into account many interacting systems that influence both risks and safety over the life course. To address this, the committee decided that this report would benefit from taking an ecological and developmental perspective. This ecological-developmental model emphasizes the importance of developmental timing for food allergy exposures and for safety planning. The committee used this approach to delineate the issues, organize the evidence, draw conclusions, make recommendations, and communicate conclusions. The committee recognized that many sectors at multiple levels of organization in private and public life must be considered to understand and protect the individuals from the risks posed by food allergies.

The current paradigm of prevention and treatment is changing. As this report was being written, new evidence on the potential benefits of early introduction of allergens was emerging to dismantle previous views about the benefits of delaying introduction of allergens until 1 year of age or even later. These new studies are causing leading organizations to rethink the current recommendations and consider promising new prevention approaches. Understandably, these changes can lead to confusion among those at risk of food allergy and even among health care providers.

Thoughtful policies at many different levels, including guidelines and

regulations, can help protect public health. Although many nongovernmental organizations and governments provide tools, guidelines, and policies to promote greater safety in various settings (e.g., food industry practices, regulatory agencies, child care settings, schools, higher education, and public transport), their implementation and enforcement varies greatly across the United States. Moreover, policies and guidelines may not be keeping pace with the science.

This report is meant to be a review of scientific questions. In addition, this report reviews some of the management approaches that are in place to improve health and quality of life for individuals with food allergy and their caregivers. Finally, the committee envisions that this report will serve as a tool for all the stakeholders and the public to recognize the importance of this disease as well as to join forces in efforts to improve markedly our ability to understand, effectively manage, and ultimately cure food allergy, and to make the world safer for those afflicted with this disease.

The committee responsible for the report is varied in expertise, with members chosen for their experience in allergic diseases, immunology, pediatric medicine, epidemiology, genetics, epigenetics, public health, nutrition, food science, and the food industry. The chapters are authored jointly by committee members, who contributed their expertise to appropriate areas, subject to review and comment from the entire committee. Committee members volunteered countless hours to long but productive days of meetings in Washington, DC, and to research, deliberations, and preparation of the report. Many other people contributed significant time and effort to support the preparation of the report during open committee sessions and through presentations at a workshop. We are grateful for their efforts.

The committee could not have done its work without the initiative and collaboration from the Board on Children, Youth, and Families and superb guidance and support provided by the Food and Nutrition Board staff: Maria Oria, Study Director; Alice Vorosmarti, Research Associate; Anna Bury, Research Assistant; and Kyra Cappelucci and Noa Nir, Senior Program Assistants. The committee also benefited from the overall guidance of Ann Yaktine, Director of the Food and Nutrition Board. The committee is also especially thankful to Anne Rodgers, who edited this report.

Lastly, as chair, I express my sincere appreciation to each member of this committee and staff for their extraordinary commitment to the project and to the wonderful opportunity to work with them on this important task to improve the health and future of people around the world with food allergy.

Virginia Stallings, *Chair*
Committee on Food Allergies:
Global Burden, Causes, Treatment, Prevention, and Public Policy

Contents

Summary

Food allergy, an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food, affects the health and quality of life of individuals and their caregivers across a range of dimensions. A food allergy can cause skin, respiratory, and gastrointestinal reactions. The quality of life of individuals with food allergy is diminished as their social interactions and routine life activities are affected. For some individuals, a food allergy can lead to severe allergic reactions and death. Food allergies typically develop within the first year of life but they can also develop later in life. Eight food groups are considered to be major allergens. These are milk, egg, peanut, tree nuts, wheat, soy, fish, and crustacean shellfish.

Questions persist about whether food allergy prevalence has been on the rise within the past two decades and why. The current data do not unequivocally support the occurrence of such a rise. Multiple hypotheses have been generated about potential genetic and environmental factors that lead to food allergies and a potential rise in food allergy cases. Concomitant with a widespread perception of an increase in prevalence, the public and other stakeholders frequently misinterpret a food allergy and its symptoms, how to differentiate a food allergy from other immune and gastrointestinal diseases, and what effective management and prevention approaches to use. For example, lactose intolerance symptoms can be misinterpreted as a food allergy, when in fact their physiological origin and management approaches are vastly different.

Food allergy is a complex disease at the molecular and cellular level and although much research data have accumulated, many fundamental

questions remain. For example, researchers are struggling to identify factors in utero and during the first year of life, such as the timing of introduction of solid foods or breastfeeding duration, that could lead to the onset of allergies. Overall, gaps in knowledge at the mechanistic level represent barriers to developing strategies for disease prevention and management. Not surprisingly then, recommendations by public health authorities or professional associations for preventing or managing a food allergy are limited by the scarce or inconsistent research findings. Although promising therapeutic approaches are being tested, no effective treatments currently exist for patients with food allergies.

In the absence of approved treatments, patients are advised to avoid the allergen, which can be very difficult, especially in some circumstances. For example, under the Food Allergen Labeling and Consumer Protection Act, food allergens must be listed in the ingredient list of a packaged food. Unfortunately, during production or manufacturing, cross-contamination may occur, resulting in the food product having a hidden allergen that does not appear on the label. In addition, food service establishments are not required to list food allergens, so an individual's safety depends on clear communication and on employees' knowledge of the allergen content of the food being served and on the establishment's management practices. Even with the most stringent management practices, accidents, such as cross-contact events, can still occur when people with a food allergy eat outside of the home. Concerted efforts by policy makers, industry leaders, and others are necessary to bring about a safe environment for those with food allergy.

In summary, many stakeholders, including policy makers, the food industry, scientists, clinicians, and especially individuals with food allergy and their caregivers, are concerned about the misunderstandings, and the lack of effective treatment and clear approaches to prevent food allergy. This report collects and evaluates the scientific evidence on the prevalence, origins, diagnosis, prevention, and management of food allergy and makes recommendations to stakeholders to maximize safety and to increase research activities related to food allergy.

THE TASK AND COMMITTEE'S INTERPRETATION

An ad hoc committee of 15 experts was selected to respond to the statement of task (see Box S-1). The plan for the study included an advisory panel made up of nine parents of children with food allergy and one individual with food allergy. This panel was asked to present to the committee at public meetings; their testimonies were invaluable as examples of the challenges and burden of living with food allergies.

Given the misunderstandings related to food allergy, a first assignment

BOX S-1
Statement of Task

A committee will be formed to examine critical issues related to food allergy, including the prevalence and severity of food allergy and its impact on affected individuals, families, and communities; and current understanding of food allergy as a disease, and in diagnostics, treatments, prevention, and public policy. This consensus study will engage a broad array of stakeholders, including government agencies, organizations, academic institutions, industries, policy makers, and patient organization groups; to bring together leading investigators from relevant fields, clinicians, and parents; and to develop a framework for future work; and to recommend actions by both government and nongovernment agencies. The committee's review of the evidence will consider the following key questions:

1. What are current trends in food allergy prevalence?
   - What is an appropriate definition of food allergy to use in measuring prevalence?
   - What data or methods are most appropriate to use in measuring prevalence and how may they be implemented?
   - Should there be an effort to assess prevalence for allergens other than the eight most common that are required to be disclosed on food packages? If so, should the same methods be used for these allergens?
2. What are the key prenatal/early life determinants of food allergy?
   - For example, are there dietary factors that impact development of food allergy and are these modifiable?
3. What are the current data gaps in understanding the diagnosis and prognosis for food allergy?
   - What new approaches are being developed to address these data gaps?
4. What steps can be taken to educate providers and the public in order to create safe environments for food allergic children both within and outside the home?
   - What and where are the most risky food scenarios and how can these be better managed?
   - What guidance can be given to individuals about exposure to low levels of allergens in food products?
5. What is the status of assessing allergen thresholds in individuals? What additional methods or tools are needed?
6. What research gaps need to be filled in order to provide better guidance to health care providers and policy makers?

The committee will develop a framework for future direction in understanding food allergy and its impact on individuals, families, and communities; recommending steps to increase public awareness of food allergy; promoting research on both disease causation and management; and informing preventive approaches to food allergy. Research gaps will be identified and recommendations made to fill them.

for the committee was to define the types of food allergies to address in this report. Food allergy, as opposed to a food intolerance, which does not have an immunologic component, arises from a specific immune response. Food allergy has two key classifications: immunoglobulin E (IgE)-mediated or non-IgE-mediated. The recommendations in this report focus on IgE-mediated food allergies, which have better defined underlying cellular mechanisms and physiological reactions. Other food-related diseases, such as celiac disease, food intolerances (e.g., lactose intolerance) are not covered. However, other non-IgE-mediated food allergies are mentioned when appropriate, particularly while discussing diagnostic methodologies. With a focus on the United States, many recommendations could apply in other countries.

A DEVELOPMENTAL AND ECOLOGICAL PERSPECTIVE ON FOOD ALLERGY

For every individual, the risks and protections from food allergies vary over the life course, depending on individual genetic factors, biological development, exposures to allergens, and the contexts in which the individual lives (i.e., a developmental perspective). Before birth, a fetus interacts indirectly with systems because influences (e.g., diet) are mediated by maternal biological function. After birth, children continue to develop and they interact directly with numerous new systems, including peers, schools, social media, workplaces, and social contexts. But individuals are influenced by many additional systems beyond their proximal interactions, through cultural practices and governmental or nongovernmental policies or rules. The safety and well-being of individuals with potential food allergies, then, require recognition that risks and protections for public safety are spread across many systems, including food production and distribution systems, health care systems, and education systems (i.e., an ecological perspective). The committee developed a model to depict those important interactions (see Figure S-1).

THE ROADMAP TO SAFETY

In mapping the road to greater public safety regarding food allergy, in addition to the health care system, the committee selected the following settings for their relevance to the task at hand: food establishments, early care and education, schools, higher education, and the travel industry. These settings vary in policies and practices, and many improvements are both feasible and would likely contribute to preventing and managing severe allergic reactions and improving quality of life.

The committee's roadmap to safety is multifaceted, involving many

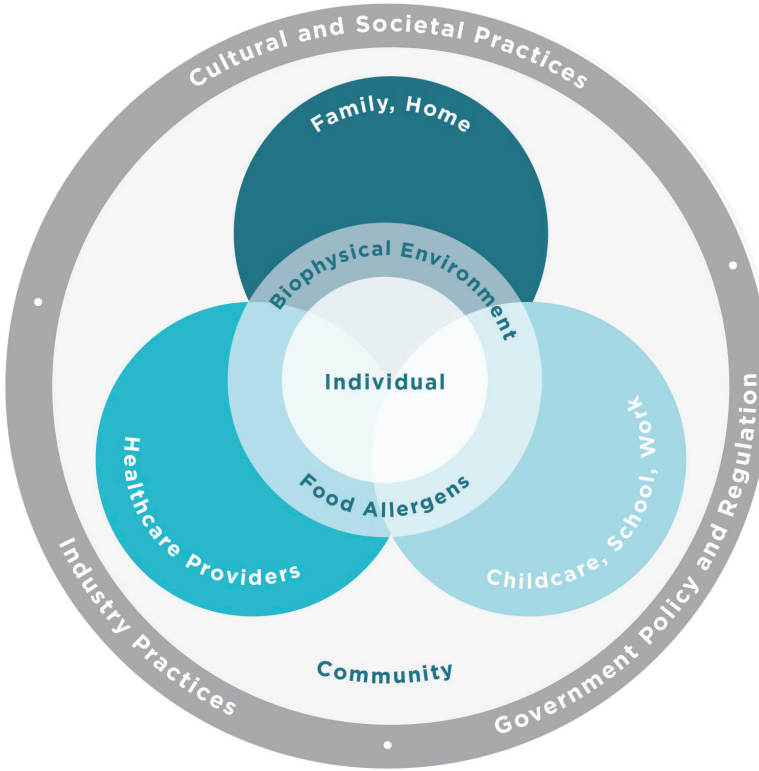

FIGURE S-1 Ecological-developmental model for food allergies. Different systems that an individual interacts with are depicted as proximal (e.g., food, biophysical environment) and distal (e.g., industry, government).
NOTES: **Industry practices** refers to all the manufacturing processes and allergen control plans followed during food production, distribution, preparation or cooking, and serving. They also refer to mandatory and voluntary labeling of food allergens and to recall procedures followed when a product is contaminated with a food allergen. **Cultural and societal practices** refer to the particular diets and foods of regions and countries. **Biophysical environment** refers to the external proximal environment (e.g., air) while **Individual** refers to all systems internal to a developing human, including genome, epigenome, proteome, metabolome, central nervous system, immune system, microbiomes, and many other self-regulatory systems involved in adaptation and sustaining life. **Health care providers** include the persons (e.g., physicians, dieticians) and the institutions that protect individual and public health. **Child care, school, work** includes all proximal settings that interact with an individual at different life stages. Finally, **family, home** refers to the system of people, relationships, routines, and practices occurring at home. Interactions (e.g., communication, physical contact) occur between and among all those systems and the individual to support (or not) food safety.

stakeholders and the following actions (see Figure S-2): (1) obtain accurate prevalence estimates, (2) use proper diagnostic methods and provide evidence-based health care, (3) identify evidence-based prevention approaches, (4) improve education and training, (5) implement improved policies and practices to prevent the occurrence of severe reactions, and (6) expand research programs. This section summarizes these actions and related recommendations.

Obtain Accurate Prevalence Estimates

To prioritize food allergy as a public health concern and ensure that adequate resources are directed at the issue, the extent of the problem must be defined. No study in the United States has been conducted in a systematic manner, with sufficient sample size, and in various populations to determine the true prevalence of food allergy. Because of the low quality of data, particularly the use of self-reported data instead of the gold standard oral food challenge (OFC)[1] method, the true prevalence of food allergy is likely overestimated in most published studies.

The committee recommends that the Centers for Disease Control and Prevention obtain prevalence estimates on food allergy in a systematic and statistically sound manner.

Prevalence should be assessed in a systematic fashion in a sufficiently large population, with consideration given to using stratified sampling for cost-efficiency, with frequency-weighting used to obtain population-wide estimates. Prevalence estimates should be conducted in both children and adults and in groups defined by race, ethnicity, and socioeconomic status to determine differences in diagnosis and prevalence within these subgroups. To support population risk assessments, the committee also recommends that the dietary intake history of those reporting food allergy be compared to those who do not, particularly for the specific foods of interest.

Although a new study design (or the use of other data surveillance systems) is possible, the National Health and Nutrition Examination Survey (NHANES) is a feasible option to systematically examine the prevalence of food allergy by collecting data on

[1] Oral food challenge is a feeding test that involves gradual, medically supervised ingestion of increasingly larger doses of the food being tested as a possible food allergen. The test is positive when the individual experiences food allergy symptoms, such as skin, respiratory, and gastrointestinal reactions.

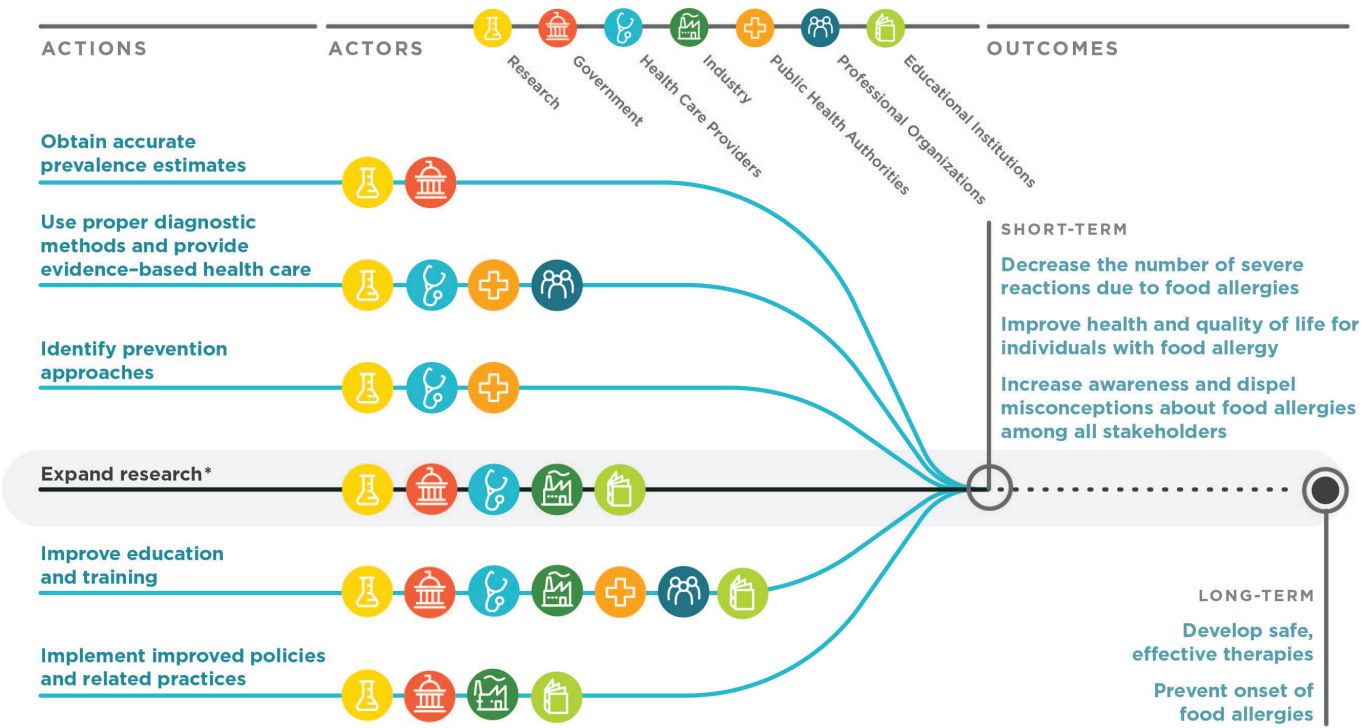

FIGURE S-2 Roadmap to food allergy safety in six actions.
* Research is needed to achieve all other actions and to reach the short- and long-term goals (see Chapter 9 for all specific areas of research). The actors represent the primary stakeholders that will be involved in implementing the actions.

self-reported food allergies, food-specific immunoglobulin E concentrations, food-specific skin prick test results, and oral food challenge results.[2] Specific suggestions for use of NHANES (or other data surveillance systems), such as oversampling of young children (<6 years) as an important group, are included in Chapter 3.

Use Proper Diagnostic Methods and Provide Evidence-Based Health Care

No simple diagnostic tests exist for food allergy, and the selection and interpretation of tests depend upon the nature of the disorder and the individual medical history. The OFC carries risk and expense and is underused. The medical history and other test results (e.g., skin prick test) can suggest the likelihood of a food allergy, but in some cases an OFC is needed to confirm the presence of a clinical disease.

The committee recommends that physicians use evidence-based, standardized procedures as the basis for food allergy diagnosis and avoid nonstandardized and unproven procedures (e.g., applied kinesiology, immunoglobulin G panels, electrodermal testing). When food allergy is suspected, a patient should be evaluated by a physician who has the training and experience to select and interpret appropriate diagnostic tests.

Although this process often may include an initial evaluation by a primary physician, it is important that those with suspected food allergy be diagnosed appropriately, which is likely to involve referral to or consultation with a physician specialist who can diagnose, comprehensively evaluate, and manage the food allergy.

Food allergy evaluation procedures include a medical history and physical examination, and also may include a food-specific skin prick test, food-specific serum immunoglobulin E test, diagnostic food elimination diet, and OFC. Selection of the specific tests needs to be individualized based on the medical history of each patient. Health care providers trained in food allergy, leaders of health care facilities, and health care payor groups can facilitate the appropriate use of OFCs, including personnel, facilities, and safety guards, so that physicians are not deterred from performing

[2] The gold standard OFC is an expensive method and must be administered in a clinic and under supervision of a trained physician. The testing sequence, therefore, is meant to lead to a population sample that is enriched with individuals reporting food allergy and that minimizes cost and effort.

the types of diagnostic testing that are appropriate for the patient's diagnosis and care.

Identify Evidence-Based Prevention Approaches

Although many factors have been postulated to contribute to the onset of food allergy, strong evidence is lacking about any association, mainly due to methodological limitations and variations in study designs. The strongest data derive from recent studies supporting the dual allergen exposure hypothesis, which proposes that a food allergy may occur through exposure to low doses of allergen through damaged skin (such as in eczema) followed by oral exposure to these allergens through consumption early in infancy. The hypothesis proposes that the practice of delaying the introduction of allergens may have contributed to the presumptive rise in food allergy prevalence.

The committee recommends that public health authorities and clinical practice guidelines include consistent, clear, and evidence-based advice for families and health care providers, including dietitians, about the potential benefits of introducing allergenic foods (e.g., peanut products, egg, dairy, and wheat) in the first year of life to infants, when an infant is developmentally ready (around 6 months of age), but not before 4 months of age, particularly to those at high risk of allergy. Guidelines also should include information about the circumstances in which health care providers should advise their patients about the safest way to introduce in their diet peanut products (and/or other foods, as determined by the results of ongoing research).

Improve Education and Training

Public Health Authorities, Health Care Providers, and Their Patients and Caregivers

The committee generally supports current guidelines and U.S. practice parameters for food allergy management and emphasizes those areas where improvements would lead to significant changes in the quality of life of patients and their caregivers, such as training and education.

The committee recommends that the Centers for Disease Control and Prevention work with other public health authorities to plan and initiate a public health campaign for the general public, individuals with food allergy, and all relevant stakeholders to increase

awareness and empathy as well as to dispel misconceptions about food allergy and its management.

For example, as part of that campaign and taking advantage of the popularity of digital media among the public, particularly children and adolescents, public health authorities could develop effective media engagement programs. To plan for this campaign and develop media programs, public health authorities could conduct formative research with all potential audiences.

The committee recommends that public health authorities, such as the National Institutes of Health and the World Health Organization, and professional organizations, such as the American Academy of Pediatrics; the American Academy of Allergy, Asthma & Immunology; American Academy of Family Physicians; and the Academy of Nutrition and Dietetics, regularly update guidelines on diagnosis, prevention, and management of food allergy based on strong scientific evidence, as emerging scientific data become available.

For example, current evidence is insufficient to associate any of the following behaviors with prevention of food allergy: food allergen avoidance diets for pregnant or lactating women, prolonged allergen avoidance in infancy, vaginal delivery, breastfeeding, infant formulas containing extensively or partially hydrolyzed protein, and supplementation with specific nutrients (e.g., vitamin D, folate, fatty acids) in children or adults.

The committee recommends that medical schools as well as residency and fellowship programs and other relevant schools include training for health care providers in the management of food allergy and anaphylaxis. Health care providers, including dietitians and mental health professionals, also should receive training on approaches to counseling patients and their caregivers. Counseling training is envisioned to be provided, in part, by professional organizations through various means, including the Internet.

The following elements of food allergy training are appropriate for all health care providers, including emergency medical technicians, emergency room staff, nurses, dietitians, and others:

- *Emergency management*. This includes training to recognize and manage an anaphylaxis emergency, such as the use

of intramuscular epinephrine as a first line of emergency management for episodes of anaphylaxis.
- *Counseling on food allergy management and anaphylaxis*. This includes identifying food allergies as well as managing and treating them in various settings (e.g., home, school, restaurants), as well as emergency management of anaphylaxis.

As appropriate, physicians and other health care providers also may receive training to provide the following:

- *Nutrition counseling*. This includes discussion of safe and nutritionally adequate avoidance diets to individuals with food allergies, particularly children and their caregivers. The training also could include offering referral to a dietitian when needed and as part of reimbursable care. In addition, dietitians may receive training in providing individualized dietary advice to people with food allergy and their caregivers.
- *Psychosocial counseling*. This includes identifying and discussing with patients and caregivers psychosocial concerns (e.g., bullying), validation of feelings, and balancing management with participation in daily activities. Training also could include offering referral to a mental health professional when needed and as part of reimbursable care. In addition, mental health professionals may receive training in counseling individuals with food allergy and their caregivers.

The committee recommends that health care providers counsel patients and their caregivers on food allergy following the most recent food allergy guidelines and emphasizing the need to take age-appropriate responsibility for managing their food allergy. Counseling is particularly important for those at high risk of food allergy and severe food allergy reactions, such as adolescents, young adults, and those with both food allergy and asthma.

The committee recommends that health care providers and others use intramuscular epinephrine (adrenaline) in all infants, children, and adults as a first line of emergency management for episodes of food allergy anaphylaxis. The Food and Drug Administration should evaluate the need for, and, if indicated, industry should

develop an auto-injector with 0.075 mg epinephrine specifically designed for use in infants.

Current auto-injectors have 0.15 mg or 0.30 mg epinephrine, which is not suitable for infants. Consensus is currently lacking on first aid management using available auto-injectors when managing infants. A dose of 0.075 mg from an auto-injector could fill this gap. Labeling the auto-injectors in a standard manner to differentiate doses also could be beneficial.

Training First Responders and First Aiders

Food anaphylaxis can occur in any setting, and proper emergency management can be life-saving. The public, particularly first responders and first aid personnel, need to be prepared to assist with food-related severe reactions. Overall, food allergy anaphylaxis is not included in training curricula of organizations that offer certifications on emergency training or specialized training for professionals, such as pediatric specialization for early care and education providers.

The committee recommends that organizations, such as the American Red Cross or the National Safety Council, who provide emergency training (e.g., first aid training, basic life support) to the general public and to first responders and first aid personnel in various professions and workplaces, include food allergy and anaphylaxis management in their curricula.

Training Food Industry Personnel

The committee found deficiencies in the knowledge of food industry personnel, including poor communication within the establishment, staff failure to prevent cross-contact, and lack of knowledge about hidden ingredients.

The committee recommends that food industry leaders provide the necessary resources for integrating food allergy training (e.g., food allergen identification and preventive controls, effective risk communication with customers) into existing general food safety and customer service training for employees at all levels and stages in the food industry, as appropriate, encompassing processing, retail food and grocery stores, restaurants, and other food service venues.

Training for employees could be offered through, for example, supporting conferences, workshops, or webinars to share best practices related to allergen preventive controls, food allergen risk communication, and other food allergen safety topics. State health departments could develop a certification process for allergy awareness and management in restaurants modeled after the letter grading system that rates their food safety performance.

Implement Improved Policies and Practices to Prevent the Occurrence of Severe Reactions

Policies Regarding Labeling of Packaged Foods

The food processing industry and the federal government have an essential role in informing individuals at risk of food allergy about the presence of allergens in foods. There are two types of allergen labeling: (1) mandatory, when the allergen is added as an ingredient; (2) voluntary, when the allergen might be inadvertently in the food as a result of cross-contact.

The list of major allergens to be labeled in food packages, which has been adopted by many countries, has not been reviewed since it was developed by the Codex Alimentarius Commission (CAC) in 1999. Also, some U.S. labeling policies are not effective in informing consumers about the risks from food allergens.

In terms of voluntary labeling, unintentional allergens at levels that could cause a reaction can be identified on the labels of packaged foods using precautionary allergen labels (PALs) with wording such as "X may be present." Currently, PALs bear no relationship to risk. To improve the labeling of unintentional allergens, the Allergen Bureau of Australia and New Zealand has developed the VITAL® (Voluntary Incidental Trace Allergen Labeling) program, which is based on risk assessment principles.

The committee recommends that the Codex Alimentarius Commission and public health authorities in individual countries decide on a periodic basis about which allergenic foods should be included in their priority lists based on scientific and clinical evidence of regional prevalence and severity of food allergies as well as allergen potency.

For example, in the United States, some foods listed by the Food and Drug Administration as tree nuts (i.e., beech nut, butternut, chestnut, chinquapin, coconut, gingko nut, hickory nut, lichee nut, pili nut, shea nut) could be removed from the current priority

list based on the paucity of data or low frequency of allergic reactions. In addition, evidence of the allergy prevalence and reaction severity to sesame seeds may warrant their inclusion on the priority allergen list in the United States.

The committee recommends that the Food and Drug Administration makes its decisions about labeling exemptions for ingredients derived from priority allergenic sources based on a quantitative risk assessment framework.

A quantitative risk assessment is based on knowledge of the detectable level of protein, its presence in the ingredient, exposure levels to the ingredient, and threshold dose-distributions for individuals allergic to the food.

The committee recommends that the food manufacturing industry, the Food and Drug Administration (FDA), and the U.S. Department of Agriculture (USDA) work cooperatively to replace the Precautionary Allergen Labeling system for low-level allergen contaminants with a new risk-based labeling approach, such as the VITAL program used in Australia and New Zealand.

To meet this risk-based approach, the following three steps are recommended:

1. The FDA and the USDA should establish Reference Doses (thresholds) for allergenic foods, where possible. The committee concludes that at this time, sufficient data exist on milk, egg, peanut, certain tree nuts (i.e., cashew, walnut, hazelnut), wheat, soybean, fish, and crustacean shellfish (shrimp) to establish Reference Doses. The FDA and the USDA should review the Reference Doses periodically, with particular attention to the remaining tree nuts for which data to establish Reference Doses are not currently available (i.e., almond, Brazil nut, macadamia nut, and pine nut).
2. Once Reference Doses are established, a food product would carry an advisory label (e.g., "peanut may be present") only in situations when ingesting the product would expose the individual to a level above the Reference Dose for that allergen. The FDA should restrict the number of allowable advisory labels to one phrase. Because this labeling is voluntary, the product should clearly inform the

consumer, through labeling as appropriate, as to whether a risk-based approach (such as VITAL) has been followed for each specific product. The FDA and the USDA should educate health care providers and consumers about the meaning of such a food allergy advisory statement.

3. The FDA and the USDA, together with the food industry and the analytical testing industry, should develop and validate detection methods and sampling plans for the various food allergens for which Reference Doses are established. A common unit of reporting also should be established, such as parts per million of protein from the allergenic source, so that comparisons can be made between methods and between levels in the food and clinical threshold values.

Policies at Specific Settings

The FDA Food Code provides advice from the FDA for uniform systems and practices that address the safety of food sold in food establishments. The 2013 FDA Food Code includes provisions on preventing food allergic reactions but it has not been adopted by all states.

The committee recommends that all state, local, and tribal governmental agencies adopt the 2013 Food and Drug Administration Food Code, which includes provisions for food establishments on preventing food allergic reactions. Working in collaboration with other stakeholders, the agencies also should propose that the next Food Code requires that the person in charge in food establishments pass an accredited food safety certification program that includes basic food allergy management in order to decrease or prevent the risk of food allergen exposure. In addition, agencies should develop guidance on effective approaches to inform consumers with food allergies in food service establishments.

Guidance on effective approaches to inform consumers with food allergens in food service establishments could include menu designations of allergens and posters, and other forms of displaying information about food allergens in food establishments.

The CDC *Voluntary Guidelines for Managing Food Allergies in Schools and Early Care and Education Programs* (the CDC Food Allergy Guidelines) includes essential management approaches, such as preparing for food allergy emergencies, but they have not been implemented widely in all schools. Higher education institutions do not have similar guidelines.

Although reports of severe reactions while flying are rare, accidents can occur and improving policies and practices might prevent them. In response to its task, the committee developed specific recommendations for ways to assure that appropriate guidance and education are in place to create a safe public environment for individuals with food allergy. In doing so, the committee recognized that its task did not include recommendations for therapeutic intervention or clinical management of food allergies.

The committee recommends that, within the next year, relevant federal agencies (e.g., the Food and Drug Administration [FDA], the Centers for Disease Control and Prevention [CDC], the Federal Aviation Administration) convene a special task force that includes participants from the medical community, food companies, and advocacy stakeholder groups to establish and implement policy guidelines to:

- **Assure emergency epinephrine capabilities are in place for children and adults in public venues, including schools, early care and education facilities, and on-board airlines;**
- **Provide standardized food allergy and anaphylaxis first aid training (e.g., identification of major food allergens, signs and symptoms of allergic reactions, and emergency treatment protocols) to appropriate school and university health staff, early care and education providers, and on-board flight crews; and**
- **Implement education standards for responding to and managing food allergy emergencies in schools and early care and education facilities (e.g., CDC Food Allergy Guidelines), and on airlines.**

The committee recommends that the FDA continue to work together with other relevant federal, state, and local agencies to develop and implement labeling policies specific to allergenic ingredients in packaged and prepared foods that are distributed through airlines and other public venues, including schools and early care and education facilities.

Expand Research Programs

The committee lists research needs in areas of mechanisms of action, better diagnostic tools, effective educational approaches, and evidence-based guidelines for all stakeholders, and prospective and clinical trials to support or refute current hypotheses on the development of food allergies. In addition, although the committee did not review emerging therapeutic

approaches to cure food allergies, it included development of effective and safe therapies as a key long-term goal. The details of the research needs are in Chapter 9.

The committee envisions that this report will reach many stakeholders, including consumers, patients, health care providers, school leaders, food manufacturers, and food establishment managers, and serve as guidance for future understanding and management of food allergies. The committee also has confidence that the recommendations in this report, if implemented, will stimulate progress in the understanding of food allergies, reduce further uptakes in prevalence, and improve the quality of life of those with this chronic disease and their caregivers.

1

Introduction

FOOD ALLERGIES: CHARTING A ROADMAP TO SAFETY

Over the past 20 years, public concerns have grown in response to the apparent rising prevalence of food allergy and related atopic conditions,[1] such as eczema. Although evidence on the true prevalence of food allergy is complicated by insufficient or inconsistent data and studies with variable methodologies, many health care experts who care for patients agree that a real increase in food allergy has occurred and that it is unlikely to be due simply to an increase in awareness and better tools for diagnosis. Many stakeholders are concerned about these increases, including the general public, policy makers, regulatory agencies, the food industry, scientists, clinicians, and especially families of children and young people suffering from food allergy.

Food allergy has important implications not only for those individuals directly affected but also for their families, day care and school settings, and society (Gupta, 2014; Pawanker et al., 2011). Some children naturally grow out of a food allergy, while other children or adults develop a food allergy for the first time later in life. In either case, having a food allergy is a chronic disease that can influence a person's quality of life throughout the lifespan and, in some unfortunate individuals, lead to death. The human stories of food-related anaphylaxis and the heavy burden of protecting children from foods that might initiate such serious allergic conditions are

[1] The atopic conditions of childhood consist of the triad of asthma, allergic rhinitis, and atopic dermatitis. All share a common pathogenesis, being mediated by immunoglobulin E (IgE), and are frequently present together in the same individual and family.

BOX 1-1
Statements from Children or Their Caretakers

Statements from children and adolescents (6-15 years old) with food allergy in focus groups (DunnGalvin et al., 2009)

"There's always food around you know . . . it doesn't have to be a food party"

"When I take a first bite, there's a moment when you think, is this it?"

"Nearly everything says 'may contain' so what can you eat?"

"Unlike my friends, I always have to be on [my] guard. . . . I envy them not having to be."

"They say you're just looking for attention."

". . . the same thing again and again . . . be careful, be careful . . . do you have your pen . . . watch what you eat . . . I need to have a life."

"I was at a barbecue and Mum forgot to ask what was in the burger . . . there were eggs in the burger and my eyes and lips swelled up and it was scary."

"You feel like you are choking; you have to get given the pen and then go to the hospital."

"I get lumps in my stomach and my eyes get red and I'm in agony."

"You know your throat is meant to be this size [indicates] and it swells to about this size [indicates]. It gets really hard to breath. . . . I can't get my breath . . . and you feel scared . . . so scared."

"I only go to friends' houses who I know for ages . . . it's safer that way"

particularly compelling. This burden includes fear of accidental consumption, difficulties with missing (or misunderstood) food labels, and bullying at school. Those not afflicted with such a disorder may have difficulty even imagining what life is like for severely food-allergic individuals, some of whom are allergic to multiple commonly encountered foods, such as milk, eggs, peanuts, tree nuts, and shellfish. To illustrate some of these issues, Box 1-1 includes real-life example statements from children, adolescents (DunnGalvin et al., 2009) and caretakers (Kahn, 2014; Monaco, 2015) as

"The girl next to me in school always has nuts . . . and I feel worried but I don't like to say anything; nobody needs to know."

"On Halloween they throw nuts at me but you can't tell the teacher or they'll say you're a whiney baby; you only tell your best friends; I only told my best friend but she told everyone . . . and then I was teased."

"It's not the teasing . . . it's the isolation . . . that's what gets you."

Statement from a caretaker

". . . at seven months old, he was diagnosed with food allergies. The diagnosis was not to just one, but to four different food allergens: dairy, wheat, eggs and peanuts. . . . This was no mere intolerance. These were life-threatening allergies. . . . What I can do is to make sure that, as my baby grows, he learns to protect himself. . . . As a parent of a child with food allergies, I always have to be prepared. This is no simple feat. I carry emergency medications such as epinephrine auto-injectors, antihistamines, and an asthma inhaler. I vigilantly stay prepared with food. You never know when you will wind up somewhere that does not have a safe choice, such as a friend's house where they cannot accommodate your child's allergies."

By Adrienne Kahn; posted on September 11, 2014, at AllergicLiving.com.

"Ever since my children were diagnosed with these [food] allergies, each moment has been a growing educational (and often empowering) experience. My husband and I felt it was very important from the initial diagnosis to be honest with Vincent about what would happen if he ingested peanuts, tree nuts, or anything that was cross-contaminated with them. We taught him how to carry and use the epinephrine auto-injector, how not to accept food from anyone but family, and never to take off his medical ID bracelet."

By Meghan Monaco; posted on June 9, 2015, at AllergicLiving.com.

they describe quality-of-life impacts and hazards of having a severe food allergy.

Ultimately, answering questions about the actual prevalence of food allergy, the mechanisms underlying allergen sensitization and the development of food allergy, and how to estimate the severity of disease in affected individuals, among many other research questions, requires adequate support from research funding sources. Similarly, protecting those with food allergy from accidental exposure and providing appropriate treatment for

those who develop reactions, demand effective governmental policy and consumer protections across multiple sectors, including agricultural production, the food industry, product labeling, regulatory authorities, and the food and entertainment industries. At the present time, however, despite a mounting body of data on the prevalence, health consequences, and associated costs of food allergy, this chronic disease has not garnered the level of societal attention that it warrants. Moreover, for patients and families at risk, recommendations and guidelines have not been clear about preventing exposure or the onset of reactions or for managing this disease.

In brief, the scientific knowledge about food allergy has significant gaps and, for those at risk, few or no reliable prevention strategies or treatments exist. How did we get to this situation? First, the accepted gold standard for identifying a food allergy—the oral food challenge (OFC)—has not been used widely due to difficulties of the procedure (e.g., risk of a severe reaction, length of procedure, the need to standardize the food), especially in research where large numbers of study participants are needed.

Second, conducting research on food allergy presents various types of practical barriers: studies are very costly due to the long duration of typical therapeutic studies (e.g., 2 to 4 years); the heterogeneity of participants; difficulty recruiting participants; and notably, too few research centers and researchers equipped to conduct high-quality studies.

Third, food allergy is a complicated, multifactorial disease and researchers do not fully understand its causes, mechanisms, and effects. Except for having atopic parents (i.e. parents with a predisposition to allergic reactions), the contributions of various factors to food allergy remain unclear and under investigation. Genetics, time, route of allergen exposure, diet, factors related to pregnancy and lactation, and the microbiome all are being studied as potential influences on the development of food allergy. The fact that food allergy develops in infants makes the research difficult, as conducting trials during pregnancy or in infants could be unethical.

Finally, few effective therapies for food allergy currently exist. The gaps in scientific understanding have impaired the development of effective therapies, although many promising ones are being investigated.

Professional medical associations continue to update their practice guidelines for food allergy despite limitations in the evidence, based on the most recent knowledge on diagnosis, prevention, treatment, and management. Yet, unlike other chronic diseases related to diet, such as diabetes or cardiovascular diseases, where specific strategies for prevention or management have been established (ADA, 2015; Goff et al., 2014), recommendations by governments or professional associations for preventing the onset of a food allergy have been hampered by limited or inconsistent data. Recent and ongoing research and clinical progress on assessment, diagnosis, and treatment of food allergy hold the promise of improving future practice

and management strategies. These advances include the safe use of OFCs as the gold standard for diagnosis, emerging data on the role of early exposure to potential allergens for favoring prevention, and high-quality studies of effective therapies. Indeed, based on the latest findings in food allergy prevention science, and particularly the latest findings on the protective effects of early exposure to peanut, leading organizations are rethinking the current recommendations and considering promising new approaches. Still, new thinking and approaches can have the unintended consequence of confusing parents and all the institutions that interact with people with food allergy, including schools, airlines, and restaurants.

For individuals who are already diagnosed, complete avoidance is still the only established method for preventing a reaction and, as indicated in Box 1-1, it is not easy to achieve. This is particularly the case when effective policies and practices are not implemented in places where foods are purchased or consumed (e.g., the hospitality and food service industries). Likewise, policies to ensure that relevant settings are prepared to identify and treat a severe reaction are not always enacted, implemented, or enforced. For example, epinephrine may not be available in relevant places, such as early care and education centers, schools, afterschool programs, camps, or airplanes. To promote greater safety in such settings, nongovernmental organizations are creating tools and guidelines to increase awareness, help parents and children with strategies for avoiding allergens, advocate for better policies, and/or increase the effectiveness of research efforts. Likewise, professional organizations of various industry sectors (e.g., manufacturers, retailers, food service) have created guidelines and training programs for their stakeholders. Federal, state, and local governments also are beginning to include allergy management as an element of their food safety policies. However, despite all the policies and guidelines for the various settings (e.g., food industry practices, regulatory agencies, early care and education centers, schools, higher education, and public transport), their development may not be keeping pace with the science and their implementation and enforcement varies greatly across the United States.

In addition, food allergy is a major global challenge and prevention strategies are needed across the globe. Although the prevalence and implementation of policies will vary by country, similar management approaches could be adopted across countries.

For all of these reasons, it was thought to be timely and important, in the interest of public health, for the National Academies of Sciences, Engineering, and Medicine to conduct a consensus study to review the science and management practices of food allergy. The committee intends that this report will (1) clarify the nature of the disease, its causes, and its current management, (2) highlight gaps in knowledge, (3) encourage the implementation of management tools at many levels and among many stakeholders,

and (4) delineate a roadmap to safety for those who have, or are at risk of developing, food allergy, as well as for others in society who are responsible for public health.

STATEMENT OF TASK

This study originated as a result of the broad public interest in the health aspects of food allergy; the relevance to public health, health care, and society; and the current lack of solutions both for the prevention of food allergy and its management. The apparent increase in food allergies, and concerns about a lack of good management strategies, prompted informal discussions that resulted in a planning meeting in Washington, DC, under the auspices of the National Academies of Sciences, Engineering, and Medicine on May 24, 2014. Various experts gave presentations on what is known about food allergy prevalence, causes, and risk determinants; perceptions regarding food labeling; and treatment approaches. Representatives from stakeholder groups with an interest in food allergy also attended. The group discussed the concerns related to those topics and provided comments about questions that would be of value to include in a consensus study from the National Academies. Following this meeting, a Statement of Task (see Box 1-2) was developed with contributions from all stakeholders.

APPROACH OF THE COMMITTEE

Expert Committee and Advisory Panel

An ad hoc committee of 15 experts was selected and nominated to respond to the statement of task. Committee members were drawn from a broad range of disciplines, including food allergens and methods of detection, pediatrics, clinical medicine, immune-related illness, genetics, epigenetics, the microbiome, epidemiology, biostatistics, nutrition/dietetics, food safety, public education, public health policy, clinical trials, prediction and prevention of food allergy, and child development. To expand the geographical context and experiences, food allergy experts from the United Kingdom and Australia were included in the committee. The committee held one public session on June 22, 2015, and one public workshop on August 31-September 1, 2015, to gather information. The committee also met on five occasions in closed sessions to discuss the findings, draw conclusions, and craft recommendations. The public session and workshop were valuable in providing the committee with the perspectives of sponsoring organizations and with information regarding diverse aspects related to the task (see Appendix A for public sessions and workshop agenda).

In order for the committee to consider the perspectives of those affected

BOX 1-1
Statement of Task

A committee will be formed to examine critical issues related to food allergy, including the prevalence and severity of food allergy and its impact on affected individuals, families, and communities; and current understanding of food allergy as a disease, and in diagnostics, treatments, prevention, and public policy. This consensus study will engage a broad array of stakeholders, including government agencies, organizations, academic institutions, industries, policy makers, and patient organization groups, to bring together leading investigators from relevant fields, clinicians, and parents; and to develop a framework for future work; and to recommend actions by both government and nongovernment agencies. The committee's review of the evidence will consider the following key questions:

1. What are current trends in food allergy prevalence?
   - What is an appropriate definition of food allergy to use in measuring prevalence?
   - What data or methods are most appropriate to use in measuring prevalence and how may they be implemented?
   - Should there be an effort to assess prevalence for allergens other than the eight most common that are required to be disclosed on food packages? If so, should the same methods be used for these allergens?
2. What are the key prenatal/early life determinants of food allergy?
   - For example, are there dietary factors that impact development of food allergy and are these modifiable?
3. What are the current data gaps in understanding the diagnosis and prognosis for food allergy?
   - What new approaches are being developed to address these data gaps?
4. What steps can be taken to educate providers and the public in order to create safe environments for food allergic children both within and outside the home?
   - What and where are the most risky food scenarios and how can these be better managed?
   - What guidance can be given to individuals about exposure to low levels of allergens in food products?
5. What is the status of assessing allergen thresholds in individuals? What additional methods or tools are needed?
6. What research gaps need to be filled in order to provide better guidance to health care providers and policy makers?

The committee will develop a framework for future direction in understanding food allergy and its impact on individuals, families, and communities; recommending steps to increase public awareness of food allergy; promoting research on both disease causation and management; and informing preventive approaches to food allergy. Research gaps will be identified and recommendations made to fill them.

by food allergy, the study also included an advisory panel made up of nine parents of children with food allergies and one individual with food allergy. The advisory panel members were selected from a group of approximately 50 individuals recommended by the sponsor organizations. All members of the advisory panel live with the challenges of food allergy on a daily basis and some are active advocates in their communities, participants in policy work and public speaking, or mentors for families who are new to food allergy. Although their opinions may not represent those of all people with the disease, they were invaluable to the committee as good examples of the sentiments and burden of living with food allergy. Some of the concerns brought up by this panel included the need for more clarity in food labeling, appropriate training for emergency personnel, access to epinephrine, and for improvements in well-being and safety at specific settings, such as schools, camps, restaurants, and transportation.

Boundaries and Clarifications About the Task

As mentioned above, food allergy, as a chronic disease, shares characteristics with other conditions and diseases. It is therefore necessary to be very clear about the task and its interpretation by the committee. The committee focused its efforts on the questions in the statement of task as they refer to the definition of food allergy by the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH). This definition states that food allergy is "an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food." Food allergies fall into two major types—immunoglobulin E (IgE)-mediated and non-IgE-mediated—and the committee focused mostly on IgE-mediated food allergies (see Chapter 2 for definitions). Some of the discussions, where appropriate, also pertained to non-IgE-mediated food allergies, such as food protein–induced enterocolitis, particularly when discussing diagnostic methodologies that are unique for each type of food allergy. However, the literature reviews, findings, conclusions, and recommendations reviewed in this consensus study refer exclusively to IgE-mediated food allergies. Other food-related diseases, such as celiac disease, or food intolerances, such as lactose intolerance, or toxicity of food additives, are not covered in this report because they were beyond the scope of the statement of task.

Although any protein can be allergenic, certain proteins and specific foods that contain them (e.g., Ara h 2 in peanut) are characteristically allergenic and have been recognized as such because of the frequency or severity of the symptoms they cause in individuals at risk. The list of common allergenic foods varies by country. This variation is often due to the nature of diets or native foods in a given region but also to different criteria that are used

to qualify a food for inclusion in the list. The committee's literature reviews were conducted from the perspective of foods that are considered allergenic in the United States. However, global evidence was considered to the extent that it informed the central issues the committee reviewed. Moreover, most recommendations also apply to any allergenic food today or those that may become clinically important allergens in the future. The committee did not review the scientific or regulatory aspects of the potential for proteins from genetically modified foods to be allergenic. The reader is referred to the 2016 National Academies of Sciences, Engineering, and Medicine report *Genetically Engineered Crops: Experiences and Prospects* for a review and recommendations on this topic (NASEM, 2016).

Although the study is meant to have a global perspective, it would not be feasible to answer all the questions in the statement of task from the perspective of all countries. Research data are being generated worldwide but implementation of research findings depends on contextual factors that would be different for each country or region. When it was valuable and feasible to do so, data collected about implementation in the United States, as well as in other countries, were used to guide the committee's deliberations and recommendations. It should be noted that while the recommendations are focused on the United States, many could be implemented in other regions of the world.

This report is not meant to duplicate or replace important guidelines that have been developed in the past and that will continue to provide essential information about progress in diagnosis, treatment, and management of food allergy in the United States. Instead, this report is meant to be a call for unified action among all stakeholders and the public, both to recognize the importance of this disease and to join forces in efforts to markedly improve our ability to understand, effectively manage, and ultimately, cure this disease, and to make the world safer for those afflicted with it. Rather than conducting evidence-based reviews for all topics relevant to the task, the committee offered the support of specific guidelines where appropriate. In addition, the committee has conducted selected evidence-based reviews of the scientific literature where recent developments or the need for reinforcement deemed it necessary. Moreover, the committee did not review therapeutic approaches that are currently being investigated and instead recommended more research efforts in this area. These key guidelines include the following: 2010 NIAID/NIH-sponsored *Guidelines for the Diagnosis and Management of Food Allergy in the United States: Report of the NIAID-Sponsored Expert Panel* (Boyce et al., 2010), the European Academy of Allergy & Clinical Immunology (EAACI) *Food Allergy and Anaphylaxis Guidelines* (Muraro et al., 2014), two Practice Parameters (Lieberman et al., 2015; Sampson et al., 2014), and two Clinical Reports (Sicherer et al., 2007, 2010). Table 1-1 includes the guidelines (and system-

TABLE 1-1 Food Allergy Guidelines and Systematic Reviews

Title	Organization	Authors and Date	Referenced in This Report as
Guidelines for the Diagnosis and Management of Food Allergy in the United States: Report of the NIAID-Sponsored Expert Panel	National Institute of Allergy and Infectious Diseases (NIAID)/ National Institutes of Health (NIH)	Boyce et al., 2010	NIAID/NIH-supported Guidelines
		Systematic review: Chafen et al., 2010	RAND systematic review
Food Allergy and Anaphylaxis Guidelines	European Academy of Allergy & Clinical Immunology (EAACI)	Muraro et al., 2014	EAACI Guidelines
		Systematic reviews: • de Silva et al., 2014 • Dhami et al., 2014 • Nwaru et al., 2014 • Panesar et al., 2013 • Salvilla et al., 2014 • Soares-Weiser et al., 2014	EAACI systematic reviews

Food Allergy: A Practice Parameter Update	Joint Task Force on Practice Parameters representing the American Academy of Allergy, Asthma & Immunology (AAAAI) American College of Allergy, Asthma & Immunology (ACAAI) Joint Council of Allergy, Asthma & Immunology (JCAAI)	Sampson et al., 2014	AAAAI Guidelines
Anaphylaxis—A Practice Parameter Update	Joint Task Force on Practice Parameters, representing AAAAI, ACAAI, and JCAAI	Lieberman et al., 2015	AAAAI Practice Parameter
Clinical Report—Management of Food Allergy in the School Setting	American Academy of Pediatrics (AAP)	Sicherer et al., 2007	2007 AAP Clinical Report
Self-Injectable Epinephrine for First-Aid Management of Anaphylaxis	AAP	Sicherer et al., 2010	2010 AAP Clinical Report

atic reviews on which they were based) and the names by which they are referred to in this report.

Gathering the Evidence

In addition to holding the public session and the information gathering workshop mentioned above and detailed in Appendix A, the committee used various approaches to respond to the questions in the statement of task. For example, it was possible to rely on the scientific literature to answer some of the questions. However, for questions related to current practices in the various settings encountered by those with food allergies, the committee relied more often on information gathered at workshops and/or by consulting the "gray literature" (published reports or research outside the traditional peer-reviewed scientific journals and commercial publications).

For example, to answer questions related to the prevalence of food allergy and the key prenatal and early life determinants of food allergies, evidence-based reviews were conducted as described in the report. To answer questions related to the definition, diagnosis, and prognosis of food allergy, as well as those related to managing food allergy in the health care setting, the committee did not conduct an extensive review of the literature because relevant recommendations have already been addressed in very recent authoritative reports. In such cases, primary resources for the findings, conclusions, and recommendations of the committee were derived from the 2010 NIAID/NIH-sponsored Guidelines (Boyce et al., 2010); the 2014 EAACI Guidelines and systematic review (de Silva et al., 2014; Dhami et al., 2014; Muraro et al., 2014), as well as the 2015 American Academy of Allergy, Asthma & Immunology (AAAAI) Guidelines (Lieberman et al., 2015), the 2014 AAAAI Practice Parameter (Sampson et al., 2014), and the two American Academy of Pediatrics (AAP) Clinical Reports (Sicherer et al., 2007, 2010). Additional searches in scientific databases were performed to identify specific items in the literature to supplement the discussion about specific topics, paying special attention to papers published after the aforementioned reports.

A DEVELOPMENTAL AND ECOLOGICAL PERSPECTIVE ON FOOD ALLERGY

During its review and deliberations, the committee recognized that addressing the task and goals of the consensus study would benefit from taking a developmental and ecological perspective. Preventing and treating food allergy, and delineating a roadmap to safety are a multifaceted undertaking that must take into account many interacting systems that

influence both risks and safety. For every individual, the risks and possible protections for food allergy vary and change over the life course, depending on individual genetic factors, biological development, exposures to allergens, and the nature of the contexts in which the individual lives. From a societal and public health perspective, the safety and well-being of many potential individuals with food allergy requires recognition that risks and protections for public safety are spread across many systems, including food production and distribution systems, health care systems, and education systems, among others. This section explains how the committee undertook a developmental and ecological approach toward the health and safety of individuals with food allergy.

Ecological Models of Individual Development

Ecological models of individual human development emphasize that the individual interacts with many social, cultural, and environmental systems throughout life and these interactions shape the development, health, and well-being of the individual over the life course (Boyce and Kobor, 2015; Bronfenbrenner and Morris, 2006; Gottlieb, 2007; IOM, 2005; Lickliter, 2013; Overton, 2013). These interactions span genetic to societal levels (Gottlieb, 2007; Lerner, 2006; Lickliter, 2013; Overton, 2013). The importance of taking a relational developmental systems approach to health promotion also has been applied by others (Halfon et al., 2014). From this perspective, the health and well-being of a developing individual is constantly changing as the individual interacts with the physical and biological environment, schools, family, and other contexts throughout life.

Proximal ecological systems (i.e., the social, cultural, and physical contexts) with which individuals interact directly over the life course have been termed "microsystems" in Bronfenbrenner's bioecological model (Bronfenbrenner, 1979; Bronfenbrenner and Morris, 2006). In general, the health and well-being of individuals and populations with respect to food allergy are influenced by biological systems within individuals, including the microbiome, as well as human biological systems, and also their interactions with their physical contexts, including the built environment, plants, animals, microbiotic organisms, water quality, or climate, that could influence food allergy risk and/or protective processes.

Throughout the life course, however, the systems with which a person interacts vary. Before birth, a developing fetus interacts indirectly with systems in the broader context because the mother's body is the entire proximal context and essentially all current extrinsic influences (e.g., diet or psychological trauma) are mediated by processes linking the fetus to the mother's biological function. After birth, the caregiving system (i.e., parents and other caregivers) plays a primary role in mediating the experiences

of a baby, but now the child has additional direct experiences with other people and physical environments (e.g., health care, early care and education centers, and the social environments). As children continue to develop, they join and interact directly with numerous new systems, including peer groups, schools, and community services for children and families. Eventually, children begin to interact directly with social media, workplaces, and social and recreational contexts, such as sport teams, and religious or other cultural contexts.

Individuals also are influenced by many additional systems beyond their proximal interactions, through the influences of cultural practices and governmental or nongovernmental policies or rules that shape their contexts and experiences within societies and social groups. These relatively distal systems in the social ecology that influence individual development indirectly have been termed "macrosystems" (Bronfenbrenner, 1979; Bronfenbrenner and Morris, 2006). In the context of food allergy, for example, macrosystems include the laws and regulatory systems that affect food or the transportation industries and health care systems, religion, or mass media.

Human individuals adapt to the contexts of their development in multiple ways. An organism can adapt to a wider range of environments because developmental plasticity makes it possible for the developing phenotype to adjust to the environment in which it will live (Boyce and Kobor, 2015; Del Giudice et al., 2011; Hochberg et al., 2011; Szyf and Bick, 2013). For example, many of the adaptive systems that sustain health and well-being, including immune functions, stress responses, and language development, require some calibration for effectiveness within a given environment. It is conceivable that changes in modern life, including urbanization, mobility, and rapid environmental change, may have disrupted some processes of adaptive calibration, such that an individual could be "tuned" for one environment but live in or move to a radically different context. For example, exposure to microorganisms may trigger different responses depending on the timing. Growing up on a farm in a context of exposure to a rich assortment of microorganisms early in life may have protective influences on the risk for developing asthma. However, initial exposure to the same organisms later in life can trigger allergic responses (Figueiredo et al., 2013; Guerra and Martinez, 2008; von Mutius and Radon, 2008). The *developmental timing* of a person's interactions with his or her context is an important consideration for understanding the origins and prevention of food allergy. Research is revealing that the timing of exposure to potential allergens can be a key determinant of whether or not food allergy develops in those at risk. The development and vulnerabilities to food allergy likely depend on an array of sensitivities to context that also may be shaped by the timing of exposures to potential allergens and other environmental fac-

tors. The committee considers these to be vital factors in promoting health and well-being for those at risk of developing food allergy.

From the perspective of an individual person or that person's caregivers, a roadmap for safety in regard to food allergy must include a developmental understanding of current individual vulnerabilities and risks, informed by individual history, plus a detailed analysis of the risks and protective factors embedded in the contexts in which that person lives. A parent or caregiver actively protects a child with an allergy until that individual can manage on his or her own. As Box 1-1 illustrates, management of food allergy at the individual level can be challenging and complex. However, the task of a society to protect all its members with food allergy is even more complicated.

Complex Adaptive Systems in the Prevention, Treatment, and Management of Food Allergy

Health care and public safety systems have been described as examples of complex adaptive systems (Hammond, 2009; IOM and NRC, 2015; Lipsitz, 2012; Reiman et al., 2015). A complex adaptive system is composed of many heterogeneous elements whose interactions drive the system in ways that cannot be easily understood from considering only the separate elements. The elements can be social, physical, or biological. Specific properties characterize a complex adaptive system: individuality and adaptation, feedback and interdependence, heterogeneity, spatial complexity, and dynamic complexity (IOM and NRC, 2015).

Considering public risk, adaptation, and safety in relation to food allergy, examples of complex adaptive system features include the independent behavior of many individuals or their parents acting to avoid allergen exposure in the diet of self or child (adaptation and independence); the diverse responses of individual consumers to labels about allergens in food and to the experience of severe reactions to specific foods (independence, adaptation, heterogeneity); the actions of many independent businesses to customer concerns about allergies (independence, adaptation, heterogeneity, feedback) or to implementation of new state and federal regulations governing food production or sales (adaptation); the variation in sensitivity of individuals to the same potential allergen (adaptation, heterogeneity); the fact that different foods are considered allergenic in different countries (spatial complexity); and immunological changes during early development (dynamic complexity).

Efforts to change the safety of complex adaptive systems are complicated, whether the target of change is the entire public health care system, the commercial transportation systems, or the food production and service industries. Change is likely to require attention to issues of leverage,

resistance, cascading effects, and unanticipated consequences, as well as recognition that a single strategy is unlikely to change a large and multifaceted adaptive system. Changing one element in a complex system can have unanticipated consequences that raise problems in another part of the interconnected systems network. Moreover, it is difficult to move a complex system in the desired direction due to the complexity, heterogeneity, independence, and dynamic nature of its many component systems. Thus, solving problems in a complex adaptive system involves consideration of multiple levels and systems, multiple sectors, and multiple strategies. From this perspective, managing food allergy would include consideration of the roles of diverse actors, a multiplicity of processes, nonlinear and unexpected-emergent effects, counter-regulatory feedback loops, and many systems operating at different levels to achieve disparate goals. Examples of the many actors and settings (i.e., elements) that have a role in preventing and treating food allergy are individuals, families, schools, workplaces, food and transportation industries, and health care systems. As Reiman et al. (2015) stated, "Safety management of complex adaptive systems presents a great challenge" (p. 90). It may require appreciation of complexity in understanding and addressing the issues, distribution of adaptive capacity across levels, a balance of rules and flexibility, and an interactive process to steer the system toward greater safety.

ORGANIZATION OF THE REPORT

This introductory chapter describes how and why the study originated, the charge to the committee, and the developmental and ecological context. Chapter 2 is a background chapter that describes the definition of food allergy that the committee adopted, explains common food allergy signs and symptoms, summarizes common allergenic foods, and explains the mechanism of food allergy. It also comments on the misinformation among the many stakeholders in regard to what a food allergy is and how to prevent and manage it. Chapter 3 summarizes what is known about the prevalence of food allergy in the United States and abroad, highlighting the limitations in methods, especially in regard to prevalence trends. Chapter 4 includes the current diagnostic and prognostic methods used and others that are under investigation. Chapter 5 presents current knowledge about prenatal and early life determinants of food allergies, including genetic and environmental factors. Chapters 6, 7, and 8 contextualize the ways in which food allergy is currently managed in the health care system (Chapter 6), the food manufacturing industry (Chapter 7), and other settings such as schools and restaurants (Chapter 8). Chapter 9 includes all the committee's recommendations for research. Finally, Chapter 10 culminates with the committee's vision of a roadmap to safety, discussing how food allergy

can be prevented and managed based on evolving knowledge, taking into consideration the roles and responsibilities of the many actors and settings that an individual interacts with throughout the life course.

The committee envisions that this report will reach the many stakeholders, including the general consumer, patients, health care providers, school leaders, food manufacturers and establishment managers, and serve as guidance for future understanding and management of food allergies. The committee also has confidence that the recommendations in this report, if implemented, will stimulate progress in the understanding of food allergies, reduce further uptakes in prevalence, and improve the quality of life of those with this chronic disease and their caregivers.

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2

Definitions

Collecting the evidence needed to develop effective diagnostic approaches, prevention strategies, therapies, and management procedures to prevent, manage, and treat food allergy requires that the physicians, biomedical and pharmaceutical scientists, policy makers, affected individuals and families, and all other stakeholders share a common understanding of what food allergy is and is not. In addition, although all proteins in foods have the potential to elicit a food allergy, some have been recognized as major allergens due to their potency in inducing a food allergy or in affecting the prevalence of allergy to those food constituents in the population. The list varies depending on the country but several ones are common globally. This introductory chapter begins by defining food allergy both by describing its signs and symptoms and by presenting our current understanding of how food allergy develops in affected individuals. The chapter also distinguishes food allergy from the many other adverse effects or conditions that could be related to foods but that have a nonimmunological origin. Considering the diversity of food adverse conditions with similar symptomatology and clinical manifestations (see Figure 2-1), it is no wonder that many misconceptions persist about food allergy. Even today, many questions are still unresolved. The most pressing research questions are detailed in Chapter 9.

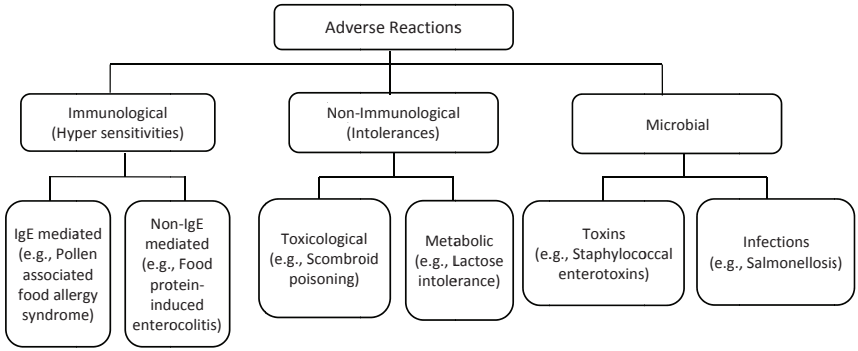

FIGURE 2-1 Types of adverse reactions to foods.

FOOD ALLERGIES: DEFINITIONS

Commonly Accepted Definitions

Food allergy is "an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food," according to the 2010 National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIAID/NIH)-supported *Guidelines for the Diagnosis and Management of Food Allergy in the United States* (NIAID/NIH-supported Guidelines) (Boyce et al., 2010). "Exposure" in the food allergy context can be through ingestion, skin contact, or exposure to airborne particles. The immunologic component is central to the discussion of food allergy, including the underlying mechanisms of allergic reactions and methods of diagnosis and treatment. Adverse reactions to foods or food components that lack an identified immunologic pathophysiology are not considered food allergy, but instead are typically called food intolerances (Boyce et al., 2010). These reactions are not a focus of this report. The mechanisms behind these other conditions may include metabolic, pharmacologic, or toxic factors.

A food is defined as "any substance—whether processed, semi-processed, or raw—that is intended for human consumption, and includes drinks, chewing gum, food additives, and dietary supplements" (Boyce et al., 2010). Food allergens are the components within foods that trigger immunologic reactions. These are most often specific glycoproteins, which can interact with the body's immune cells in a way that initiates the development of a food allergy.

The broad terms **allergy** and **allergic disease** refer to a disease caused by immunologic dysfunction that fall under one of two key classifications: immunoglobulin E (IgE)-mediated or non-IgE-mediated (see Tables 2-1 and 2-2). This report focuses almost exclusively on IgE-mediated food allergy, which has better defined underlying cellular mechanisms and an established link to many prevalent food allergy reactions. Non-IgE-mediated food allergy reactions (e.g., food protein–induced enterocolitis) are less common and the mechanisms of the reactions are less well characterized. Celiac disease is a well-characterized, immune-mediated disease that has food as an exacerbating factor but will not be detailed in this report.

Immunoglobulin E is an antibody that, if bound to certain cells bearing receptors for IgE, can trigger intense inflammatory reactions in response to the allergen for which the cell-bound IgE has specificity. The presence and quantity of such allergen-specific IgE antibodies is a key metric in diagnosing and evaluating food allergy sensitivities. However, the quantity of IgE antibodies ranges widely, making quantification an incomplete

TABLE 2-1 Overall Differences Between IgE- and Non-IgE-Mediated Food Allergies

Class	IgE-Mediated	Non-IgE-Mediated
Time to onset of reaction	Immediate <2 hours[a]	Delayed Often >4-6 hours
Volume usually required for reaction	Small	Sometimes larger
Typical symptoms	Urticaria Angioedema Vomiting Diarrhea Oral itching Anaphylaxis	Diarrhea Food refusal Failure to thrive Gastroesophageal reflux Irritability/abdominal distension Eczema
Common diagnostic procedures	Above signs or symptoms by history or oral food challenge and positive IgE antibody (skin prick test or serum specific IgE)	Sometimes can do home-based elimination and rechallenge sequence; some require rechallenge in hospital setting

[a] In the case of mammalian meat, onset times for reactions related to galactose-alpha-1, 3-galactose (alpha-gal) can be longer than 2 hours. (See "Delayed Anaphylaxis Associated with Mammalian Meats" in Chapter 4.)

TABLE 2-2 Types of Food Allergies

GI Food Allergies	
IgE-mediated	
Immediate gastrointestinal (GI) hypersensitivity	Upper GI symptoms may occur within minutes; lower GI symptoms may occur either immediately or with a delay of up to several hours. Immediate vomiting is the most common reaction and the one most clearly mediated by IgE.
Pollen-associated food allergy syndrome (PFAS)	PFAS is an IgE-mediated allergy, often to raw fruits or vegetables, with symptoms including itching or swelling of the lips, mouth, and throat.
Non-IgE-mediated	
Eosinophilic gastroenteritis (EG)	EG is thought to be non-IgE-mediated although IgE-mediated is possible. EG symptoms vary depending on the portion of the GI tract involved and the localized or widespread infiltration of the GI tract by eosinophils.
Eosinophilic esophagitis (EoE)	EoE symptoms vary depending on the age of the person, from reflux-like symptoms and vomiting in school-age children, to refusal to eat and impaction in teenagers and adults.
Food protein–induced enteropathy	Vomiting, diarrhea, and sometimes protein-losing enteropathy occur in this condition.
Food protein–induced allergic proctocolitis (AP)	AP typically presents as specks or streaks of blood mixed with mucus in the stool of otherwise healthy infants. Food-specific IgE is generally absent. The suspected role of food allergy is based on history of exposure to allergens, not diagnostic tests.
Food protein–induced enterocolitis syndrome (FPIES)	Non-IgE-mediated FPIES usually occurs in infants and presents as chronic emesis, diarrhea, and failure to thrive. Milk and soy protein are the leading, but not exclusive, causes. The reaction is delayed, occurring approximately 2 hours or later after ingesting the food.
Cutaneous	
IgE-mediated	
Acute urticaria	Round and irregular pruritic (itchy) lesions appear quickly after ingesting an allergenic food. Although IgE-mediated food allergy often causes urticaria, it is not the leading cause.
Angioedema	Likely IgE-mediated when caused by food and involves "non-pitting, non-pruritic, well-defined edematous swelling that involves subcutaneous tissues, abdominal organs, or the upper airway." Upper airway involvement signifies a likely medical emergency.

TABLE 2-2 Continued

Contact urticaria	Can be induced by either an IgE-mediated food allergy or a nonimmunologic histamine reaction.
Non-IgE-mediated	
Atopic dermatitis (AD)	AD involves complex interactions between skin barrier dysfunction and environmental factors, linked in some individuals to mutations in the protein filaggrin. The role of food allergy, from sensitization to subsequent skin reaction, remains a topic of debate.
Allergic contact dermatitis (ACD)	ACD is a form of eczema caused by reactions to chemical haptens in foods; it is associated with marked pruritus, erythema (redness of the skin), papules, vesicles, and edema.

SOURCE: Boyce et al., 2010.

indicator of function, allergen sensitivity, or reaction severity. Moreover, some individuals with measurable IgE specific for particular food allergens do not exhibit clinical signs and symptoms of food allergy when they ingest such allergens. This supports the conclusion that allergen-specific IgE is (by definition) required for a person to exhibit clinical food allergy to that allergen, but the presence of such allergen-specific IgE is not sufficient for a person to exhibit a food allergy to that allergen. IgE is typically measured in serum or determined through allergen skin prick tests (Berin, 2015). The IgE-mediated reactions observed in patients with food allergy are often grouped into immediate onset reactions and immediate plus late-phase reactions and can include life-threatening anaphylaxis, gastrointestinal hypersensitivity, urticaria, and pollen-associated food allergy syndrome (Berin, 2015). Allergen-specific IgE may be detectable in atopic dermatitis (AD) and eosinophilic esophagitis (EoE) and these may be food-responsive disorders, but a direct correlation of the pathology in these disorders with IgE and specific food allergen triggers is less clear (see Box 2-1 for these and other basic definitions).

Common Food Allergy Signs and Symptoms

Food allergy can manifest through a wide range of signs and symptoms with varying severity, which makes diagnosis challenging, particularly if a history of allergic reactions has not already been established (see Chapter 4). The most common signs and symptoms typically manifest on the skin (i.e., cutaneous), in the gastrointestinal (GI) tract, in the respiratory system, or in all of these areas. These signs and symptoms include development of uticaria (hives), angioedema (tissue swelling), circulatory collapse, dizziness, coughing, vomiting, stomach cramps, nausea, and others (ACAAI, 2015).

BOX 2-1
Definitions

Allergen-specific IgE is an IgE that recognizes a specific allergen and that is formed by the immune systems of some individuals after they have been exposed to that allergen in food.

Anaphylaxis is an acute, potentially life-threatening syndrome with multisystemic manifestations due to the rapid release of inflammatory mediators.

Desensitization is a state of clinical and immunological nonresponsiveness to an allergen, including food allergens, that can be induced by the careful, physician-guided administration of gradually increasing amounts of the offending allergen over a relatively short period of time (hours to days). The maintenance of such desensitization typically requires continued regular exposure to the offending allergen (also see **Tolerance**).

Food allergens are the components within foods that trigger adverse immunologic reactions; these are most often specific glycoproteins that can interact with the body's immune cells in a way that initiates the development of a food allergy.

Food allergy is an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food, and that can be either IgE-mediated or non-IgE-mediated.

Food intolerance is an adverse reaction to foods or food components that lacks an identified immunologic pathophysiology.

Food allergy is rarely the principal cause of respiratory conditions, but IgE-mediated respiratory symptoms can be a key finding in diagnosing anaphylaxis (James, 2003). In addition, occupational asthma caused by exposure to food occurs more frequently among individuals in certain professions such as bakers, millers, or grain elevator workers. A number of specific cutaneous and GI food allergy conditions, as defined by the NIAID, are listed in Table 2-2. Food-induced anaphylaxis—which may accompany or encompass other conditions—is an acute, potentially life-threatening syndrome with multisystemic manifestations due to the rapid release of inflammatory mediators (Boyce et al., 2010). It can occur within minutes to a couple of hours of ingesting the food (or longer for alpha-gal reactions related to mammalian meat). The reaction usually develops and, if appropriately treated, resolves completely within hours, but in rare

Immunoglobulin E (IgE) is a type of antibody that can trigger intense inflammatory reactions. IgE causes the IgE-mediated allergic response by binding strongly to IgE receptors (FcεRI) found on the surface of mast cells and basophils, and triggering these cells to release powerful inflammatory mediators once the cell-bound IgE recognizes the offending food allergen.

Pollen-associated food allergy syndrome (PFAS) is a type of food allergy with signs and symptoms that include itching or swelling of the lips, mouth, or throat in response to eating certain raw fruits and vegetables. PFAS typically develops in adults with hay fever. The specific IgE antibodies formed exhibit reactivity with both proteins found in pollen and similar proteins found in certain fruits and vegetables.

Sensitization is a condition in which an individual produces detectable IgE to a particular allergen or allergens. It precedes and is required for the clinical manifestations of a food allergy, but not all individuals with detectable IgE will experience a food allergy reaction to the allergen recognized by that IgE.

Tolerance is a state of unresponsiveness of the immune system to substances or tissue that have the capacity to elicit an immune response. It can be natural (e.g., to the body's own proteins) or acquired (e.g., to external proteins). It is also said that some persons can "grow out" of an allergy; this can be envisioned as a form of acquired tolerance to the offending allergen(s). In some instances, the state of tolerance may be transient (also see **Desensitization**) and in others it can be durable.

instances symptoms can occur hours later. For some individuals, exercise after ingesting an allergenic food may increase the likelihood of anaphylaxis and severity of clinical symptoms (Romano et al., 2001). In those with severe and potentially life-threatening anaphylaxis, findings include airway compromise (swelling of tissues in the throat and upper airways), impaired breathing (e.g., nasal congestion and rhinorrhea and narrowing of airways in the lungs), and/or circulatory problems (e.g., changes in heart rate, shock). Skin and mucosal changes usually, but not always, also occur (e.g., flushing, pruritus, hives in the skin; swelling of the tissues of the lips, mouth, and GI system). For a more detailed description of anaphylaxis and its diagnosis and management, see Chapter 6.

Common Allergenic Foods and Food Allergens

Although, in theory, any protein molecule could be allergenic and a large number of foods have been noted to cause IgE-mediated food allergy, a small number of foods cause most of the clinical reactions (Boyce et al., 2010). Foods that are categorized as allergenic differ by country because the prevalence of food allergy caused by various foods differs by region of the world and according to the eating habits within a population. In the United States, the foods listed below are currently considered allergenic for regulatory purposes. However, the committee did not restrict its findings, conclusions, and recommendations to this list, and has included foods that are viewed as allergenic by other countries (e.g., sesame and some fruits and vegetables). The lists have regulatory implications for managing allergens (e.g., food product labeling) that affect many stakeholders. Importantly, the foods that are or are not on these "official" lists of allergens affect consumers who need to avoid specific allergens, both in their country and when they travel internationally. Chapter 7 includes a description of the criteria that different countries follow in order to categorize a food as allergenic and a list of foods that are commonly considered allergenic in various countries. Chapter 7 also includes the committee's recommendations to update the list of allergens in the United States.

In each of these allergenic foods, specific glycoproteins trigger the reaction and production of IgE antibodies that are reactive with those glycoproteins (during the period when the patient is becoming sensitized to those allergens). Clinical reactions are then triggered upon re-exposure to such foods after sensitization has occurred. Identifying and tracking these allergenic proteins and how they are affected by factors such as variation in food preparation is crucial to understanding mechanisms of food allergy reactions and potential avenues of prevention or treatment. For example, it will be important to understand how and why certain processes of food preparation can neutralize or diminish the ability of allergens either to induce sensitization or elicit clinical reactions (see also Chapter 7). Each type of allergenic food can contain a major or several allergenic proteins, as illustrated by the following list:

- **Peanuts:** Ara h 1, Ara h 2, Ara h 3, Ara h 8, Ara h 9
- **Milk:** aS_1-casein, aS_2-casein, β-casein, κ-casein, β-lactoglobulin, α-lactalbumin
- **Eggs:** ovomucoid, ovalbumin, ovotransferrin, lysozyme
- **Fish:** parvalbumin
- **Shellfish:** tropomyosin
- **Wheat:** Tri a 12, Tri a 14, Tri a 19, Tri a 21, Tri a 26
- **Soy:** Gly m 1, Gly m 4, Gly m 5, Gly m 6, Gly m 8

Food Allergy Misconceptions

Perceptions of food allergy conditions, patterns, and treatments can have a profound impact on both patient safety and cultural/societal accommodations for those with food allergy. Misconceptions persist among doctors, patients with allergies, and the general public—some of which could be potentially dangerous. Misconceptions are particularly significant among parents or guardians, as food allergy often manifests first in children.

Misconceptions fall into two major types: those related to basic concepts or management of a food allergy. This section addresses the former. The timing of the clinical symptoms after food ingestion, how long symptoms of food allergy actually last after ingestion, and the foods more or less likely to cause severe symptoms are often misunderstood. Bock (1987) reported that 28 percent of parents thought that their children had adverse reactions to foods but only 8 percent of the children actually did when challenged with the food. The Chicago Food Allergy Research Survey for Parents of Children with Food Allergy, a study conducted in 2008, solicited answers from 2,945 parents from across the United States (Gupta et al., 2010a); significant misconceptions or absences in knowledge were revealed. Some 52 percent of parents answered that anaphylaxis was more likely to be fatal in children than in adolescents, while the opposite is true. Almost half of participants believed that there is a cure for food allergy and more than two-thirds believed that a medicine could be taken as prevention. Furthermore, 40 percent of respondents reported "experiencing hostility from other parents when trying to accommodate their child's food allergy." That perceived hostility might point to a lack of awareness among the general public, which can fail to recognize legitimate food allergy dangers. However, another study (Gupta et al., 2009) concluded that most members of the public recognize the real risk of food allergy–related deaths and can even identify key symptoms. Other misconceptions among surveyed parents include a belief that food additive allergies are common (actually rare, despite the prevalence of additives in processed foods) and a lack of awareness about the rates at which children outgrow certain food allergy sensitivities (Gupta et al., 2010a).

These inaccurate beliefs were less common among parents who visited allergists rather than primary care physicians, which points to the potential lack of knowledge outside of specialists. Medical practitioners, and especially allergists, have an ongoing responsibility to educate the public, patients, and their fellow physicians (see Chapter 6). However, numerous studies suggest deficits in understanding these basic concepts among many different stakeholders, including physicians (Desjardins et al., 2013; Morawetz et al., 2014). Various surveys indicate misunderstandings among medical professionals in recognizing risk factors for food allergy reactions,

including anaphylaxis (Clark et al., 2004; Gupta et al., 2010b; Turner et al., 2016; Wang et al., 2014).

Knowledge deficits regarding food allergy also have been noted among school nurses (Carlisle et al., 2010), child care providers (Greiwe et al., 2015), emergency response providers (Jacobsen et al., 2012), restaurant personnel (Ahuja and Sicherer, 2007; Bailey et al., 2011), and teachers (Ercan et al., 2012; Polloni et al., 2013). Overall, stakeholders and the general public are currently insufficiently educated (see also Chapters 4, 5, and 6).

MECHANISMS

Mechanisms of Disease

This report is not meant to delve deeply into the basic mechanisms underlying food allergy, but mainly to address more practical aspects, such as diagnosis and management. Still, unraveling the pathological processes of food allergy is critical for understanding how to diagnose and clinically evaluate food allergy and for developing short- and long-term mitigation strategies. The intricate biological systems involved and the wide range of clinical manifestations of food allergy make this a long-term process characterized by incremental, albeit ultimately important, progress. For purposes of this report, this section briefly explores two principal aspects of clinical food allergy: the mechanism of the reaction and the mechanism of immunological tolerance. Figure 2-2 represents the mechanistic interactions and complexities of food allergy, which are not fully described in this section. For a more detailed description of the processes readers are referred to other publications (e.g., Berin, 2015; Chinthrajah et al., 2016).

Specific food allergies likely are a result of complex interactions among genes and the environment (including not only factors in the "external environment," such as pollen, pollution, and pathogenic microbes, but also effects of the microbes that normally reside in us—the "internal environment" of the microbiome) (see Chapter 5 for a detailed description of current knowledge on food allergy determinant factors).

With IgE-mediated food allergy—the classification under review here—allergic sensitization must precede manifestation of the full reaction. Sensitization is defined as the process by which an individual produces detectable IgE to a particular allergen (allergen-specific IgE [sIgE]). This can be called, operationally, the "offending allergen." (See also Figure 2-2 for an explanation of this process and Box 2-2 for definitions of key cellular components in food allergy reactions.) However, it is important to recognize that sensitization alone does not constitute clinical food allergy. In fact, sensitization can persist without the patient manifesting any clinical signs of food allergy.

This finding is an important part of understanding the diagnostic workup in food allergy. Having sIgE against a food allergen means the person has been sensitized to that allergen and therefore might exhibit a clinical food allergy reaction to that allergen, but a more specific test (the double-blind, placebo-controlled oral food challenge) would be required to diagnosis an allergy to that food in such a sensitized person.

Some allergens produce organ-specific reactions, but the mechanisms that could explain such clinical variation are not well understood. For example, peanut and egg are the most common triggers of GI symptoms, and peanut causes more respiratory reactions than other allergens (Berin, 2015).

It has been increasingly recognized that skin exposure can be a powerful driving factor in food sensitization. One leading hypothesis about how sensitization occurs is that humans naturally become tolerant to food encountered orally in the diet, but sensitization is favored, at least in "susceptible" individuals, through skin exposure (see Chapter 5). The interplay between reactions occurring in the skin and within the GI tract is thought to be an important element of sensitization. For example, loss-of-function variants in the gene encoding filaggrin, a key protein in the regulation of epidermal barrier function and health, have an established link to eczema, but research also links variants in filaggrin to food allergy (Lack, 2012). Lack of normal skin barrier integrity facilitates the development of food allergy. Peanut sensitization in particular is linked with skin exposure, but studies also show that childhood use of lotions containing oat led to much higher rates of oat allergies (Boussault et al., 2007). The molecular underpinnings of this hypothesis, however, are not fully understood.

Mechanisms of Tolerance and Desensitization

Two major terms that are used for defining a situation that is commonly known as "growing out" of a food allergy are desensitization and tolerance (see Figure 2-1). In some instances, natural tolerance (as opposed to the tolerance induced by specific therapeutic interventions) to some foods that once induced food allergy in that individual will develop over time. Accounts of spontaneous resolution of IgE-mediated food allergy vary according to food, age, and geography, but estimates indicate that 65 to 80 percent of individuals will develop such natural tolerance for cow milk, wheat, soy, and egg, and only 10 to 20 percent for peanut and tree nuts (Campbell et al., 2015).

For those who have not acquired tolerance naturally, a cure for food allergy does not exist yet. Strategies of management and treatment include avoidance of allergens, immediate treatment of symptoms, and the induction of tolerance. Multiple mechanisms play a role in regulating food allergy, many of which are extrathymic, resulting in a range of clinical

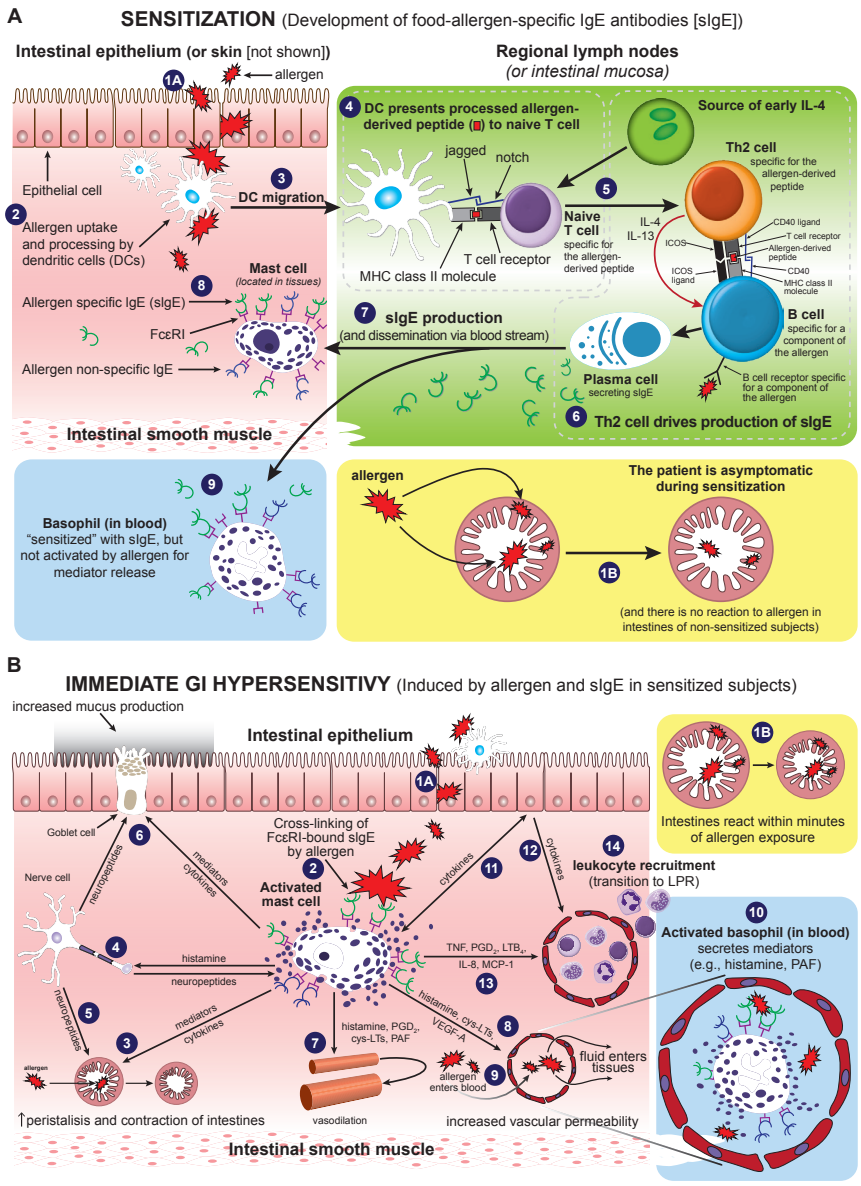

FIGURE 2-2 Mechanisms by which a person first becomes sensitized to a food allergen and subsequently can develop an acute allergic reaction when exposed again to that food allergen.

A. Sensitization is the process by which food allergens induce the development of food-specific serum IgE (sIgE). **1A.** Allergens present in foods cross the small intestinal epithelium (if present in the individual's environment; for example, peanut proteins also may enter the body through the epidermis of the skin [not shown]). These processes can be enhanced at sites that have genetically-determined or acquired defects in normal barrier function, such as at sites in the skin affected by atopic dermatitis (also known as eczema). **1B.** This initial exposure to allergen does not elicit an acute reaction, such as in the intestines, because there is no allergen-specific IgE present at this time. However, (**2**) the allergen is taken up and processed by a dendritic cell (DC) located in the intestinal mucosa (or skin [not shown]) which then (**3**) migrates to a regional lymph node (or to another location in the intestinal mucosa or skin). **4.** The DC presents the processed allergen-derived peptide to a naïve T cell whose T cell receptor is specific for that allergen-derived peptide. The DC does this by presenting the allergen-derived peptide (that is physically associated with a major histocompatibility complex (MHC) class II molecule on the DC membrane) to the T cell by way of the T cell's membrane-associated T cell receptor (TCR). The DC and naïve T cell also are bound to each other by co-stimulatory molecules (e.g., jagged on the DC membrane and notch on the T cell membrane) that enhance this cell-cell interaction. **5.** In the presence of IL-4 (that can be derived from any of a number of cell sources) such naïve T cells acquire features of a T helper cell type 2 (Th2 cell, a type of T cell that can help to drive the sIgE production seen in patients who become sensitized to allergens) and this T cell clone expands by proliferation. **6.** A Th2 cell bearing the TCR that recognizes the specific allergen-derived peptide interacts with a B cell whose B cell receptor has recognized some component of the same allergen (that may have entered the environment of the B cells located in lymphoid tissue by travelling through lymph draining the tissues of the intestines or skin) and has internalized and processed it into an allergen-derived peptide that it presents to the allergen-derived peptide-specific Th2 cell by way of the MHC class II molecule on the B cell surface. The Th2 cell and B cell also interact physically through co-stimulatory molecules (shown are Th2 cell ICOS and CD40 ligand interacting with B cell ICOS ligand and CD40, respectively). This Th2 cell-B cell interaction activates both cells (e.g., the Th2 cells increase production of IL-4 and IL-13, which, along with the CD40-CD40 ligand interaction, stimulates the B cells to switch to production of sIgE) and to differentiate into plasma cells that (**7**) can produce and secrete large amounts of the sIgE, which can diffuse locally in the tissues and enter the blood, resulting in the systemic distribution of sIgE to other sites in the body. **8 & 9.** The sIgE is bound with high affinity (i.e., strongly) to special receptors for IgE (FcεRI) that are present in large numbers on the surface of (**8**) mast cells, that are located in the tissues of the gastrointestinal tract and (not shown) the skin, upper and lower airways, and many other anatomic sites, and (**9**) basophils, leukocytes that are present in low numbers in the circulating blood. Because mast cells and basophils have thousands of FcεRI on their surface, they can bind many IgE antibodies, including those specific for this allergen (sIgE, shown in green in the figure) and those with specificities for other allergens or non-allergens (shown in blue in the figure). The presence of these sIgE molecules on the surface of mast cells and basophils gives little or no activation signal to the cells, but prepares them to undergo activation upon subsequent exposure to the allergen recognized by the sIgE.

continued

FIGURE 2-2 Continued

B. Immediate GI Hypersensitivity. This is the rapidly developing reaction observed when some sensitized subjects are exposed to allergen recognized by their sIgE. It is important to emphasize that, for reasons not understood, many sensitized subjects do not develop any clinical reactions upon exposure to the allergens recognized by their sIgE whereas other sensitized individuals can rapidly develop severe reactions upon exposure to the same allergen. **1A.** The sensitized individual consumes a food containing the allergen recognized by that person's sIgE, and the allergen passes through the intestinal epithelium, initiating a series of processes that can (**1B**) rapidly (within minutes for many common food allergens, but within hours for certain allergens present in red meats) induce a clinical response, including contraction of the smooth muscle of the intestines. **2.** The allergen, now in the intestinal tissues, is recognized by two or more sIgE molecules bound to FcεRI on the surface of a mast cell, causing aggregation of the sIgE and the FcεRIs to which they are bound, thereby activating the mast cell to release histamine and a wide variety of other chemicals ("mediators," such as prostaglandin D_2 [PGD_2], cysteinyl leukotrienes [cys-LTs], leukotriene B_4 [LTB_4], and platelet activating factor [PAF]) and cytokines (such as tumor necrosis factor [TNF], interleukin 8 [IL-8], monocyte chemoattractant protein-1 [MCP-1], and vascular endothelial growth factor [VEGF]) that can have diverse effects on the local cells and tissues, and, when released in large quantities, can enter the blood and cause signs and symptoms in other sites like the skin, upper and lower airways, and cardiovascular system. Effects of the released mast cell mediators and cytokines include (**3**) increased intestinal peristalsis and contractions, (**4**) stimulation of local nerves to release neuropeptides, which (**5**) can induce effects on intestinal smooth muscle and (**6**) together with products derived from activated mast cells, can increase mucus production by epithelial goblet cells, (**7**) vasodilatation of blood vessels, (**8**) increased permeability of certain blood vessels, resulting in the leakage of fluid into the tissues, which (**9**) favors the entry of allergens from the tissues into the blood stream. Once allergen has entered the blood, it can (**10**) bind to sIgE on the surface of blood basophils, causing aggregation of their FcεRIs, thereby activating the basophils to release biologically active mediators and cytokines that partially overlap with those secreted in the tissues by mast cells. Products of activated mast cells also can (**11**) induce local structural cells, such as intestinal epithelial cells, to (**12**) release products that can in turn influence mast cell functions, including enhancing their secretion of mediators (**11**). Along with (**13**) products secreted by activated mast cells, such products derived from epithelial cells can have effects on local blood vessels that favor the local development of inflammation, such as (**14**) the recruitment of circulating leukocytes. These recruited leukocytes can help perpetuate the local inflammation, resulting in "late phase reactions" (LPRs) that are associated with clinical signs and symptoms that may persist or recur even hours after the initial exposure to the offending allergen, and that may need continued treatment.

BOX 2-2
Definition of Key Cellular Components in Food Allergy Reactions

Basophils (basophilic granulocytes), the least abundant of the granulocytes (the others being neutrophils and eosinophils), can release histamine, lipid mediators, and cytokines in response to the aggregation of their cell surface FcεRI, which is induced when IgE bound to these FcεRI recognizes specific allergens, including those from foods. Unlike mast cells, basophils mature in the bone marrow and circulate in the blood, but can enter tissues at sites of allergic inflammation.

Cytokines are small proteins produced by various immune cells and other cell types that carry signals to facilitate communication and interaction between cells.

Epitopes are the specific fragments of food allergens (antigens) that the immune system recognizes; if recognized by IgE bound to FcεRI on the surface of mast cells and basophils, epitopes can trigger an allergic reaction that may include anaphylaxis.

FcεRI is the high-affinity receptor for IgE that binds IgE and thereby permits cells bearing FcεRI on their surface (e.g., mast cells, basophils, some dendritic cells, and macrophages) to become "sensitized" so that they then can be activated to release inflammatory mediators by allergens recognized by the bound IgE. For the FcεRI to initiate the cell signaling that results in activation of mast cells and basophils to release their mediators requires that the receptors are aggregated when their bound IgE reacts with allergens that are at least bivalent (e.g., have two epitopes that can bind IgE). This permits such allergens to bridge adjacent IgE molecules and to aggregate the FcεRI receptors that bind such IgE.

Mast cells are derived from hematopoietic precursors that mature after migrating into essentially all vascularized tissues, where they can reside for long periods of time. Mast cells are present within the mucosal tissues of the entire GI tract (and many other anatomical sites, including the skin and airways) and contain cytoplasmic granules rich in histamine, proteoglycans (depending on the mast cell population, these consist of heparin and/or chondroitin sulfates), serine proteases (depending on the mast cell population, these can consist of carboxypeptidase A3, tryptases, and/or chymase). Upon activation by IgE and specific antigens (including food allergens), mast cells can release such granule-associated inflammatory mediators and also secrete newly synthesized lipid mediators and cytokines. Mast cells also can be activated by diverse agents that act independently of IgE, which can result in the release of the same products produced by mast cells activated through IgE.

T cells are lymphocytes produced by the thymus that guide many aspects of the immune system, particularly its adaptability and ability to recognize threats.

recommendations and conflicting data (Campbell et al., 2015). Hallmarks of tolerance include a reduction in sIgE production, decreased allergen-IgE-induced basophil activation, increased allergen-specific IgG4, and induction of T regulatory (Treg) cells (Berin, 2015; Campbell et al., 2015; Chinthrajah et al., 2016).

Recent studies have begun to investigate specific treatments to induce food allergy desensitization or tolerance. It is important to understand that the term desensitization is used here to mean that, while continuing on a specific course of treatment with the offending allergen, the individual will tolerate more of the food on food challenge, even in some cases to the point of not reacting to "serving sized" amounts of the food. Desensitization, however, does not guarantee true tolerance (defined here as a long-term loss of clinical reactivity to the allergen under conditions of no further exposure to the offending allergen). A more recent term, "sustained unresponsiveness" was coined to describe what happens when the treatment for food allergy is stopped. In some such individuals, unresponsiveness to the offending allergen lasts weeks to months, while in others, desensitization is lost more quickly. The mechanisms that may explain desensitization versus sustained unresponsiveness versus true tolerance are being intensely investigated, as are approaches of immune system monitoring that might help classify individuals into one of these three groups with respect to the outcome of treatment. Some of the mechanisms by which treatments for food allergy may be associated with changes in the clinical symptoms include the occurrence during the treatment of natural tolerance noted above (this is one reason why clinical studies of new treatments would include a placebo group), reduction in production of allergen-specific IgE, decreased antigen- and food-specific IgE-dependent basophil activation, increased allergen-specific IgG4 (one effect of which may be to bind allergen before it can be encountered by sIgE and the surface of basophils and mast cells), and the induction of Treg cells or anergic T cells (Campbell et al., 2015). However, these possibilities, and others, are still under investigation). The major unknown about the mechanism of oral treatment–induced desensitization or tolerance is whether ongoing exposure to the protein in the food is necessary to sustain long-term beneficial effects of the treatment.

OVERALL CONCLUSIONS

Food allergy is defined as an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food. Various types of food allergies, such as immediate gastrointestinal hypersensitivity or eosinophilic gastroenteritis, occur and they can be classified as IgE-mediated and non-IgE-mediated food allergies. Many of them present common respiratory, gastrointestinal, and cutaneous signs and symptoms.

The definition and diagnosis of an allergy is rendered even more complicated because other gastrointestinal conditions, such as a food intolerance, can easily be misinterpreted as a food allergy. Given this diversity in signs and symptoms and underlying mechanisms, many misconceptions exist among the general public about what a food allergy is and how to identify one. More importantly, these misconceptions also are common among physicians, emergency care personnel, nurses, and others who are recognized as public health professionals. These misconceptions have tremendous implications for the public at large and specifically for allergic individuals and their families. For example, a diagnostic error can affect health outcomes, including psychological distress, or can lead to unnecessary management strategies.

Many fundamental mechanisms are now understood regarding how IgE-mediated food allergies develop and what is responsible for the signs and symptoms induced during allergic reactions to food. For example, it is well known that upon re-exposure following sensitization to an antigen, the antigen-induced aggregation of antigen-specific IgE binds to receptors on specialized cells (including mast cells in tissues and basophils in the blood). Such aggregation activates those specialized cells, releasing a variety of potent biological mediators that in turn result in the typical food allergy signs and symptoms. However, many questions are still being explored. A better understanding of the mechanistic processes underlying food allergy, and of the mechanisms that contribute to the various potential host responses to different forms of therapy for food allergy, will be invaluable in advancing the development of better prevention strategies, diagnostic methods, and treatments of food allergy.

RESEARCH NEEDS

Conducting research related to the mechanistic processes underlying food allergy is essential in making significant advances to develop better methods to prevent disease or reduce its severity; predict, diagnose, and monitor disease; and optimally manage and treat, and ultimately to cure, food allergy. These mechanistic processes include disease predispositions, origins and onset, normal and disordered oral tolerance to foods, factors that contribute to disease severity, and variation in individual responses to different forms of therapy.

One of the most prominent hypotheses for how food allergy develops—the dual-allergen hypothesis—proposes that environmental exposure to food allergens through the skin early in life can lead to allergy, while consumption of these foods during a developmentally appropriate period early in life results in tolerance. Under this hypothesis, children who avoid allergens in their diet but are still exposed to them in the environment might

be more likely to develop an allergy than those not exposed. Supporting this hypothesis are data suggesting that early dietary introduction of peanut products may confer protection against peanut allergy as well as data suggesting that loss of function of filaggrin, a protein important for epithelial structure, confers a risk for food sensitization. However, many questions remain about the mechanisms by which sensitization and tolerance occur and about which elements of the immune system represent the most important contributors to the severity of food allergy or the establishment of tolerance. For example, studies have shown that biochemical indicators of tolerance include a reduction in allergen-specific IgE production, decreased allergen-IgE-induced basophil activation, increased allergen-specific IgG4, and induction of Treg cells or anergic T cells. However, some of the data are conflicting and more studies are needed to better understand the role of these factors in food allergy

Another prevalent hypothesis is the microbial hypothesis, which states that the decrease in early childhood exposure to microbes may alter the development of early immunoregulatory responses, leading to the development of allergic disorders. For example, exposure to microbes during the perinatal period, may influence interactions between the developing microbiota and the immune system at the cellular and molecular levels and in turn affect health outcomes. Although the potential relationships between exposure to microbes early in life and the onset of food allergies have been explored, specific changes in the microbial profile of individuals, their particular interactions with the immune system, and how these interactions might be associated with food allergy have not been studied in depth.

To fill gaps in knowledge in this area, studies should be conducted to accomplish the following objectives:

- Elucidate the molecular and cellular mechanisms that account for the differences between innate tolerance versus food sensitization and between food sensitization versus food allergy.
- Identify the mechanisms, in patients with food allergies, for acquiring tolerance to the offending food allergen, without therapeutic intervention, as well as for responding to therapeutic interventions by developing transient desensitization versus sustained unresponsiveness versus true tolerance to the offending food allergens.
- Define how particular products and functions of mast cells, basophils, and other effector cells can contribute to the signs and symptoms of food allergic reactions, including anaphylaxis, and identify factors that may contribute to individual variation in the pathophysiological responses to such products.

- Study the role of immunoglobulins other than IgE, such as IgG4 or IgA, and of effector cells in addition to mast cells and basophils, in modulating (i.e., enhancing or reducing) food allergic responses.
- Identify and describe the roles of the skin and intestinal barriers in protecting individuals from developing food sensitization or a food allergy, and identify ways in which protective aspects of barrier function can be enhanced and factors that diminish barrier function be reduced.
- Examine the interactions between the microbiota and the host immune system that may favor or protect against the development of a food allergy, and define the extent to which the microbiota or its products can be manipulated to enhance resistance to the development of food allergy.

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3

Prevalence

Overall, food allergy has been estimated to cost $24.8 billion annually in the United States, including direct medical costs and costs borne by the family (Gupta et al., 2013a). To determine more accurate estimates of cost and to prioritize efforts, accurate prevalence[1] data are needed. Prevalence data also are important in helping to identify relationships between risk determinants and food allergies in specific populations. Various surveys of pediatricians and family practitioners, school teachers, school nurses, and the general public generally agree that the prevalence of food allergy in children has been increasing over the past two decades. A Data Brief published by the Centers for Disease Control and Prevention (CDC) in 2013 (Jackson et al., 2013) based on the National Health Interview Survey supports this notion (see Figure 3-1), but the true prevalence of food allergy in the past, or even the present, is uncertain and difficult to ascertain.

The term "food allergy" is often misunderstood and misused by the public and also by health care providers and researchers (see "Food Allergy Misconceptions" in Chapter 2), leading to inflated figures of prevalence reported from population-based surveys, ranging from 10 percent to 30 percent depending on the rigor of the questionnaires used. Even the definition of "food allergy" is not uniform (see "Commonly Accepted Definitions" in Chapter 2).

Unfortunately, no simple laboratory tests can be used to diagnose food allergy, especially non-immunoglobulin E (IgE)-mediated allergic reac-

[1] Prevalence is the proportion of a population who have a specific characteristic (e.g., illness) in a given time period.

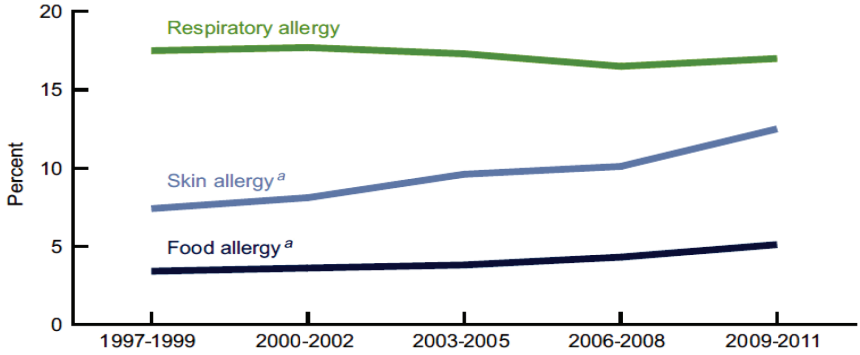

FIGURE 3-1 Increased prevalence of food and skin allergies in children ages 0 to 17 years, 1997-2011.
NOTES: Food allergy prevalence: Estimated based on an affirmative response to the National Health Interview Survey (NHIS) question: "During the past 12 months, has your child had any kind of food or digestive allergy?"
Respiratory allergy prevalence: Estimated based on affirmative responses to either of the two NHIS question(s): "During the past 12 months, has your child had hay fever?" and "During the past 12 months, has your child had any kind of respiratory allergy?"
Skin allergy prevalence: Estimated based on an affirmative response to the NHIS question: "During the past 12 months, has your child had eczema or any kind of skin allergy?"
[a] Significant increasing linear trend for food and skin allergy from 1997-1999 to 2009-1011.
SOURCES: CDC/NCHS, National Health Interview Survey, NCHS Data Brief, May 2013 (Jackson et al., 2013).

tions. Instead, physicians must rely on a combination of medical history, food-specific skin prick test (SPT) and/or food-specific serum IgE (sIgE) results, and/or oral food challenges[2] (OFCs) (preferably blinded) in order to accurately diagnose a food allergy (see Chapter 4). In a research setting, the gold standard to measure food allergy as an outcome is double-blind, placebo-controlled OFC (DBPCOFC). However, using such an approach in

[2] There are three types of oral food challenges (OFCs) depending on the protocol. An open OFC is one where the food is in its natural form; a single-blind OFC is one where the food is masked from the patient's perspective so less patient bias occurs because of anxiety; a double-blind, placebo-controlled OFC involves masking the tested allergen and feeding it or indistinguishable placebo randomly without the patient or observer knowing if the allergen or placebo is being tested.

large population-based studies to ascertain prevalence is impractical, very labor-intense, and extremely expensive, and is therefore almost never done. The first real attempt to assess food allergy prevalence in the United States was conducted in 1987 (Bock, 1987). Although the study might be limited by selection bias and the small number of subjects, the use of OFC make this a landmark study.

This chapter addresses the difficulties inherent in attempting to ascertain the true prevalence of food allergy and the strength of the evidence based on the design of various trials. It summarizes current knowledge about IgE-mediated food allergy prevalence data in the United States and abroad. Given the complexity of diagnosing food allergy in population-based studies, both the prevalence of food sensitization (i.e., by SPT or serum IgE concentrations) and food allergy (i.e., the presence of clinical allergy as documented by an unequivocal clinical history and supportive laboratory studies or OFC) are presented. The prevalence of food allergies resulting from sensitization to the food and systemic reactions involving the skin, respiratory tract, gastrointestinal tract, and/or cardiovascular system will be considered. Prevalence data based on systematic reviews and meta-analyses from the United States and Europe are presented first, followed by data from individual studies in all countries, where available. It should be noted that the vast majority of data on the prevalence of food allergy has been ascertained in the pediatric population, often children in the first decade of life. Recommendations for data collection and analysis to improve the prevalence estimates for food allergy are included at the end of the chapter, along with research needs.

APPROACH TO LITERATURE REVIEW

The primary resources for this chapter on prevalence were derived from the 2010 National Institute of Allergy and Infectious Diseases/National Institutes of Health (NIAID/NIH)-supported *Guidelines for the Diagnosis and Management of Food Allergy in the United States* and its associated systematic reviews[3] (based on 51 publications) (Boyce et al., 2010; Chafen et al., 2010; Rona et al., 2007), and the 2014 European Academy of Allergy & Clinical Immunology's (EAACI's) *Food Allergy and Anaphylaxis Guidelines: Diagnosis and Management of Food Allergy* and its associated

[3] According to the Cochrane Collaboration, "a systematic review is a review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyze data from the studies that are included in the review" (Moher et al., 2009). Statistical methods are often used to analyze and summarize the results of the studies included in the review.

systematic review and meta-analysis[4] (based on 65 publications based on 50 primary studies) (Nwaru et al., 2014). In addition, searches of EMBASE and Medline were selectively performed to identify studies and reports in the literature since 2012 (see Appendix B for literature search strategy). Meta-analyses, systematic reviews, and population-based or cohort prevalence studies were included. The summary of the findings of the individual studies and systematic reviews and meta-analysis used are presented in Appendix B.

DIFFICULTIES IN ASCERTAINING FOOD ALLERGY PREVALENCE

A variety of methodologies have been employed in an attempt to determine the prevalence of food allergy in various populations. Implementing designs and interpreting results from studies on food allergy prevalence have a number of challenges; some are commonly encountered within other research fields and others are unique to the field of food allergy. For example, the type of food allergy being assessed and the methodology used to assess it can have major impacts on the outcome. In this Chapter, prevalence figures will reflect IgE-mediated food allergies (except where otherwise noted), not non-IgE-mediated disorders. Pollen-associated food allergy is considered a form of IgE-mediated food allergy that typically results in oral and pharyngeal pruritus and mild edema. Pollen-associated food allergy occurs in some patients with allergic rhinitis when ingesting certain raw fruits, vegetables, tree nuts or peanuts. Pollen-associated food allergy[5] is the result of sensitization to airborne pollen allergens that cross-react with homologous proteins in plant-derived foods. Ingesting the plant-derived foods elicits symptoms (Kazemi-Shirazi et al., 2000). With 47 to 70 percent of patients with allergic rhinitis reporting such symptoms (Katelaris, 2010), this form of food allergy could account for a food allergy prevalence of 5 to 19 percent in some regions (Sicherer, 2011). Also, the form of a food used in an OFC can affect the prevalence of food allergy (Osborne et al., 2011). Table 3-1 lists the challenges and below is a description of a selected number.

[4] Meta-analysis refers to the use of statistical techniques in a systematic review that are used to integrate the results of included studies.

[5] The homologous food allergens are generally heat-labile and susceptible to gastric digestion, thus limiting symptoms primarily to the oropharynx (Wang, 2013). Examples of allergenic pollens (and cross-reacting foods) that might result in pollen-associated food allergy include birch tree (apple, carrot, hazelnut, etc.), ragweed (melons and bananas), and grass pollens (tomatoes and strawberries).

TABLE 3-1 Factors Affecting the Accuracy of Prevalence Surveys

Methodologies	History only versus history + laboratory data (SPT and/or serum IgE) versus history + laboratory data + physician diagnosis versus history + oral food challenge versus history + double-blind placebo-controlled oral food challenges.
Food challenge material	Cooked/baked versus raw food.
Selection bias	Selected cohort (e.g., allergy clinic based versus birth cohort) or unselected cohort.
Nonparticipation bias	Those affected are more likely to participate.
Timing of survey	Children "outgrow" many food allergies; adults may acquire food allergies late; varies with specific food being investigated (e.g., milk versus shrimp).
Definition	Pollen-associated food allergy, fairly frequent compared to classic generalized immediate food allergies.
Geographical region	Westernized countries tend to have greater prevalence of food allergies than less well developed countries.
Statistical analyses	Methods employed to handle missing data and nonparticipation.

Selection Bias and Methodologies

Food allergy prevalence studies are conducted either on general populations or on specific cohorts (e.g., hospital cohort of individuals with signs of food allergy). Both approaches have advantages and disadvantages. Earlier prevalence studies often incorporated selected cohorts from hospital-based or allergy practices and extrapolated the results to the general population, which typically led to inflated prevalence figures. Population-based surveys are often employed given the ease of administration and an ability to incorporate large numbers of subjects at relatively low cost. Although tens of thousands of individuals can be included in such surveys, these studies rely on self-reporting of specific food allergies, or "perceived prevalence," which uniformly results in higher prevalence rates than do studies incorporating more rigorous diagnostic methods. For example, the NIAID/NIH-supported Guidelines noted a self-report rate of food allergy in adults of 13 percent compared to a rate of 3 percent when food allergy was confirmed by DBPCOFCs (Boyce et al., 2010). More recent surveys have attempted

to use progressively more extensive questionnaires, inclusion of IgE testing (food-specific SPT and/or serum IgE levels), and rigorous statistical methods in an attempt to derive a more accurate picture of true prevalence.

In this chapter, studies reporting prevalence figures from questionnaires only have generally been excluded unless the investigators appropriately corrected for inherent biases or the study provided insights related to geographic or ethnic variation. Also, only population-based studies have been included as evidence.

Nonparticipation Bias

Even with increased rigor, such surveys are likely flawed by unintentional selection bias. For example, families and individuals affected by food allergy are more likely than unaffected families to participate in and complete a study involving extensive questionnaires and testing, leading to falsely elevated prevalence rates of food allergy. To minimize such bias, some investigators are now attempting to adjust for "nonresponse" bias. In the Surveying Prevalence of Food Allergy in All Canadian Environments study, Soller et al. telephoned 17,337 households, of which 14,113 were reached (Soller et al., 2015). Of this total, 5,734 households (representing 15,022 individuals) completed the full survey instrument, a 45 percent participation rate, which is a rate similar to that seen in other recent studies. An additional 524 households (4 percent) refused to answer the full questionnaire but agreed to answer an abbreviated form, and 6,504 households (51 percent) answered the phone but refused to provide any information. The self-reported prevalence of food allergy among the full participants was 6.4 percent (95% confidence interval [CI]: 6.0%-6.8%), which was significantly greater than the 2.1 percent (95% CI: 1.4%-2.9%) prevalence reported by those answering the abbreviated questionnaire. This study clearly shows that when assessing the outcome of prevalence surveys, it is essential to determine the percentage of individuals randomly selected who participated in the study, the percentage who dropped out before completion, and whether the rate of food allergy in those dropping out differed from those completing the trial.

Timing of Survey

It also is essential to note the timing of the evaluation and the type of food involved, as a survey of young children will yield a much higher prevalence of allergy to foods such as cow milk, egg, soy, or wheat than a survey conducted in the same children at age 10 years because the majority of young children will outgrow these food allergies.

FOOD ALLERGY PREVALENCE IN THE UNITED STATES AND EUROPE

Systematic Reviews and Meta-Analyses

Systematic reviews and meta-analyses have become increasingly important for addressing a variety of questions in health care and disease prevalence. International guidelines have evolved over the past decade to improve the quality of systematic reviews, such as the *Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)* (Moher et al., 2009). More recently the *PRISMA-P* (Protocols) contains a checklist of 17 items considered to be essential and lists minimal components of a systematic review or meta-analysis protocol (Shamseer et al., 2015). Relatively few systematic reviews in the literature have incorporated all aspects of the *PRISMA-P* checklist. In this report, systematic reviews have been assessed based on the PRISMA checklist.

Based on a meta-analysis by Rona (Rona et al., 2007) and systematic reviews by the RAND Corporation (Chafen et al., 2010) and Zuidmeer (Zuidmeer et al., 2008), the NIAID/NIH-sponsored Guidelines (Boyce et al., 2010) reported that the prevalence of food allergy in the United States and several European countries was 12 to 13 percent by self-report, but only 3 percent when confirmed by laboratory studies and DBPCOFCs. As depicted in Table 3-2, several foods were analyzed individually, with marked differences dependent upon the stringency of the diagnostic criteria used. In general, the food challenge-proven prevalence of food allergy appears to be about one-quarter to one-third the rate of self-reported food allergy by questionnaire.

In 2012, the European Food Safety Authority published a review of the prevalence data in Europe (EFSA, 2013). In many studies prevalence was self-reported and, when OFC were conducted, protocols varied substantially. This work was not peer-reviewed so its findings are not included in this report. One of the EAACI systematic reviews and meta-analyses reviewed studies published from January 2000 through September 2012 on food allergy prevalence in Europe of eight foods or food groups (cow milk, egg, peanut, tree nuts, wheat, soy, fish, and shellfish) (Nwaru et al., 2014). Their analysis included only systematic reviews, meta-analyses, cohort, case-control, cross-sectional, and routine health care studies. The authors also analyzed the risk of bias in the studies using a modified relevant version of the Critical Appraisal Skills Programme quality assessment tool (http://www.casp-uk.net). Overall, 65 publications were reviewed representing 50 studies of which 27 were cross-sectional studies, 17 cohort studies, 3 systematic reviews, and 3 case-control studies. Only one study had an evidence grading of "strong" and the rest had a "moderate" grading. Although the

TABLE 3-2 Prevalence (Percent) of Food Allergy to Various Foods Ascertained by Self-Report or Oral Food Challenge

	Peanut (%)	Milk (%)	Egg (%)	Fish (%)	Crustacean shellfish (%)	Tree nuts (%)	Wheat (%)	Soy (%)
Diagnostic Criteria								
Self-report	0.6	3	1	0.6	1.2	0-4.1	0.2-1.3	0-0.6
Oral food challenge	Not estimated	0.9	0.3	0.3	Not estimated	0.1-4.3	0-0.5	0-0.7

SOURCE: Boyce et al., 2010.

TABLE 3-3 Prevalence (Percent) of Food Allergy to Various Foods Ascertained by Self-Report or Oral Food Challenge (Open Challenge or DBPCOFC)

	Peanut (%)	Milk (%)	Egg (%)	Fish (%)	Shellfish (%)	Tree nuts (%)	Wheat (%)	Soy (%)
Diagnostic Criteria								
Self-report	0.4	6	2.5	2.2	1.3	1.3	3.6	Not estimated
Oral food challenge	0.2	0.6	0.2	0.1	0.1	0.5	0.1	0.3

SOURCE: Nwaru et al., 2014.

42 studies included in the meta-analysis showed considerable heterogeneity, the authors ascertained overall lifetime prevalence estimates (see Table 3-3). The perceived prevalence rates of food allergies in the EAACI Guidelines were slightly higher than those noted in the NIAID/NIH-supported Guidelines, but the challenge-proven prevalence rates were generally lower. As noted in the NIAID/NIH-supported Guidelines, the prevalence of allergy to milk and egg were more common in young children, while the prevalence rates to peanut, tree nuts, fish and shellfish tended to be higher in adults. The authors caution about interpreting the results of this report because participation rates varied widely across the studies (17.3 to 99.5 percent) and in several studies no information was provided on participation rates.

More recently, two systematic reviews on the prevalence of specific foods have been published: soy (Katz et al., 2014) and tree nuts (McWilliam et al., 2015). Katz et al. (2014) included 40 studies published between 1909 and 2013 on soy allergy in their systematic review and meta-analysis out of 357 potential studies initially identified. In addition, they judged the quality of the publications using the GRADE scoring system (Atkins et al., 2004). The majority of the studies were cross-sectional or cohort studies with moderate to low quality methodological design and evident bias largely due to insufficient sample size, patients' countries of origin, and the length of time followed in longitudinal studies (follow-up data collection is important because the prevalence of food allergy changes with age). The authors calculated the prevalence of soy allergy in the general population based on self-reporting to be 0.2 percent (95% CI: 0.0%-0.3%). Based on OFC outcomes, the prevalence in the general population was 0.27 percent (95% CI: 0.1%-0.44%) and in patients referred to centers for evaluation of allergy, 1.9 percent (95% CI: 1.1%-2.7%). The prevalence of sensitization based on positive SPT results was 0.1 percent (95% CI: 0%-0.2%) in the general population and 12.7 percent (95% CI: 5.8%-16.7%) in referred patients. In 11 studies where participants had both OFCs and SPTs or sIgE performed, only 11.2 percent of sensitized patients reacted to soy following ingestion. Interestingly, of 1,430 infants younger than age 6 months identified in three studies, only 0.1 percent (2 infants) likely had soy allergy, suggesting that the prevalence of soy allergy is much lower than presently believed. However, it should be noted that 9 out of the 11 studies were conducted in Europe, 1 was conducted in Israel), and none was conducted in the United States, where the prevalence of soy allergy is believed to be higher.

McWilliam et al. performed a systematic review and meta-analysis on the prevalence of tree nut allergy, which was defined as allergy to almond, Brazil nut, cashew, hazelnut, macadamia nut, pecan, pistachio, or walnut (McWilliam et al., 2015). The authors identified 36 studies published between January 1996 and December 2014. The majority of studies were in children (24 of the 36 studies identified) and from European countries (18

from Europe, 8 from the United Kingdom, and 5 from the United States). Studies reporting tree nut allergy based on self-report, allergic sensitization (skin tests and/or serum IgE to individual tree nuts), food challenges (OFC or DBPCOFC) or convincing clinical histories were considered eligible for inclusion. In an attempt to reduce selection bias, only population-based cross-sectional and cohort studies were included. Studies on selected patient groups or those performed in a hospital or allergy clinic settings were excluded. In assessing the quality of the studies included in the analysis, 28 studies were graded as moderate and 8 were graded as poor due to participation rates, objectivity of outcomes, and study design. In seven studies using OFCs or recent convincing history, plus evidence of tree nut–specific IgE to define nut allergy, the overall prevalence of tree nut allergy ranged from 0 to 1.6 percent. In nine studies using less rigorous criteria, namely self-reported allergy with physician diagnosis or evidence of sensitization (positive skin tests or specific IgE to tree nuts), the overall probable prevalence of tree nut allergy was calculated to be 0.05 to 4.9 percent. The majority of studies were based on self-reporting of tree nut allergy and yielded an overall prevalence range of 0.18 to 8.9 percent in adults and 0.0 to 3.8 percent in children. The authors noted regional differences in the prevalence of tree nut allergies, with northern European countries reporting the highest rates, largely due to pollen-associated food allergy. [Pollen-associated food allergy in northern Europe is due primarily to cross-reactivity with a homologous pollen protein (*Bet v 1*) in patients with allergic rhinitis to birch pollen.] The most common tree nut allergy reported in the European studies was hazelnut allergy, accounting for 17 to 100 percent of all tree nut allergies, whereas walnut (20 to 30 percent of all tree nut allergy) and cashew (15 to 30 percent) were the most common tree nut allergies reported in the United States. Brazil nut (24 to 33 percent) was the most common nut allergy reported in the United Kingdom (McWilliam et al., 2015). Limited evidence was available to address the question of whether tree nut allergy has been increasing in prevalence, but as depicted in Figure 3-2, using the same random digit-dial survey, in the United States (an unselected cohort, not a national survey) the prevalence of tree nut allergy in children younger than age 18 years was estimated to have increased significantly from 0.2 percent in 1997 to 1.1 percent in 2008 (Sicherer et al., 2010). In the 1997 survey, 5,300 households (13,534 individuals) participated, of which 188 households (3.6%; 95% CI: 3.1%-4.1%) reported 1 or more individuals with peanut allergy, tree nut allergy, or both. Race/ethnicity was determined only from the responding household member. The authors concluded that heterogeneity in tree nut allergy prevalence in different parts of the world appears to be significant, but that the limited high-quality data make it difficult to ascertain the true prevalence of tree nut allergy, especially to individual tree nuts (McWilliam et al., 2015).

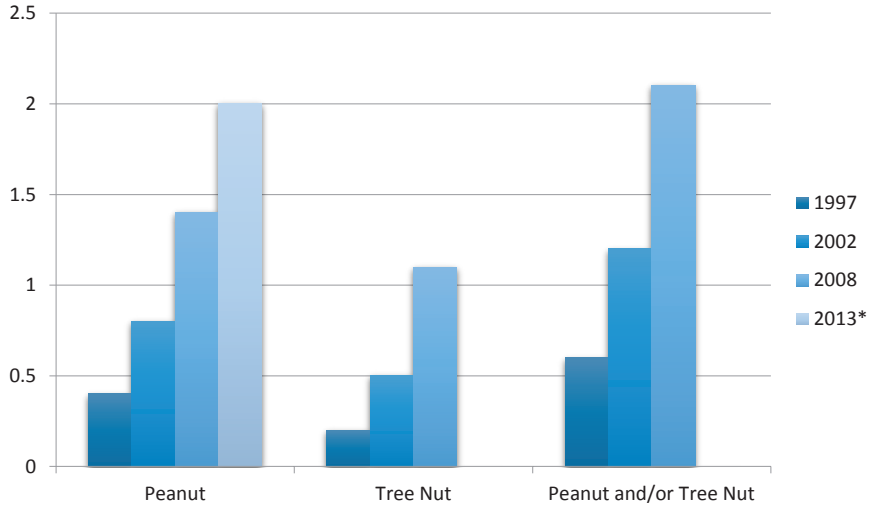

FIGURE 3-2 Change in the prevalence of peanut and tree nut allergy in children, United States. Data from an unselected cohort, not a national survey.
SOURCES: *Bunyavanich et al., 2014; Sicherer et al., 2010.

Given the known racial disparity in other atopic disorders such as asthma, two recent systematic reviews attempted to address the question of racial disparities of food allergy in the United States. In one report, the authors were able to analyze 20 out of 645 articles initially identified (Greenhawt et al., 2013). The analyzed studies used a variety of criteria to define food allergy, including self-reporting, evidence of IgE sensitization, discharge codes (i.e., ICD-9), chart reviews, and event-reporting databases. Although 12 studies suggested that African American children had significantly increased odds of food sensitization and allergy, major differences in methodology and reporting did not permit calculation of pooled estimates or confirmation of definitive racial or ethnic disparities in food allergy among African American and white children in the United States. In the second study, the authors evaluated 27 different surveys representing more than 450,000 children covering the period from 1988 to 2011 (Keet et al., 2014). As noted in the previous systematic review, no summary estimates of food allergy prevalence in the different racial or ethnic groups could be determined because of the heterogeneity of the surveys.

In summary, both systematic reviews and meta-analyses have examined questions related to the prevalence of food allergy in the United States and in other countries. However, limitations in the quality of the data make it difficult to come to firm conclusions about the prevalence of food allergy.

Recent Population-Based Studies in the United States

No large population-based or unselected cohort studies that include both laboratory and OFC confirmation of food allergy have been performed in the United States.

A CDC report suggested that 3.9 percent of American children younger than age 18 years had a food allergy (Branum and Lukacs, 2009). The authors' prevalence figure was based on an assessment of cross-sectional survey data from the 1997-2007 National Health Interview Survey, the 2005-2006 National Health and Nutrition Examination Survey (NHANES), 1993-2006 National Hospital Ambulatory Medical Care Survey (NHAMCS) and the 1998-2006 National Hospital Discharge Survey (NHDS). These surveys consisted of reports of food allergy and assessments of serum IgE antibody levels for specific foods, ambulatory care visits, and hospitalizations. A related CDC analysis (Branum and Lukacs, 2008) used NHDS data to show an increase in the rate of hospital discharges related to food allergy (see Figure 3-3).

In 2014, the prevalence of sensitization to food and environmental allergens was published based on the results from NHANES 2005-2006 data and compared to earlier sensitization rates determined in the previous NHANES III survey (Salo et al., 2014). NHANES 2005-2006 included

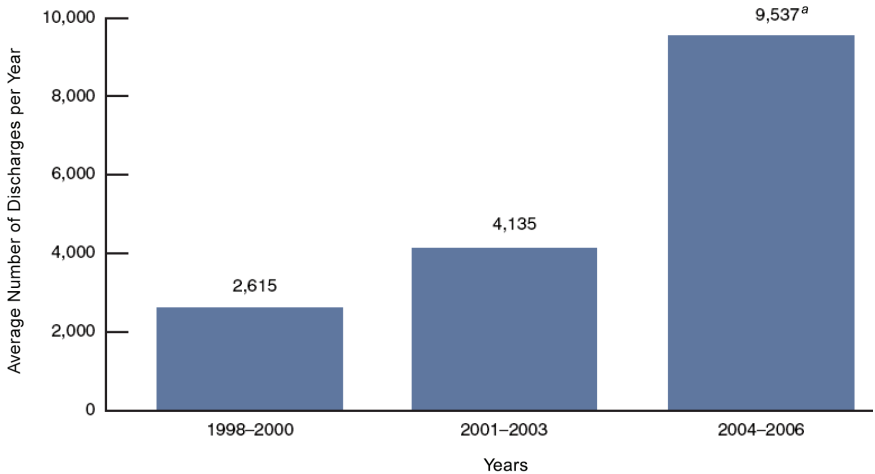

FIGURE 3-3 Change in the rate of food allergy–related hospital discharges in the United States among children younger than age 18.

[a] Statistically significant trend.

SOURCES: CDC/NCHS (Branum and Lukacs, 2008).

10,348 participants from throughout the United States and, and to ensure adequate samples for subgroup analyses, contained an oversampling of persons of low income, adolescents ages 12 to 19 years, adults ages 60 years and older, African Americans, and Mexican Americans (see http://www.cdc.gov/nchs/nhanes2005-2006/nhanes05_06.htm [accessed August 31, 2016] for a description of survey design and methods). Of the 1,355 children ages 1 to 5 years, 856 (63.2 percent) were determined to have had IgE antibody levels to three food allergens: egg, cow milk, and peanut, and of 8,086 participants, ages 6 years and older, 7,268 (89.9 percent) had IgE determined for egg, cow milk, peanut, and shrimp. Food-specific IgE (sIgE) levels ≥0.35 kU_A/L were considered positive for sensitization. Each group also was tested for IgE antibodies to 6 and 15 inhalant allergens, respectively. Overall, 36.2 percent of children ages 1 to 5 years and 44.6 percent of individuals ages 6 years and older were sensitized to at least one environmental and/or food allergen. Sensitization to milk and egg were significantly greater in the ages 1 to 5 years group (22 percent and 14 percent, respectively), compared to the age 6 years and older group (5 percent and 3.3 percent, respectively), with a marked decline in the prevalence of sensitization occurring over the first decade of life. The prevalence of peanut sensitization was similar in the two groups, about 7 percent and 8 percent, respectively. Among children ages 6 years and older, sensitization to food allergens was most prevalent in the South, and only peanut sensitization showed regional differences. In children ages 1 to 5 years, only sIgE levels to peanut were associated with urbanization. NHANES 2005-2006 data provide a good snapshot of IgE sensitization to the three most common food allergens in the United States—egg, cow milk, and peanut—but as described above, sensitization does not equate with clinical reactivity and so the actual number of Americans at risk of clinical reactions to these foods cannot be determined.

In the past 5 years, a few population-based, cross-sectional surveys have been conducted in an attempt to determine the prevalence and severity of food allergy in the United States. In one study, administered between June 2009 and February 2010, Gupta et al. collected data on 40,104 children from U.S. households (Gupta et al., 2011, 2013b); 6,100 were recruited from a web-enabled panel that was statistically representative of U.S. households with children and an additional 33,900 were obtained from an online sample of U.S. households with children that had access to the Internet. Food allergy was categorized as "convincing" or "confirmed." A convincing history was based on the report of one or more allergic symptoms after ingesting a food and a confirmed food allergy was considered a convincing history plus a physician diagnosis with evidence of IgE antibody testing to the food or a positive OFC. Reportedly, 70.4 percent of children considered with a food allergy in the analysis had a physician's diagnosis

and evidence of sIgE antibodies (47.3 percent were evaluated by SPT and 39.9 percent by serum sIgE levels) or a positive OFC (20.2 percent) (Gupta et al., 2013b). Overall, complete data were available on 38,480 children (96 percent), but due to the method of sampling, a rate of nonparticipation, which could affect selection bias, could not be provided. Based on this study, the overall prevalence of convincing and confirmed food allergy in children in the United States was estimated to be 8 percent (95% CI: 7.7%-8.3%), with more than one food allergy reported in 2.4 percent of all children (95% CI: 2.2%-2.6%), or about one-third of the children with a reported food allergy (Gupta et al., 2011). The prevalences of reported allergy to individual foods in the U.S. pediatric population are depicted in Table 3-4. Severe reactions (defined as reports of anaphylaxis, low blood pressure, trouble breathing or wheezing, or a combination of vomiting, angioedema, and coughing) were reported in 38.7 percent of the children with food allergy, with the odds of severe reactions progressively increasing with age and peaking in adolescent ages 14 to 17 years. The authors noted that the odds of having a food allergy were significantly higher among Asian and African American children compared to Caucasian children, which is in agreement with the NHANES 2005-2006 data described above. Although this study provides some insight into the perceived prevalence of food allergy in children, the survey was not validated and, moreover, results from a self-reporting survey must be interpreted with caution.

In subsequent publications using data from their 2009-2010 survey, Gupta et al. evaluated the geographical variability of food allergy in the United States (Gupta et al., 2012). The odds of having a food allergy was found to be significantly greater in southern and middle latitudes of the United States as compared to northern latitudes, suggesting a north-to-south increase in the prevalence of food allergy. Interestingly, this finding is in contrast to an analysis of food-related admissions to U.S. emergency departments based on the NHAMCS data for emergency department visits to noninstitutional hospitals from 1993 to 2005 (Rudders et al., 2010), which suggested that acute food-allergic reactions are higher in northeastern regions as compared to southern regions. Similarly, a survey of epinephrine auto-injector prescriptions, used as a partial surrogate for food allergy, indicated a strong north-south gradient, with the highest prescription rates found in New England (Camargo et al., 2007). Gupta et al. (2012) also reported that the prevalence of food allergy was higher in urban centers compared to rural areas, 9.8 percent versus 6.2 percent, respectively, with peanut allergy being the most prevalent in urban centers and milk the most prevalent in rural areas (Gupta et al., 2012). There appeared to be a direct correlation between the density of the population in an area and the prevalence of food allergy, but no difference in severe food allergy based on urban versus rural status or latitude.

TABLE 3-4 Prevalence of Food Allergy to Various Foods Ascertained by Convincing History Plus a Physician Diagnosis with Evidence of IgE Antibody Testing to the Food or a Positive Oral Food Challenge, Children in the United States

	Peanut (%)	Milk (%)	Egg (%)	Fish (%)	Shellfish (%)	Tree nuts (%)	Wheat (%)	Soy (%)
Prevalence	2	1.7	0.8	0.5	1.4	1.0	0.4	0.4

SOURCE: Gupta et al., 2011.

In an attempt to ascertain the prevalence of peanut allergy in American children, Bunyavanich et al. used data from the Viva Project's unselected observational birth cohort to determine the frequency of the allergy in children ages 7 to 10 years (Bunyavanich et al., 2014). The study of 2,128 children was designed to examine maternal dietary and other factors that could influence their child's health. Overall, 1,277 children underwent a mid-childhood visit following their baseline visit in early childhood. Of these children, 616 (29 percent of the original cohort) had serum peanut-specific IgE antibody levels measured. Children who returned for the mid-childhood visit tended to be from a higher socioeconomic status than children who failed to follow up, but parental atopy[6] was comparable in both groups. Various criteria for diagnosing peanut allergy to determine prevalence in this cohort were provided: self-reported peanut allergic reactions—4.6 percent; peanut allergy based on serum IgE sensitization (IgE ≥0.35 kU_A[7]/L; as used in NHANES 2005-2006)—5.0 percent; peanut-IgE + prescription for epinephrine auto-injector—4.9 percent; peanut-IgE ≥14 kU_A/L—2.9 percent; and peanut-IgE ≥14 kU_A/L + prescription for epinephrine auto-injector—2.0 percent. Although less than one-third of the children in the original cohort were evaluable and diagnoses were not established by OFC, OCF data suggested a higher prevalence of peanut allergy, i.e., 2.0 percent, than previously reported in the United States. The authors noted that this study was conducted in the northeast, which other studies suggest tends to have higher rates of peanut allergy than other regions in the United States (Salo et al., 2014).

In summary, since the systematic review and meta-analysis published by the RAND Group in 2010 suggesting that food allergy in the United States affects more than 2 percent and less than 10 percent of the population (Chafen et al., 2010), attempts to define the prevalence of food allergy in the U.S. population have been confined to self-reports with variable confirmatory evidence in two large cohort studies and information from the NHANES 2005-2006 survey, but no large prospective studies involving confirmatory food challenges have been conducted. Based on this more recent evidence, it is likely that 3.9 to 8 percent of the U.S. population ages 18 years and younger is affected by food allergy (Branum and Lukacs, 2009; Gupta et al., 2011), but regional and racial differences are likely. Well-designed population-based studies are needed.

[6] The genetic tendency to develop the classic allergic diseases—atopic dermatitis, allergic rhinitis (hay fever), and asthma.

[7] Kilo units of allergen-specific IgE.

Recent Population-Based Studies in Europe

In 2005, the European Union launched the EuroPrevall Surveys, a series of multinational epidemiological surveys aimed at determining the prevalence of food allergy in children and adults across Europe. These surveys were performed as multicenter, cross-sectional studies in general populations with case-control studies nested within the surveys. Studies were performed in children ages 7 to 10 years and adults between ages 20 to 54 years in the eight centers representing different social and climatic regions in Europe (Kummeling et al., 2009). Participants for these studies were selected in stages. The first stage involved community-based surveys using a short questionnaire to collect basic information on adverse reactions to foods. The sampling for these surveys was not random, but was based on established criteria. Surveys needed to be administered in areas with pre-existing boundaries that had total populations of at least 200,000 people and had current registries that could be used to sample children ages 7 to 10 years and adults ages 20 to 54 years. Each center targeted a population of about 3,000 respondents, and attempts were made to determine and code reasons for nonresponse. In the second stage, all those in the first stage who indicated some type of adverse reaction to priority foods and a random selection of those reporting no reaction completed a detailed questionnaire and provided a blood sample to determine IgE sensitization. In the third stage, all those who indicated a reaction to a food and demonstrated IgE antibodies to the food were invited for a full clinical evaluation, including a standardized DBPCOFC. The study excluded those with a history of anaphylaxis, which could lead to a small error. However, conducting oral challenges in such individuals raises ethical concerns. Aside from this limitation, EuroPrevall and its protocols were well designed. It should be noted, however, that adherence to and completion of the OFC protocols showed considerable variability.

To date, the EuroPrevall group has published self-reporting and IgE sensitization rates on 17,366 adults from the eight centers participating in the study (Burney et al., 2014). Overall, 21 percent of the adults reported reactions to particular foods, ranging from 37 percent in the Alpine area of Europe to less than 2 percent in Northern Europe. Physician-diagnosed food allergy was 4.4 percent overall and ranged from 7.5 percent in Alpine and Mediterranean regions to <1 percent in Northern Europe and the Balkans. The overall prevalence rate of IgE sensitization to all foods was 15.81 percent and ranged from 23.6 percent in the Alpine region to 6.6 percent in the Northern Maritime region. Birch pollen–related foods, i.e., hazelnut, peach, apple, carrot, celery, and peach accounted for highest overall rates of sensitization, from 9.3 percent to 6.3 percent, while egg, milk, and fish accounted for the lowest rates, 0.86 percent to 0.22 percent,

with significant regional variation. The prevalence of true food allergy in European adults remains to be established because DBPCOFCs have not been performed in adults. However, it was noted that in different regions of Europe, the prevalence of sensitization to foods is strongly associated with the prevalence of IgE sensitization to aeroallergens (e.g., birch pollen, mugwort) whereas sensitization to nonpollen-related foods (e.g., egg, milk, and fish) is quite rare.

In an expanded multicenter epidemiologic study involving 12 European centers, the EuroPrevall group identified 731 adults from a cross-sectional survey of 2,273 participants who reported reactions to hazelnut occurring 2 hours or less following ingestion (Datema et al., 2015). Twenty-two individuals had a clear-cut history of anaphylaxis and 124 agreed to undergo a DBPCOFC. In those challenged, 87 (70 percent) were found to be responders. Birch pollen–driven hazelnut sensitization (Cor a 1) dominated in most areas, except in Iceland and the Mediterranean areas. Sensitization to the hazelnut storage proteins Cor a 9 and 14 (i.e., those more often associated with generalized allergic reactions) was significantly more common in children compared to adults, 42.0 percent versus 5.8 percent, respectively, except in the Netherlands where 90 percent of adults were sensitized to Cor a 9 or 14. No potential explanation was given for such high rates.

In parallel with the EuroPrevall study, Dutch investigators sought to determine the difference in reporting and prevalence of food allergy among community participants in the EuroPrevall study and those referred to a tertiary allergy center with suspected food allergy (Le et al., 2015). The investigators confirmed the previously reported discrepancies between self-reported food allergy, food allergy defined by suggestive history plus supporting lab data (sIgE), and food allergy confirmed by DBPCOFC—10.8 percent versus 4.1 percent versus 3.2 percent, respectively. They also found large differences in self-reported food allergies between the community-based EuroPrevall cohort and those referred to allergy centers, but sensitization and DBPCOFC-proven food allergies did not differ significantly between the two groups except for milk and egg allergy. These differences in clinically confirmed food allergy rates in the community versus in the allergy centers reinforce the need to use population-based studies when determining the prevalence of food allergy in the general population and not to extrapolate from referral populations, particularly when using questionnaires.

The EuroPrevall group also enrolled a birth cohort of 12,049 from 9 centers throughout Europe between October 2005 and March 2007 (McBride et al., 2012), and followed up at ages 1 year and 2 years. This is the largest birth cohort reported to date. Overall, 1,928 parents contacted the study centers about possible adverse food reactions in their children

and, based on annual follow-up questionnaires, an additional 684 children were suspected of having potential allergic disease (Schoemaker et al., 2015). Of this group, 358 children met the criteria to undergo a DBPCOFC to milk and 248 (69 percent) agreed to at least one food challenge. Fifty-five children experienced a positive result for an overall incidence of cow milk allergy of 0.54 percent (95% CI: 0.41%-0.70%). The incidence varied by country with the highest incidence of cow milk allergy in the United Kingdom and the Netherlands (1 percent) and the lowest (<0.3 percent) in Germany, Lithuania, and Greece. Nearly 25 percent of the children had non-IgE-mediated cow milk allergy, especially those from the United Kingdom, the Netherlands, and Poland. Of the 32 children with cow milk allergy who were evaluated 1 year later, 22 (69 percent) were tolerant to milk, including all those with non-IgE-mediated cow milk allergy and 57 percent of those with the IgE-mediated form of the allergy. This study reports the lowest incidence of cow milk allergy in recent times, but is subject to a number of limitations. First, about 30 percent of the children did not undergo a DBPCOFC. Second, the numbers of eligible infants in each center who did not participate in the study were not reported so it is not possible to assess the role of selection bias. Finally, only a limited number of children underwent a rechallenge to cow milk at 1 year and so the true proportion of children that became tolerant is less certain.

A similar evaluation of hen egg allergy was conducted in the EuroPrevall birth cohort (Xepapadaki et al., 2016). Overall, 2,612 children were identified by parental report (N=1,928) or during annual follow-up questionnaires (N=684) about possible adverse food reactions in their children to hen egg. Following a standardized evaluation, 298 (27 percent) of the children were invited for a DBPCOFC to egg and 172 (58 percent) agreed to be challenged; 86 (50 percent) experienced a positive challenge to pasteurized egg powder, for an overall raw incidence of 0.84 percent (95% CI: 0.67%-1.03%). After adjusting for eligible children who refused the challenge, the overall incidence of egg allergy in Europe was estimated to be 1.23 percent (95% CI: 0.98%-1.51%), with the United Kingdom reporting the highest prevalence at 2.18 percent (95% CI: 1.27%-3.47%) and Greece reporting the lowest prevalence at 0.07 percent (95% CI: 0.00%-0.37%). This rate of egg allergy was markedly lower than the recently reported 8.9 percent prevalence of egg allergy in a population-based cohort in Australia of infants age 1 (Osborne et al., 2011), discussed below. Overall, one-half of the egg allergic children reportedly became tolerant to egg within 1 year following the initial diagnosis (Xepapadaki et al., 2016). A major limitation of this study was the large numbers of parents who refused to have their children challenged and no indication of the number of eligible children from each site who did not participate, eliminating the possibility of identifying selection bias. Nevertheless, this study represents the largest multi-center birth

cohort evaluated for egg allergy and demonstrated a variable rate of egg allergy across different regions of Europe.

In 2010, a cohort of 2,612 children (ages 11 to 12 years) from three Swedish municipalities (96 percent participation) were evaluated by questionnaire and a random subset was further evaluated by skin testing and DBPCOFC. Overall, 4.8 percent (95% CI: 4%-6%) reported allergy to one or more common foods, i.e., cow milk, egg, fish, and/or wheat (Winberg et al., 2015). About one-fourth of the children who underwent clinical examination (1.4 percent) were diagnosed with a food allergy, and only 0.6 percent were diagnosed after undergoing a DBPCOFC. This study provides some insight on the prevalence of food allergy in Sweden and further evidence that self-reported rates of food allergy consistently overestimate true prevalence of food allergy.

A cross-sectional survey was conducted in 19 children's day care centers from two Portuguese cities selected following randomization and cluster analysis (Gaspar-Marques et al., 2014). Questionnaires derived from the International Study of Asthma and Allergies in Childhood and supplemented with questions on food allergy were distributed to 2,228 parents and returned by 1,225 (55 percent). The median age of the children sampled was 3.5 years; 38.3 percent were ages 0 to 3 years, and 61.7 percent were ages 4 to 6 years. Parents reported that 10.8 percent (95% CI: 9.1%-12.6%) of the children ever had a food allergy and 5.7 percent (95% CI: 4.6%-7.2%) currently had a food allergy. Milk (2.8 percent), strawberry (2.3 percent), chocolate (1.4 percent), egg (1.0 percent) and shellfish (0.7 percent) were the most commonly reported foods. Although no attempt was made to validate food allergy with laboratory studies or OFC, the prevalence of parental-perceived food allergy is considerably lower than that reported for some countries in the EuroPrevall study, such as Germany (30 percent), Iceland, the United Kingdom, and the Netherlands (20 to 22 percent), but similar to those in others, such as Lithuania, Greece, Poland, and Spain (5 to 8 percent) (McBride et al., 2012). Like many epidemiological studies on food allergy, the use of parental reporting by questionnaire may lead to misclassification, which could explain the high perceived prevalence of allergy to strawberry and chocolate, and selection bias due to the high rate of nonresponders.

In summary, a variety of studies have been conducted in European countries to ascertain prevalence of food allergy in various populations and to various food allergens. In the most ambitious study, the EuroPrevall Surveys, 8 European centers enrolled about 3,000 individuals each to conduct questionnaires, IgE sensitization tests, and DBPCOFC. The results from DBPCOFCs in children have been published for milk and eggs; additional prevalence data will be forthcoming. No OFC were performed in adults. Although these studies provide some insights, inconsistencies

in the implementation across countries make it difficult to come to firm generalizations about food allergy prevalence in Europe for children or for adults.

PREVALENCE OF FOOD ALLERGY IN OTHER PARTS OF THE WORLD

Australia

One of the most comprehensive population-based studies to date was conducted in Melbourne, Australia, as part of the HealthNuts Study (Osborne et al., 2011). Importantly this study used a formal sampling frame to ensure that the study is truly population-representative (Osborne et al., 2010). Parents of infants between the ages of 11 and 15 months attending one of 120 immunization clinics were enrolled and a short interview was conducted with all nonparticipants to assess potential participation bias. Overall, 3,898 parents were approached and 2,848 (73.1 percent) agreed to participate; 99.1 percent of the nonparticipants completed the nonparticipant interview. Of those infants enrolled, 98.4 percent had SPT to four of five foods (egg, peanut, sesame, shrimp, or cow milk). Any participant with a detectable wheal size (1mm greater than the negative control) was invited for an OFC, which was conducted with research staff blinded to SPT result and history of previous reaction. The challenges were undertaken irrespective of wheal size or history of previous reaction unless the reactions occurred in the previous 1 month and predetermined objective stopping criteria were used (Koplin et al., 2012). At the time of OFC, repeat SPT wheal (i.e., small swelling) diameters 1 mm or greater than the negative control were considered positive, and 21.0 percent (95% CI: 19.5%-22.5%) were positive to one or more foods: raw egg—11.8 percent (95% CI: 10.6%-13.0%); peanut—6.4 percent (95% CI: 5.5%-7.3%); sesame—1.6 percent (95% CI: 1.2%-2.1%); shellfish—0.4 percent (95% CI: 0.2%-0.7%); and milk—5.6 percent (95% CI: 3.2%-8.0%). More than 90 percent of infants with a positive SPT to egg, peanut, and/or sesame underwent a food challenge regardless of skin test size, with an overall prevalence of challenge-confirmed food allergy among participants of 10.4 percent (95% CI: 9.3%-11.5%): raw egg—9.0 percent (95% CI: 7.8%-10.0%); peanut—2.9 percent (95% CI: 2.3%-3.6%); and sesame—0.7 percent (95% CI: 0.4%-1.0%). Of 88 infants reactive to raw egg, 80.3 percent did not react to 1.1 g of egg protein baked in a cake. Oral food challenges to milk were not performed, but IgE-mediated type reactions to milk were reported in 2.7 percent (95% CI: 2.1%-3.4%) of infants. Accounting for differences among participants and nonparticipants only marginally decreased the estimated prevalence of food allergy, e.g., peanut—2.9 percent (95% CI: 2.3%-

3.6%) to 3.0 percent (95% CI: 2.4%-3.8%) (Osborne et al., 2011). One of the greatest strengths of this survey is the diagnosis of food allergy based on challenge-proven outcomes. Despite the use of such rigorous diagnostic criteria, the prevalence of food allergy in this population of children age 1 year is the highest reported to date and may reflect the apparent higher prevalence of allergic disease in Australia or the increasing prevalence of food allergy worldwide. This cohort, which is now being followed and has been re-examined at ages 2, 4, 6, and 10 years (Koplin et al., 2015), will provide interesting insights into the natural history of food allergy.

Africa

Few epidemiologic studies on the prevalence of food allergy have been performed in other parts of the world. Kung et al. attempted a systematic review of food allergy in Africa and found very limited information from 11 countries (Kung et al., 2014). No population-based surveys and few case-controlled cross-sectional studies have been conducted. Most studies relied on self-reporting and in some cases skin testing in selected populations. Nevertheless, the investigators concluded that while not common, food allergy is an increasing problem in several emerging African countries. A preliminary feasibility study of food sensitization and challenge-proven food allergy was conducted in Cape Town, South Africa (Basera et al., 2015). The authors concluded that future studies in this black African infant cohort will be helpful in determining the prevalence of food sensitization and allergy in an African population.

Asia

A systematic review of food allergy in Asia yielded 53 original articles from Southeast Asia. Of these, 13 were epidemiologic studies and most had major design limitations resulting in low-grade evidence (Lee et al., 2013). The overall prevalence of self-reported or questionnaire-based food allergy in the pediatric population ranged from 3.4 percent to 11.1 percent. Egg and milk allergy were the most common food allergies in infants and young children, 0.15 percent to 4.4 percent and 0.33 percent to 3.5 percent, respectively. Shellfish (crustaceans and mollusks) allergy was the most common food allergy in older children and adults (reportedly 5.12 percent and 5.23 percent in the Philippines and Singapore, respectively), and it was the leading cause of anaphylaxis in Southeast Asia. Wheat allergy was reportedly the leading cause of anaphylaxis in children in Japan, with a prevalence of 0.37 percent.

A population-based survey of fish allergy in the Philippines, Singapore, and Thailand was conducted in randomly selected secondary schools using

structured written questionnaires followed by an extended questionnaire in those responding positively to the initial survey (Connett et al., 2012). Overall, 19,966 out of 25,842 initial surveys were returned (11,434 [81.1 percent] from the Philippines, 6,498 [67.9 percent] from Singapore and 2,034 [80.2 percent] from Thailand). The prevalence of a convincing history of fish allergy was greatest in the Philippines—2.29 percent (95% CI: 2.02%-2.56%) compared to 0.26 percent (95% CI: 0.14%-0.79%) in Singapore and 0.29 percent (95% CI: 0.06%-0.52%) in Thailand.

Two cross-sectional studies of food allergy prevalence also have been conducted in China showing an increase in food sensitization and allergy prevalence in infants between 1999 and 2009 (Hu et al., 2010). These studies, however, were small and could be subject to selection bias and therefore could report a higher level than the actual prevalence.

A cross-sectional survey of adolescents from 34 state elementary schools in Ankara province in Turkey included an initial survey followed-up by a phone survey with families that reported a food allergy and then a clinical evaluation of children who had a history compatible with food allergy following the phone survey (Kaya et al., 2013). Of 11,233 questionnaires distributed to 6th, 7th, and 8th grade students at the 34 schools, 10,096 (89.9 percent) questionnaires were returned (mean age of students was 12.9 $\pm$ 0.9 years) and 1,139 (11.2 percent) reported a food allergy. The parent-reported lifetime prevalence of food allergy was 11.3 percent (95% CI: 10.7%-11.9%) and the point prevalence[8] was 3.6 percent (95% CI: 3.2%-3.8%). All children's families who reported a food allergy and 200 others who reported no food allergy were contacted by an allergy specialist by phone. After reviewing the case histories, 133 cases were compatible with a food allergy and 107 agreed to participate in a clinical evaluation including SPT, serum IgE levels, open OFC, and in some cases DBPCOFC. Following clinical evaluation, including OFC, the prevalence of IgE-mediated food allergy was found to be 0.15 percent, with allergy to peanut (0.05 percent) and tree nuts (0.05 percent) being the most common. Strengths of this study include its large sample size and progressive diagnostic evaluation, including OFC documentation of food allergy.

In summary, relatively few population-based studies have attempted to determine the prevalence of food allergy in countries outside of Europe and the United States. These data have been limited by a number of shortcomings: small sample size, selection bias related to sampling methodology and low response rates, use of parental reporting of food allergy and/or SPT/serum IgE levels, and when included, variable OFC methodologies. One exception is Australia, which has mounted a robust effort to determine

[8] The proportion of a population that has the condition at a specific point in time.

prevalence. Data emerging from this effort will provide valuable insights into natural history and prevalence.

PREVALENCE OF FOOD ALLERGY–INDUCED ANAPHYLAXIS

Systematic Reviews and Meta-Analysis

Umasunthar et al. performed a systematic review and meta-analysis to determine the incidence of food-induced anaphylaxis in individuals with food allergy (Umasunthar et al., 2015). The systematic review identified 34 studies, primarily from North America, Europe, and Australia, out of 2,552 article titles that could be used to contribute data to the meta-analysis. Study results showed marked heterogeneity, most likely due to the variation in study populations, definitions of anaphylaxis used, and data collection methods. In individuals with food allergy, medically coded food anaphylaxis had an incidence rate[9] of 0.14 per 100 person-years (95% CI: 0.05-0.35). At ages 0 to 19 years, the incidence rate for anaphylaxis in those with food allergy was 0.20 (95% CI: 0.09-0.43) and at ages 0 to 4 years, the authors reported an incidence rate of up to 7.00 per 100 person-years. In food-allergic patients, the incidence rate of hospital admission due to food anaphylaxis was 0.09 (95% CI: 0.0-0.67) per 1,000 person-years, with an incidence rate of 0.20 (95% CI: 0.10-0.43) at ages 0 to 19 years based on eight studies and 0.50 (95% CI: 0.26-0.93) at ages 0 to 4 years based on six studies. The authors concluded that "the incidence of medically coded anaphylaxis for a food allergic person is greater than the general population incidence of accidental death, but is likely to be significantly lower than the incidence of Emergency Department attendance due to motor vehicle accidents" (Umasunthar et al., 2015, p. 1624). The highest rates of medically coded food anaphylaxis and hospital admissions for food anaphylaxis were seen in preschool children, in contrast to reports of fatal food anaphylaxis, which are most commonly reported in adolescents and young adults.

Using the *PRISMA* guidelines, Umasunthar et al. also performed a systematic review and meta-analysis to determine the incidence of fatal food anaphylaxis in individuals with food allergy (Umasunthar et al., 2013). Out of 2,552 original titles, 13 studies, conducted in North America, Europe, Australia, Brazil, and Israel, describing a total of 240 fatal food-induced anaphylactic reactions were included in the analysis. Assuming a food allergy prevalence rate of 3 percent (3.9 percent in individuals ages 0 to 19 years and 1 percent in those with peanut allergy), meta-analysis of 10 evaluable studies (which had low-grade evidence and a high level of heterogeneity) estimates the incidence of fatal food anaphylaxis among those

[9] Incidence rate is the number of new cases per population at risk in a given time period.

with a food-allergy as 1.81 (95% CI: 0.94-3.45) per million person-years (equivalent to about 25 deaths per year in the United States, assuming an overall 3 percent prevalence of food allergy), 3.25 (95% CI: 1.73-6.10) per million person-years in children ages 0 to 19 years, and 2.13 (95% CI: 1.09-4.16) per million person-years in peanut-allergic patients. The investigators concluded that in all studies examined and in all subgroups evaluated, "the incidence of fatal food anaphylaxis for a food-allergic person is ≥100 times lower than incidence of death due to any accident in the general population, and at age 0–19, the incidence is ≥10 times lower than the accidental death incidence in the general population" (Umasunthar et al., 2013, p. 1338). In both the systematic review and meta-analysis by Umasunthar et al., the level of evidence in the studies reviewed was low due to variations in case definition of anaphylaxis, methods of data capture, limited information about food allergy prevalence in the populations studied, and likely ascertainment bias across all studies. However, both systematic reviews suggested a number of risk factors for more severe anaphylactic reactions that have been noted in previous studies, including individuals with asthma, previous severe reaction (Bock et al., 2007; Sampson et al., 1992), IgE binding to a diverse range of sequential epitopes (Flinterman et al., 2008; Lewis et al., 2005; Shreffler et al., 2004), and deficient platelet-activating factor acetylhydrolase enzyme activity (Vadas et al., 2008).

A systematic review and meta-analysis of the prevalence of anaphylaxis in Europe was conducted by Panesar et al., who identified 49 articles satisfying their inclusion criteria, but only 3 were suitable for generating a pooled estimate of anaphylaxis (Panesar et al., 2013). Meta-analysis of these studies suggested a pooled European anaphylaxis prevalence of 0.3 percent (95% CI: 0.1%-0.5%), with markedly varying estimates of anaphylaxis due to food allergy based on individual studies ranging from 0.4 percent to 39.9 percent. In children, cow milk, egg, hazelnut, peanut, kiwi, and other tree nuts were the most common triggers, and asthma and reactions in pollen-allergic patients occurring in pollen season were identified as increased risk factors for anaphylaxis.

Studies in the United States

Virtually no studies have been conducted evaluating the prevalence of food-induced anaphylaxis in the United States. Recently Wood et al. conducted two nationwide, cross-sectional random-digit-dial surveys: a public survey that included unselected adults and a patient survey that collected information from household members who reported a reaction to medications, foods, insect stings, or latex and idiopathic reactions in the previous 10 years (Wood et al., 2014). The public survey included 1,000 adults from which it was estimated that 5.1 percent (95% CI: 3.4%-6.8%) and 1.6

percent (95% CI: 0.8%-2.4%) had probable and very likely anaphylaxis, respectively. In the patient survey 344 of 1,059 respondents reported a history of anaphylaxis; 31 percent of these reactions were to foods, most commonly peanuts, tree nuts, and shellfish. Even though children were included in the patient survey, it had a significant bias toward an older population (median age was age 52 years). This age bias likely misrepresented the relative proportion of anaphylaxis triggers in the overall U.S. population, probably underestimating foods and overestimating medications. As with similar such surveys, both studies were limited by recall bias of interviewees, potential bias caused by using only a landline sample, and high rates of nonparticipation that could potentially result in further selection bias.

Other methods to estimate prevalence have been used, such as the *International Statistical Classification of Diseases and Related Health Problems* (ICD)[10] (Jerschow et al., 2014). However, ICD codes are considered inaccurate for determining the prevalence of food-induced anaphylactic deaths.

In the United States, the National Electronic Injury Surveillance System (NEISS) is an active surveillance system maintained by the Consumer Product Safety Commission (CPSC) designed to identify consumer product-related adverse events at emergency departments. The authors of a 2008 pilot study that analyzed NEISS emergency department data to assess food allergies adverse events concluded that analysis of NEISS data may be a useful tool for assessing the magnitude and severity of food-allergic events (Ross et al., 2008).

Studies in Europe

Some European countries have developed Web-based surveillance systems to gather food related severe reactions data, such as the French Allergovigilance Network (Moneret-Vautrin et al., 2005) or the European Anaphylaxis Registry. Between July 2007 and March 2015, 1,970 anaphylactic events in children younger than age 18 years were reported to the European Anaphylaxis Registry, which consisted of data retrieved from medical records of referrals to 90 tertiary allergy centers in 10 European countries (Grabenhenrich et al., 2016). Overall, 1,291 out of 1,970 (66 percent) severe allergic events were due to allergic reactions to food. The investigators found that milk (N=120) and egg (N=115) were the most common cause of anaphylaxis in children during the first 2 years of life. Cashew

[10] *The International Statistical Classification of Diseases and Related Health Problems* (or *International Classification of Diseases* [ICD]) is the international standard diagnostic tool for epidemiology, health management, and clinical purposes maintained by the World Health Organization.

(N=87) and hazelnut (N=86) reactions occurred mostly in preschoolers and peanut (N=325) occurred at all ages in European children. Grabenhenrich et al. found that most incidents occurred in private homes (46 percent) and that one-third of the children had experienced a previous reaction (Grabenhenrich et al., 2016). Skin symptoms occurred in 92 percent of children: hives (62 percent), angioedema (53 percent), pruritus (37 percent), and flushing (29 percent). Gastrointestinal symptoms developed in 45 percent of the reactions: vomiting (overall 27 percent) dominating in the preschool children, abdominal pain (16 percent), and nausea (overall 15 percent) dominating in adolescents. Overall, 70 percent of anaphylactic cases due to known factors were due to food allergy, with peanut and milk being the most common elicitors. Overall, 26 children (1.3 percent) experienced severe life-threatening reactions, mostly to foods, and 5 children died. This study represents the largest series of anaphylactic reactions reported in a pediatric population.

In summary, high-quality data on the prevalence of food-induced anaphylaxis in the United States and in other countries are lacking. In addition, it is challenging to make definitive conclusions about prevalence of anaphylaxis due to heterogeneity in populations, definitions of anaphylaxis used, and data collection methods. However, mortality due to food-induced anaphylaxis seems to be low compared to other accidental causes. Still, monitoring anaphylaxis reactions from food allergies is important not only to estimate prevalence but for understanding the causes, identifying interventions, and for bringing the information to patient care and other educational efforts.

EVIDENCE THAT THE PREVALENCE OF FOOD ALLERGY IS INCREASING

A few studies have employed consistent methodology over time in an attempt to determine whether the prevalence of food allergy has been changing over time. Sicherer et al. performed a random digit-dial telephone survey in the United States using the same methodology at set intervals (1997, 2002, and 2008) to determine the prevalence of peanut and tree nut allergy (Sicherer et al., 2010). In the 2008 study, a total of 5,300 households (13,534 participants) were surveyed (participation rates, 42 percent versus 52 percent in 2002 and 67 percent in 1997). Overall, peanut allergy, tree nut allergy, or both were reported in 1.4 percent of participants (95% CI: 1.2%-1.6%) compared with 1.2 percent in 2002 and 1.4 percent in 1997. The prevalence for adults was 1.3 percent (95% CI: 1.1%-1.6%), which was not significantly different from the earlier surveys, while the prevalence of peanut or tree nut allergy for children younger than 18 years of age was significantly different: 2.1 percent in 2008 (95% CI: 1.6%-2.7%) com-

pared with 1.2 percent in 2002 and 0.6 percent in 1997. The prevalence of peanut allergy in children in 2008 was 1.4 percent (95% CI: 1.0%-1.9%) compared with 0.8 percent in 2002 and 0.4 percent in 1997. Additionally, the prevalence of childhood tree nut allergy increased significantly across the survey waves (1.1 percent in 2008, 0.5 percent in 2002, and 0.2 percent in 1997). However, these studies had a number of limitations, including self-reporting, increasing awareness, and increasing nonparticipation rates, which could have led to increasing selection bias and higher prevalence rates.

As noted above, investigators at the CDC performed a cross-sectional survey of data from several U.S. databases and concluded that the prevalence of food allergy in children younger than age 18 years increased 18 percent from 1997 through 2007 (Branum and Lukacs, 2009). However, it remains unclear whether this represents a true increase in prevalence or a difference in awareness and coding. A recent comparison between the rate of sensitization (sIgE test) to peanut, milk, egg, and shrimp in U.S. children ages 6 to 19 years from 1988-1994 to 2005-2006 was conducted based on NHANES data. The analysis found that sensitization did not increase between 1988 and 1994 (24.3%; 95% CI: 22.1%-26.5%) and 2005-2006 (21.6%; 95% CI: 19.5%-23.7%), except for a trend toward the increased prevalence to the combination of milk, egg, and peanut among non-Hispanic blacks (McGowan et al., 2016). Sensitization, however, is not a good indicator of symptomatic food allergies.

A number of studies from other parts of the world also suggest an increase in the prevalence of sensitization and allergic reactions to foods. Three birth cohorts from the Isle of Wight in the United Kingdom were evaluated for peanut allergy in 1989 (2,181 children age 4), 1996 (1,273 children ages 3 and 4), and 2001-2002 (891 children age 3) (Venter et al., 2010). Peanut sensitization increased significantly, from 1.3 percent in the 1989 cohort to 3.3 percent (P=0.003) in the 1996 cohort before falling back to 2.0 percent in the 2001-2002 cohort (P=0.145). Clinical peanut allergy (based on positive SPT with convincing clinical history or positive OFC in the latter two cohorts) increased significantly from 0.5 percent in the 1989 cohort to 1.4 percent (P=0.023) in 1996 cohort with a subsequent fall to 1.2 percent in the 2001-2002 cohort (P=0.850). However, in this study, the cohorts are not totally comparable because the ages and participation rates varied.

In a cross-sectional survey of grade school children in Montreal, Ben-Shoshan et al. reported a non-significant rise in adjusted peanut allergy prevalence from 1.34 percent (95% CI: 1.08%-1.64%) in a 2000-2002 cohort to 1.62 percent (95% CI: 1.31%-1.98%) in a 2005-2007 cohort (Ben-Shoshan et al., 2009).

In summary, although a general perception that food allergy is increas-

ing exists, especially in westernized countries, very few studies support this likely change.

OVERALL CONCLUSIONS

An accurate assessment of the true prevalence of food allergy and a determination of whether it is increasing are needed to prioritize food allergy as a public health problem and ensure that adequate resources are directed at the problem. Although a general consensus has emerged and plentiful "soft" data, such as parental reports, surveys of school teachers and nurses, and reports from general practitioners, suggest that the prevalence of food allergy is increasing, few well-designed comprehensive studies exist to support this notion. Because of the low quality of published prevalence data, particularly the use of self-reported data, the true prevalence of food allergy is likely overestimated in most published studies. Even so, it is clear that food allergy has become a major health problem in many countries around the world. The prevalence of atopic dermatitis has increased dramatically over the past two decades (see Figure 3-1), and this may in large part account for the rise in food allergy, as children with eczema are susceptible to sensitization to various allergens, including food, through the defective and inflamed skin barrier. Figure 3-4 depicts the prevalence of food allergy based on convincing histories plus laboratory data or OFCs, primarily in young children, in various countries around the world.

It appears that a few foods, such as milk, egg, peanut and/or tree nuts, and seafood, comprise the vast majority of allergens responsible for allergic reactions around the world, and that the likelihood of severe or fatal reactions due to food allergy in food-allergic individuals is rare, being less likely than the chance of severe injury or death due to accidents in the general public.

Good studies on the prevalence of food allergy are very costly and difficult to perform, often requiring OFCs for accurate diagnosis, which are time-consuming, potentially dangerous and frequently refused by parents, and subject to a variety of biases. In general, prevalence data based on parental surveys or specialty-based practices or hospitals provide the most inflated estimates, followed by population-based surveys, sensitization-based studies, and medical history plus sensitization-based studies. Studies incorporating OFC typically provide the lowest and most accurate assessment of true food allergy prevalence. Population-wide estimates of prevalence of food allergy in both children and adults in Europe are available from the EuroPrevall studies, which encompass questionnaires, testing for IgE antibodies, and more limited testing with DBPCOFC among children. In addition, a comprehensive study of infants has been conducted in Australia in the HealthNuts Study, which is continuing to follow the infants

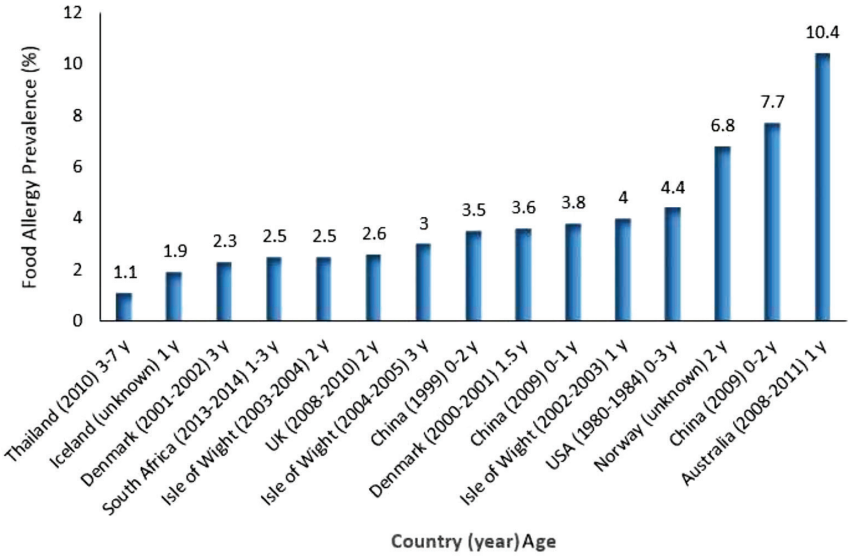

FIGURE 3-4 Prevalence of IgE-mediated food allergy at different age points younger than the age of 6 in various countries of the world determined by convincing clinical history with evidence of IgE antibodies or by OFC. Countries and median age of population surveyed posted along x-axis, percentage of food-allergic children listed on y-axis.
SOURCES: Courtesy of Michael E. Levine, Cape Town, South Africa. Data from Basera et al., 2015; Bock, 1987; Chen et al., 2011; Eller et al., 2009; Grimshaw et al., 2015; Hu et al., 2010; Kristinsdottir et al., 2011; Kvenshagen et al., 2009; Lao-araya and Trakultivakorn, 2012; Osborne et al., 2011; Osterballe et al., 2005; Venter et al., 2006, 2008.

through childhood. No such population-wide estimates of prevalence exist in the United States.

Given the difficulty of diagnosing food allergy, the committee recommends that estimation of prevalence of food allergies in general and for the specific list of priority allergens in the United States be conducted in a systematic fashion and stratified sampling be used for cost-efficiency, with frequency-weighting used to obtain population-wide estimates. In the United States, while some surveys, such as the National Survey of Children's Health, are limited to questionnaire data, other surveys, possibly including the newly launched Environmental Influences on Child Health Outcomes (ECHO) program, could incorporate more comprehensive assessment of

food allergies, particularly in children. At this time, such information could be incorporated into a population survey sampling already in place, such as NHANES.

RECOMMENDATIONS

The committee recommends that the Centers for Disease Control and Prevention obtain prevalence estimates on food allergy in a systematic and statistically sound manner. Prevalence should be assessed in a systematic fashion in a sufficiently large population, with consideration given to using stratified sampling for cost-efficiency, with frequency-weighting used to obtain population-wide estimates. Prevalence estimates should be conducted in both children and adults and in groups defined by race, ethnicity, and socioeconomic status to determine differences in diagnosis and prevalence within these subgroups. To support population risk assessments, the committee also recommends that the dietary intake history of those reporting food allergy be compared to those who do not, particularly for the specific foods of interest.

Although a new study design (or the use of other data surveillance systems) is possible, the National Health and Nutrition Examination Survey (NHANES) is a feasible option to systematically examine the prevalence of food allergy by collecting data on self-reported food allergies, food-specific immunoglobulin E (sIgE) concentrations, food-specific skin prick test (SPT) results, and oral food challenge (OFC) results.[11]

Specific suggestions for use of NHANES (or other data surveillance systems) include

- Oversample the population of children ages 0 to 6 years, due to the higher prevalence of food allergy in this group and the fact that environmental exposures at this age might affect food allergy development.
- Consistently incorporate questions on food allergy diagnosis as well as intake of common food allergens into questionnaires to capture point prevalence, change in prevalence

[11] The gold standard OFC is an expensive method and must be administered in a clinic and under supervision of a trained physician. The testing sequence, therefore, is meant to lead to a population sample that is enriched with individuals reporting food allergies and that minimizes cost and effort.

of self-reported food allergies over time, and dietary information on intake of common allergens.

- Perform assays of blood specimens for serum food allergen-specific immunoglobulin (IgE), concentrations to obtain population estimates of prevalence of allergen sensitization and assess changes in prevalence over time.
- Invite a stratified sample of participants enriched with individuals reporting food allergies to undergo food-specific SPT during the examination component of the survey.
- Invite a smaller subsample of participants to undergo double blinded placebo-controlled OFCs. This sample should be enriched with individuals reporting food allergies and/or positive SPT or IgE antibody tests.
- Elicit reasons for any nonparticipation in SPT or OFC, particularly whether the individual has had prior testing and a diagnosed food allergy. If possible, obtain medical records containing such test results.
- Obtain population-wide estimates of self-reported food allergies, IgE concentrations, positive SPTs, and positive OFCs through weighted analyses using stratified sampling weights (e.g., as is routinely used in NHANES analyses).
- Establish the sensitivity and specificity of various diagnostics as compared to the OFC.
- Use a diagnostic challenge with progressive series of doses in the subsample undergoing OFCs to establish prevalence of food allergy. Also include testing at a lower dose to validate population thresholds proposed for food labeling purposes.

RESEARCH NEEDS

In addition to sound information about the true prevalence of food allergy, the committee concluded that better methods to collect information about anaphylaxis reactions are needed. In addition, estimates of the various costs of food allergy are needed. For example, the CDC has developed tools to estimate the costs associated with some chronic diseases, such as arthritis. Medical expenditures for managing food allergy place financial burdens on society, as well as on the individuals affected and their caregivers. Additional costs relate to quality of life, productivity in school or at work, and food recalls. In addition, data from a national survey of caregivers of food-allergic children suggests considerable socioeconomic disparities in the economic impact of childhood food allergy. For instance, children in the lowest income stratum incurred 2.5 times the amount of emergency

department and hospitalization costs related to their food allergies than did higher-income children (Bilaver et al., 2016). Estimates on cost burden are necessary for prioritizing research and resources, and for effectively advocating for implementation of practices and policies that will reduce costs. The accuracy of the estimates will partially depend on collecting better prevalence data, as described in the recommendation above.

The following research needs are warranted to improve data on severe reactions and on cost estimates:

- Evaluate various methods of collecting national data on food allergy severe reactions such as by leveraging the existing surveillance systems (e.g., NHANES or the National Electronic Injury Surveillance System) or by developing a Web-based reporting system for anaphylaxis in the community.
- Collect and analyze data to estimate the economic and social costs of food allergy based on current prevalence of both mild and severe reactions and on objective measures of costs, such as data on medical expenses and time lost from school and work. Collect these data on different ethnicities and socioeconomic strata. The costs to industry due to food recalls and implementation of allergen control strategies also should be estimated.

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4

Assessments, Diagnostic Testing, Disease Monitoring, and Prognosis

OVERVIEW

A diagnosis of food allergy carries numerous health, emotional, social, and nutritional consequences. Therefore, a proper diagnosis is imperative. Unfortunately, studies suggest that many individuals needlessly avoid foods on the presumption of a food allergy without seeking medical confirmation, a practice that can lead to unnecessary risk and burden (Boyce et al., 2010; Fleischer et al., 2011; Rona et al., 2007). For example, in one meta-analysis, the rate of self-reported food allergy was 12 percent and 13 percent for children and adults compared to 3 percent when confirmation with testing was applied (Boyce et al., 2010; Rona et al., 2007). One of the major issues in food allergy is the common misconception that having a "positive test," by a blood test or allergy skin prick test (SPT, otherwise known as sensitization, or a condition in which an individual produces detectable food-specific immunoglobulin E [IgE] antibody), is equivalent to having a clinical food allergy. For example, Fleischer et al. performed 111 supervised feeding tests with 44 children avoiding foods because of positive skin or serum allergy tests and, overall, 93 percent of the children were tolerant of the avoided food (Fleischer et al., 2011). Although this was a subpopulation of children with high rate of atopic dermatitis, on a population level, many more persons are also sensitized to foods than are clinically reactive upon ingestion. For example, 2005-2006 National Health and Nutrition Examination Survey (NHANES) data showed a 7.6 percent rate of positive serum IgE tests to peanut (10.7 percent in children ages 6 to 19 years), clearly higher than the prevalence of clinical peanut allergy (Liu et al., 2010). Compounding

the problem, many physicians lack an understanding of how to apply common diagnostic tests and interpret the results. In a survey of 407 primary care physicians, less than 30 percent of the participants reported that they were comfortable interpreting laboratory tests to diagnose food allergy, and 38 percent indicated incorrectly that skin or blood tests were sufficient for a diagnosis (Gupta et al., 2010). Clearly, the lack of understanding among physicians is compounded among the lay public.

Although overdiagnosis is a concern, conversely, assuming that an allergen has been identified as a trigger of a serious allergic response, a lack of confirmation could lead to re-exposure to the true culprit, with serious consequences. It is therefore imperative that individuals with suspected food allergy seek a medical diagnosis to identify whether the cause of symptoms is a food allergy and to identify culprit foods.

Considering the various symptoms (e.g., rashes, respiratory symptoms, gastrointestinal [GI] symptoms) and medical illnesses (e.g., atopic dermatitis, anaphylaxis) attributable to food allergy, many of which have alternate diagnoses (i.e., intolerance, pharmacologic reactions), or nonfood triggers (i.e., pollen allergy, irritants), food allergy diagnosis is complicated. Additionally, no simple tests exist that, in isolation, diagnose a specific food allergy (Boyce et al., 2010; Sampson et al., 2014). The primary tools currently available for diagnosis include the medical history, elimination diets, SPT, food-specific IgE (sIgE) (serum tests for food-specific IgE against specific proteins in foods), component resolved diagnostics (CRD), and medically supervised oral food challenges (OFCs).

This chapter includes relevant aspects of mechanisms of food allergy in relation to the current accepted methods for diagnostic testing and prognosis, including misconceptions about the methods, limitations, and factors that might affect diagnosis. The chapter also describes some promising methods that need further research, validation, or standardization before being used routinely, and methods that are not recommended for use routinely. The chapter ends with overall conclusions, recommendations, and research needs.

APPROACH TO LITERATURE REVIEW

In preparing this chapter, new individual systematic reviews or meta-analyses were not conducted. The primary resources for discussion, findings, conclusions, and recommendations were derived from the National Institute of Allergy and Infectious Diseases/National Institutes of Health (NIAID/NIH)–supported Guidelines (Boyce et al., 2010), the European Academy of Allergy & Clinical Immunology (EAACI) Guidelines (Muraro et al., 2014), and associated systematic reviews (Soares-Weiser et al., 2014) as well as the American Academy of Allergy, Asthma & Immunology

(AAAAI) Guidelines (Sampson et al., 2014; see Chapter 1, Table 1-1). Additional PubMed searches were selectively performed to identify studies and reports in the literature, especially focusing on papers published after the aforementioned reports. Meta-analyses, systematic reviews, expert reports, and practice guidelines were selected when available and supplemented with more recent publications.

REASONS TO INITIATE ASSESSMENTS FOR FOOD ALLERGY

The NIAID/NIH-supported Guidelines (Boyce et al., 2010) suggest that food allergy should be considered in a number of specific circumstances. Having allergic symptoms within minutes to hours after ingestion, especially from a specific food on more than one occasion, is suggestive of a food allergy and warrants investigation. Symptoms can include skin symptoms of itchy rashes, hives, or swelling; eye symptoms of itching, tearing, redness, or swelling; oral symptoms of itching or swelling of the lips, tongue, or palate; upper airway symptoms of congestion, itching, sneezing, nasal discharge, or hoarseness; lower airway symptoms of cough, chest tightness, wheezing, or trouble breathing; gastrointestinal symptoms of nausea, pain, vomiting, or diarrhea; cardiovascular symptoms of fast or slow heart rate, dizziness, low blood pressure, confusion, loss of consciousness; uterine contractions; and a sense of "impending doom."

Food allergy diagnostic testing also may be warranted for infants, young children, and selected older individuals with moderate to severe atopic dermatitis because a higher rate of food allergy occurs in these populations, whether or not the food allergy may be contributing to the rash (Boyce et al., 2010; Sidbury et al., 2014). Disorders with subacute or chronic symptoms that indicate food-related disorders, such as food protein–induced enterocolitis (FPIES), enteropathy, and allergic colitis, also warrant investigation for food-allergic triggers. Food allergy also should be considered in children and adults with eosinophilic esophagitis (Boyce et al., 2010; Liacouras et al., 2011; Markowitz et al., 2003). Importantly, food allergy is not a typical trigger of chronic asthma or chronic rhinitis in childhood (Boyce et al., 2010; Sampson et al., 2014), although it can cause occupational asthma in certain groups, such as bakers or shellfish handlers.

The initiation of food allergy diagnostic testing also has some areas of uncertainty. For example, one expert panel (Boyce et al., 2010) concluded that there was insufficient evidence to recommend routine food allergy testing before introducing highly allergenic foods to children at high risk of food allergy, such as those with pre-existing severe allergic disease or family history of food allergy. However, they indicated value in such evaluations for selected patients, such as those having a peanut allergy or evidence of

another underlying food allergy. For example, testing for tree nut allergy in a child with peanut allergy who has not yet been exposed to tree nuts would be appropriate. Similarly, consensus recommendations regarding introduction of peanut to high-risk infants with early-onset atopic disease, such as severe eczema or egg allergy, have suggested that infants might benefit from evaluation to diagnose any food allergy and to evaluate an infant for introduction of peanut (Fleischer et al., 2015).

A common misconception or concern among caregivers is that if one sibling develops a food allergy, other siblings also will become allergic. However, a recent study of a large cohort of families with food allergies found that only a small proportion of siblings are both sensitized (based on SPT and IgE) and clinically reactive to a food (based on history of typical symptoms of an allergic reaction to a food) (Gupta el al., 2016). In support of NIAID/NIH-supported Guidelines (Boyce et al., 2010), the authors concluded that testing for food allergy in siblings without a history of clinical reactivity appears to be unjustified and that screening may lead to negative consequences related to potential misdiagnosis and unnecessary avoidance of a food.

MECHANISMS OF FOOD ALLERGY IN RELATIONSHIP TO DIAGNOSTIC TESTING

Chapter 2 described specific food allergic disorders and pathophysiology. With regard to diagnostic testing, the pathophysiology of the disorder is relevant. For example, tests for food-specific IgE antibodies (i.e., SPT, sIgE, and CRD) are relevant for IgE-mediated disorders. These tests may sometimes be performed in disorders that are non-IgE-mediated to identify a potential for acute allergic reactions if the previously consumed food has been removed from the diet after having been a part of the diet (Liacouras et al., 2011), or to determine whether there has been a change in pathophysiology to an IgE-mediated disorder, as can occur with FPIES (Caubet et al., 2014). In contrast, the medical history, elimination diets, and physician-supervised OFCs are useful in all food allergic disorder evaluations.

CURRENTLY AVAILABLE MODALITIES ROUTINELY USED TO DIAGNOSE FOOD ALLERGY

A number of modalities have been recommended for diagnosing food allergy (Boyce et al., 2010; Muraro et al., 2014; Sampson et al., 2014). These are reviewed briefly in the following section with an emphasis on utility and limitations. The diagnostic tests discussed below are generally not used in isolation (see "General Diagnostic Algorithms").

Medical History and Physical Examination

A thorough medical history and physical examination are imperative in the diagnosis of food allergy (Boyce et al., 2010; Muraro et al., 2014). They can help to identify the likelihood of the diagnosis, and suggest whether the pathophysiology is IgE or non-IgE, which is important for test selection. The history and physical examination also identify potential triggers, which help to hone specific test selection. Importantly, details of the history may disclose alternative reasons for symptoms, other than a food allergy. For example, an acute allergic reaction attributed to a food may actually be triggered by other allergens, such as medications or insect stings. Numerous triggers, such as environmental irritants, change in temperature, and infections, can initiate atopic dermatitis flares. Chronic GI symptoms can be attributed to food but may actually be caused by medical conditions such as reflux or inflammatory bowel disease. In fact, a broad differential diagnosis exists to distinguish food allergy from other allergic disorders or from disorders that are not immunologically mediated and associated with food. Food poisoning or pharmacologic effects from food components may be masqueraders of a food allergy. Many patients confuse food allergy and food intolerance (Sicherer et al., 2012). Food intolerance is not mediated by the immune system, and is characterized by symptoms such as gas, bloating, and diarrhea in the case of lactose intolerance.

No evidence-based, standard series of questions has been developed for use in taking a medical history to evaluate a possible food allergy, although creating this type of question set is under study (Skypala et al., 2015). The clinical history should include possible eliciting allergens, the timing and chronicity of the ingestion and symptoms, symptom severity, reproducibility, risk factors, identification of foods that are tolerated, and coexisting medical and allergic problems. The use of structured questionnaires on symptoms, foods, and other background information may be beneficial. However, based on limited data, the predictive value of the clinical history for immediate symptoms, either alone or in combination with SPT or sIgE, ranges from 50 percent to 100 percent (Muraro et al., 2014). Nonetheless, the clinical history is central to provide reasoning (prior probability) applicable to additional test selection and interpretation on a patient-specific basis, as will be reviewed further below.

Elimination Diets

Elimination diets, with removal of one or a few specific foods, is considered useful in diagnosing food allergy, especially for disorders with chronic symptoms, such as eosinophilic esophagitis (EoE), atopic dermatitis, and allergic proctocolitis (Boyce et al., 2010; Muraro et al., 2014). A

diagnostic elimination diet is different from a treatment elimination diet, where an identified food allergen is removed from the diet as a form of therapy. When a properly performed diagnostic elimination diet does not ameliorate the symptoms, food allergy to the eliminated food(s) is unlikely. If elimination does result in amelioration of symptoms, re-administration of the food, for example during an OFC, may be needed to prove a cause-and-effect relationship. However, experts have recognized that for some disorders, such as FPIES, a successful elimination diet in combination with a convincing history may be sufficient for diagnosis (Boyce et al., 2010; Sampson et al., 2014). The rationale for this decision is based on the concern that the OFC may provoke significant morbidity and may be better reserved for evaluating later resolution of the disorder.

Determining which foods should be eliminated is based on medical history, allergy testing, and/or the epidemiology of the illness considering common triggers. The results of the elimination diet are monitored and evaluated over a pre-specified period, such as 2 to 4 weeks. There are many caveats regarding the interpretation of a diagnostic elimination diet because chronic symptoms may vary for reasons other than ones related to foods (e.g., eczema flaring due to infection). Studies evaluating their diagnostic value are lacking, and malnutrition resulting from prolonged elimination diets that exclude multiple foods is a concern (Boyce et al., 2010).

Skin Prick Tests

Guidelines recommend using SPTs for assistance in diagnosing IgE-mediated food allergies, but the test results alone are not considered sufficient for diagnosis (Boyce et al., 2010; Muraro et al., 2014; Sampson et al., 2014). The test can be done in any age group, although reactivity may be lower in infants and the elderly. The test involves puncturing the surface of the skin to introduce an allergen and evaluating the area for a wheal (small swelling) and flare (redness) response that can be measured. The test is applied to the forearm or back and the results of the allergen tests are compared with a negative saline and a positive histamine control test. The choice of tests is guided by the clinical history. Results are read at 15 or 20 minutes. A positive test correlates with the presence of specific IgE antibodies bound to the surface of cutaneous mast cells. The test is considered safe, because systemic allergic reactions are rare. In contrast, intradermal testing[1] with food is not recommended because it is overly sensitive and could induce systemic reactions (Boyce et al., 2010; Sampson et al., 2014).

[1] Intradermal test consist of delivering the food into the dermis, the skin layer underneath the epidermis (which is the upper skin layer where an SPT is performed). The dermis is, on most places of the human body, only a few mm thick.

Various caveats have been identified regarding SPTs. Trained health care personnel are needed because of a risk of serious allergic reactions. Variables that can affect outcomes include the device used to introduce the allergen (a number of devices are on the market), operator error, the extract (not standardized), the manner of recording and reporting test results, and the timing of day, age, and sex of the patient, the patient's use of any antihistamines, and anatomical site of testing (forearm versus back). Extracts may lack relevant allergens and testing using fresh extracts of food has been suggested for some circumstances, such as testing fruits and vegetables for pollen-food allergy syndrome. False negative tests (i.e., a skin test that is negative despite the fact that the patient experiences a reaction from ingesting the tested food) are possible, requiring caution if suspicion of allergy is high. The SPT reagents and methods have not been standardized. A systematic review and meta-analysis identified varying sensitivity and specificity according to the food evaluated, at a cut-off value of 3 mm wheal diameter in studies using OFCs as the diagnostic standard (Soares-Weiser et al., 2014) (see Table 4-1). Sensitivity is generally high, whereas specificity is lower.

These tests have a low positive predictive value for making a diagnosis of food allergy but high negative predictive value. Although a positive test is generally considered a wheal diameter equal to or greater than 3 mm, studies suggest that larger mean wheal diameters correlate with a higher likelihood of clinical reactivity (Pucar et al., 2001; Saarinen et al., 2001; Sporik et al., 2000; Verstege et al., 2005). A systematic review (Peters et al., 2012) evaluated studies reporting SPT wheal sizes that correspond to high predictive values for allergy (i.e., skin tests sizes above which allergy is almost certain). However, this review (Peters et al., 2012) noted that predictive values vary between studies, likely for numerous reasons including patient selection, food challenge protocols, reagents used for testing, and manner of reporting.

Food-Specific Serum IgE

Guidelines recommend using sIgE tests to identify foods that may provoke IgE-mediated reactions, but the test result alone is not considered sufficient for diagnosis (Boyce et al., 2010; Muraro et al., 2014; Sampson et al., 2014). The choice of tests is guided by the clinical history. Modern tests use fluorescence enzyme-labeled assays and have replaced radioallergosorbent tests (RAST). The term "RAST" is therefore antiquated. In the United States, the Food and Drug Administration (FDA) has approved three automated systems to measure sIgE. Each system has slightly different methods for test development, and results from one system are not directly comparable to others (Hamilton and Williams, 2010; Hamilton et

TABLE 4-1 Sensitivity and Specificity of SPT for Selected Foods

	Sensitivity	Specificity
Cow milk	88% (95% CI: 76%-94%)	68% (95% CI: 56%-77%)
Egg	92% (95% CI: 80%-97%)	58% (95% CI: 49%-67%)
Wheat	73% (95% CI: 56%-85%)	73% (95% CI: 48%-89%)
Soy	55% (95% CI: 33%-75%)	68% (95% CI: 52%-80%)
Peanut	95% (95% CI: 88%-98%)	61% (95% CI: 47%-74%)

NOTE: CI = confidence interval; SPT = skin prick test.
SOURCE: Soares-Weiser et al., 2014.

al., 2011; Wang et al., 2008). sIgE is not affected by antihistamine use, as SPTs are.

The sensitivity and specificity of SPT and sIgE were evaluated in a 2010 meta-analysis with a conclusion that neither test was statistically superior (Chafen et al., 2010). However, SPTs and sIgE tests do not always correlate, and so doing both tests can be advantageous, as can doing one followed by the other, if clinically warranted. A 2014 systematic review and meta-analysis (Soares-Weiser et al., 2014) considered mixed cut-off levels for sIgE but chose a >0.35 kU_A/L[2] value when possible. The sensitivities and specificities for various allergenic food are in Table 4-2.

Laboratory reports of undetectable sIgE concentrations occasionally occur in patients who go on to react to the food tested probably for reasons similar to the ones described above for SPT, so caution and additional evaluation is necessary in this circumstance if a history is highly suggestive of food allergy. In addition, different laboratories or test systems may report test results at different detection limits, for example <0.10 or <0.35 kU_A/L.

Studies have correlated increasing sIgE levels with increasing risk of clinical allergy. Some studies have calculated cut-off levels suggesting 95 percent predictive values for clinical reactivity (Boyce et al., 2010; Muraro et al., 2014; Sampson et al., 2014). Although 95 percent predictive cutoff values have been calculated in specific studies, these values vary between studies, likely due to differences in patient selection, age, clinical disorders evaluated, and many other factors. The predictive values of certain cut-offs are dependent on the frequency of the food allergy and may therefore differ widely in different populations.

[2] Kilounit allergen per liter.

TABLE 4-2 Sensitivity and Specificity of Food-Specific Serum IgE (sIgE) Test for Selected Foods

	Sensitivity	Specificity
Cow milk	87% (95% CI: 75%-94%)	48% (95% CI: 36%-59%)
Egg	93% (95% CI: 82%-98%)	49% (95% CI: 40%-58%)
Wheat	83% (95% CI: 69%-92%)	43% (95% CI: 20%-69%)
Soy	83% (95% CI: 64%-93%)	38% (95% CI: 24%-54%)
Peanut	96% (95% CI: 92%-98%)	59% (95% CI: 45%-72%)

NOTE: CI = confidence interval.
SOURCE: Soares-Weiser et al., 2014.

Component Resolved Diagnostics

CRD, sometimes referred to as molecular testing, involves measuring sIgE against individual allergenic food proteins. This testing is available in single allergen formats and microarray. The comparative utility of the two approaches has not been extensively studied. Commercially available microarray provides semi-quantitative results that correlate with single allergen formats and may be more susceptible to antibody competition due to lack of allergen excess (Canonica et al., 2013). The aim of the test is to increase specificity, based on the understanding that some food proteins may be more potent for causing symptoms than others within the same food. For example, relevant proteins may resist digestion, and IgE immune responses against such proteins may have a greater diagnostic value for systemic allergy than immune responses against more labile proteins that degrade easily and are not systemically absorbed. The AAAAI Guidelines indicate that CRD can be considered for diagnosis, but is not routinely recommended because clinical utility is not fully elucidated (Sampson et al., 2014). Nonetheless, its utility in certain clinical scenarios is recognized. The EAACI Guidelines (Muraro et al., 2014) indicate that the test is promising and broadly studied, but that evidence from additional well-designed randomized controlled trials on the diagnostic test accuracy are required to assess its diagnostic value. A World Allergy Organization expert panel report suggests these tests as a third line approach following clinical history and extract-based testing, but that they may be included in second line testing for experienced users (Canonica et al., 2013). When SPT and sIgE are inconclusive, the EAACI Guidelines (Muraro et al., 2014) suggest that CRD, if available, provides additional information. The *Japanese Guideline for Food Allergy* (Urisu et al., 2014) describes advantages of using CRD for peanut, soy, and wheat allergies.

An accumulating number of studies have evaluated CRD for a variety

of foods; the best studied is CRD for peanut allergy. A systematic review (Klemans et al., 2015) found that sIgE testing to Ara h 2 had diagnostic superiority to other peanut protein components and to SPT and peanut-specific IgE using whole peanut extracts. The studies were primarily pediatric cohorts (21 of 22), and authors concluded that Ara h 2 testing should replace the other tests in clinical practice, especially in children. Although some disagreement may exist, various studies have determined that increasing levels of IgE against Ara h 2 correlates with risk of clinical reactivity (undetectable Ara h 2 does not exclude peanut allergy). Sensitivity and specificity of the test varies among studies, similar to the limitations described for sIgE and SPT, and some studies suggest geographic differences in correlation to clinical reactivity to different proteins (Agabriel et al., 2014; Ballmer-Weber et al., 2015; Beyer et al., 2015; Ebisawa et al., 2012; Eller and Bindslev-Jensen, 2013; Keet et al., 2013; Klemans et al., 2015; Kukkonen et al., 2015; Lieberman et al., 2013; Lopes de Oliveira et al., 2013). If sensitization to peanut is solely caused by Ara h 8 (the birch pollen–related protein in peanut) in regions with birch pollen exposure, systemic clinical allergy is unlikely (Asarnoj et al., 2012).

Numerous other foods have been less comprehensively evaluated by CRD. Sensitization to the hazelnut proteins Cor a 9 and Cor a 14 are associated with higher risk of food allergy to hazelnut and provide better diagnostic utility than the extract tests or other protein components (Beyer et al., 2015; Faber et al., 2014; Kattan et al., 2014; Masthoff et al., 2013). The soy proteins Gly m 4 and Gly m 5 (Berneder et al., 2013; Kattan and Sampson, 2015) appear relevant in soy allergy diagnostics. Literature on the utility of CRD testing on a number of foods is growing, including wheat, cashew, milk, egg, shrimp, carrot, and celery (Muraro et al., 2014; Savvatianos et al., 2015; Soares-Weiser et al., 2014). Sensitization to the cashew nut (Ana o 3, a protein belonging to the 2S albumin family of proteins) is highly predictive of cashew and pistachio allergy in Greek children (Savvatianos et al., 2015). Fruits typically induce mild oral allergic symptoms related to oral allergy syndrome induced by labile pollen-homologous fruit proteins. If IgE binds to stable fruit proteins, such as lipid transfer proteins, it may be associated with more severe reactions, but literature to characterize the role of component allergen testing in fruit and vegetable allergy is limited, and current studies show variable results (Lopez-Matas et al., 2015; Novembre et al., 2012; Tolkki et al., 2013; van Winkle and Chang, 2014; Vieira et al., 2014).

In summary, CRD is an emerging testing methodology in widespread use for select foods. They provide additional insights on diagnosis in specific circumstances. More studies are needed, however, to draw specific conclusions about their diagnostic utility. Component testing for peanut should be used when indicated (Dang et al., 2012; Klemans et al., 2015).

Like judicious use of the medical history, SPT and sIgE, CRD testing provides clinically useful results and can reduce the need for OFCs.

Oral Food Challenges

The OFC is a feeding test that typically involves a gradual, medically-supervised ingestion of increasingly larger doses of the food being tested as a possible food allergen. Guidelines recommend using OFCs to diagnose food allergy (Boyce et al., 2010; Muraro et al., 2014; Sampson et al., 2014). Most OFCs are conducted with the food in its natural form; this is called an open OFC. Oral food challenges also can be performed in a single-blind protocol with the food masked from the patient's perspective so less patient bias occurs because of anxiety. Bias is a concern with OFC because anticipation of a reaction can result in subjective symptoms (e.g., abdominal pain, nausea, or eczema flare) and possibly objective ones (e.g. hives). To address this concern a double-blind, placebo-controlled oral food challenge (DBPCOFC) can be conducted. This challenge, which is considered the "gold standard" for diagnosis of food allergy, involves masking the tested allergen and feeding it or indistinguishable placebo randomly without the patient or observer knowing if the allergen or placebo is being tested. However, the double-blind challenge is time-consuming and expensive, and is used more often for research, whereas open food challenges are routinely used in clinical settings. An open or single-blind OFC is considered reliable if no symptoms occur. An open feeding of a meal-sized portion of the food prepared in a usual fashion (e.g., scrambled egg, cooked fish) is also typically performed to confirm tolerance following a negative DBPCOFC with a smaller portion. If only subjective symptoms occur during a food challenge, a false impression of allergy is possible. If objective symptoms occur (e.g., urticaria, angioedema, or anaphylaxis) and the result correlates with medical history and laboratory tests, then the diagnosis is supported. Ambiguous results from an open or single-blind OFC can be evaluated by a DBPCOFC. This challenge also may be considered when patients have primary symptoms of chronic eczema or suspected anxiety.

The OFC is generally indicated to demonstrate allergy or tolerance when the medical history and supporting tests are not sufficient to make a conclusion. This may include circumstances such as a suspected allergy with ambiguous test results, or with the expectation that a food allergy has resolved. The OFC also may be used for individuals with ongoing allergy to evaluate thresholds or response to therapy. As the generally accepted gold standard, the test is highly specific. However, patients uncommonly experience reactions on subsequent ingestion despite tolerance during the test; the rate of this occurrence may vary by dosing regimen (Caffarelli and Petroccione, 2001; Miceli Sopo et al., 2016; Niggemann et al., 2012).

The OFC is useful for evaluating food allergy whatever the underlying pathophysiology or time course of symptoms, and can be used for all age groups. The test carries a risk of allergic reactions and anaphylaxis, and so caution, content monitoring, experienced personnel and equipment, and medications for managing reactions are required. Feeding a small amount of the suspected allergen and gradually increasing the amount mitigates some risk. The test is stopped at the judgment of the supervising health professional due to the onset of symptoms or at the request of the patient. Immediate symptoms typically occur within 2 hours after ingestion, but increases in atopic dermatitis symptoms may occur over hours or days. Rigorous objective criteria for determining tolerance or reactivity, consistent application of procedures, and good record keeping and documentation are paramount. No universally accepted manner of dosing, scoring, and monitoring the OFC procedure has been established, and potential dosing regimens have not been compared prospectively. Various approaches have been suggested, and issues such as indications and contraindications have been summarized (Sampson et al., 2012, 2014). Standardized dosing protocols have been published but not validated (Muraro et al., 2014; Sampson et al., 2012, 2014). For infants, open OFCs with objective scoring criteria are generally sufficient to make or refute a diagnosis of food allergy. Application of the OFC to infants, and additional limitations of the test are additionally reviewed in Chapter 5, Methodological Limitations.

The OFC is usually undertaken with the goal of the patient ingesting an age-appropriate, meal-size portion of the food prepared in a manner that will be ingested in the future. Processing and cooking methods can alter its allergenic properties. For example baked egg or milk products are less allergenic than raw forms. The matrix in which the tested allergen is mixed also can affect outcomes, as absorption rates may vary. For example, fatty foods are absorbed more slowly than other foods (Grimshaw et al., 2003). Although foods could be freeze-dried and placed into opaque capsules to mask the taste as well as early signs of reaction involving the oral mucosa, this approach is not in favor due to alteration of proteins and lack of control of release of the food from the capsules. The initial dose is generally selected to be less than a likely threshold for a reaction, or significant reaction (e.g., less than 3 mg) if the patient is suspected of being highly sensitive (Rolinck-Werninghaus et al., 2012). If a threshold-determining OFC is being undertaken, a lower starting dose may be used. Doses are given at 15- to 30-minute intervals although adjustments can be made. If symptoms occur after several doses, it cannot be concluded that the "last dose" independently triggered a reaction, as symptoms could be caused by prior doses or a cumulative effect (Blumchen et al., 2014). Also, escalating dose OFCs are similar to certain immunotherapy protocols and may therefore result in a reaction at a higher dose than would be the case if this were

the first and only dose. The time of testing can vary but is typically 3 to 8 hours depending on the doses, symptoms, and challenge format. The test may be formatted differently for non-IgE-mediated food allergies, such as FPIES, where the feeding may be dosed more rapidly and the expectation of reaction is delayed, occurring approximately 2 hours later. The test is generally undertaken when the food has been excluded from the diet. In the case of suspected chronic symptoms, the time of exclusion is typically 2 to 8 weeks to obtain a baseline.

The risk of OFC tests includes an anaphylactic reaction. On the other hand, the test might have nutritional (when the food can be added back to the diet) social, emotional, and educational (learning which trigger foods must be avoided, providing safety, and learning about reaction characteristics, treatment, and threshold) benefits. Some evidence suggests that the OFC procedure does not increase long-term post-study anxiety and can improve quality of life whether the food is tolerated or not (Franxman et al., 2015; Knibb et al., 2012). Guidelines promoting the OFC as a recommended procedure use terminology of "positive" challenge test outcome to denote that the test elicited symptoms and a "negative" test outcome to indicate the food was tolerated. (Boyce et al., 2010; Muraro et al., 2014; Sampson et al., 2014). This use of terms is deliberate to avoid terms such as "passed" and "failed" as outcomes, which carry negative implications of the patient having "failed" in some manner.

Patients may avoid having the procedure due to fear, disinterest in the food offered, or misunderstanding about risks or odds of tolerating the food. They might ingest the food on their own, against medical advice to undergo the procedure before reintroducing the food into the diet plan (Davis et al., 2015). Physicians may not offer the procedure due to patient safety risk, time constraints, lack of trained personnel, and poor reimbursement (Pongracic et al., 2012). Failure to reintroduce the food into the routine diet after tolerating the OFC has been noted, but the reasons not fully explored (Miceli Sopo et al., 2016; van Erp et al., 2014). Considering that OFC is often required to determine a definitive diagnosis of food allergy, it is clearly underused.

MODALITIES NOT RECOMMENDED FOR ROUTINE USE

Atopy Patch Test

The atopy patch test (APT) is performed in a manner similar to patch testing that is routinely used to evaluate allergic contact dermatitis, except that foods are used. The food, presented as a fresh extract or powder, is generally placed under an aluminum disc on the skin for 48 hours then removed and with the final test result determined at 72 hours after applica-

tion. Current guidelines do not recommend the APT for the routine diagnosis of food allergies (Boyce et al., 2010; Muraro et al., 2014; Sampson et al., 2014), based partly on a lack of standardized reagents, methods, and interpretation of results. The APT may have utility in evaluating non-IgE-mediated allergy in the context of atopic dermatitis and EoE. Its utility in the diagnosis of FPIES has not been substantiated (Jarvinen et al., 2012; Ruffner et al., 2013).

In a systematic review and meta-analysis, three studies were identified that evaluated the diagnostic utility of the milk APT. Sensitivity was 53 percent (95% CI: 33%-72%) and specificity 88 percent (95% CI: 76%-95%) (Soares-Weiser et al., 2014). It is notable that despite a rather large number of studies, few meet criteria for meta-analysis (Isolauri and Turjanmaa, 1996; Keskin et al., 2005; Roehr et al., 2001). Several studies suggest poor utility of the APT (Alves et al., 2015; Caglayan Sozmen et al., 2015; Celakovska et al., 2010; Mehl et al., 2006). Other studies suggest some utility of APT for milk, especially for gastrointestinal symptoms or dermatitis (Boonyaviwat et al., 2015; Chung et al., 2010; Levy et al., 2012; Mowszet et al., 2014; Nocerino et al., 2013; Yang et al., 2014). The relevance of APT for EoE remains uncertain, but some studies suggest utility (Chadha et al., 2014; Rodriguez-Sanchez et al., 2014; Spergel et al., 2012). An updated expert panel report on EoE (Liacouras et al., 2011) summarized the results from seven studies, with negative predictive values of more than 90 percent and only 50 percent for milk, and variable positive predictive values. They suggested the APT (along with SPT and sIgE) can be used to identify foods associated with EoE, but alone the test is not sufficient to make a diagnosis of food-driven disease.

Total IgE

Guidelines recommend against the routine measurement of total IgE to diagnose food allergy (Boyce et al., 2010; Sampson et al., 2014). It is recognized that atopic persons may have elevated serum total IgE, but this does not provide guidance regarding the risk of specific food allergies. However, there is a notion that total IgE concentration may relate to sIgE (Federly et al., 2013) and that very high concentration of total IgE may influence the clinical relevance of sIgE for diagnostic purposes (Muraro et al., 2014).

Theoretically, the influence of total IgE on the clinical relevance of sIgE includes assay and in vivo effects due to competition for binding to allergen and effector cells (Hamilton and Williams, 2010). The FDA recommends that very low concentrations of sIgE antibodies should be evaluated with caution when total IgE values are above 1,000 kU/L (Merkel et al., 2015) (http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/TipsandArticlesonDeviceSafety/ucm109367.htm [accessed August 30, 2016]). One

of the few clinical studies (Mehl et al., 2005) evaluated 992 controlled OFCs performed in 501 children, looking at the utility of sIgE:total IgE ratio and found a correlation with challenge outcomes for milk, egg, and wheat, but not for soy. The diagnostic value of the ratio was not better than for sIgE alone. In contrast, another study looking at the ratio evaluated 195 OFCs among 161 children, and found that the ratio was more informative than sIgE alone for peanut, tree nuts, seeds, and shellfish but not milk, egg, wheat, or soy (Gupta et al., 2014). In contrast, the component specific to total IgE ratio did not improve peanut or hazelnut diagnosis (Grabenhenrich et al., 2016).

Although the NIAID/NIH-supported Guidelines and AAAAI Guidelines concluded that total IgE is not recommended for routine use in diagnosis (Boyce et al., 2010; Sampson et al., 2014), the EAACI Guidelines based on low-level evidence and expert opinion suggested that total IGE concentration may be useful in patients with severe eczema because a very high total IgE suggests that positive sIgE should be interpreted with care, as possibly representing asymptomatic sensitization (Muraro et al., 2014).

Basophil Activation Test

Basophils are allergy effector cells found in whole blood. Basophils degranulate upon cross-linking of sIgE, which is bound to the high affinity IgE cell surface receptors, and release mediators such as histamine. The granule marker, CD63, or CD203c, an activation marker, can be measured by flow cytometry and provide a measure of basophil activation. The basophil activation test (BAT) is conducted by exposing the basophil cells to various concentrations of the allergen to be tested, either an extract or individual component proteins in the test tube. The readout is the number of cells responding, or the concentration of allergen at which 50 percent of the cells respond. About 10 percent of people are BAT nonresponders, even though they are allergic and have positive skin tests. The test is a functional assay akin to a provocation test, such as a SPT.

Guidelines suggest not using the BAT clinically on the grounds that it is nonstandardized, but recognize its use as a research tool (Boyce et al., 2010). A position paper from a task force of the EAACI reviewed the BAT and made a number of recommendations in favor of using the test for diagnosis and monitoring of food allergy, and a recommendation to pursue standardization to make it available in diagnostic laboratories (Hoffmann et al., 2015). The EAACI task force evaluated diagnostic studies on peanut (N=4), hazelnut (N=2), peach (N=3), wheat (N=4), milk (N=2), egg (N=2), shellfish (N=1), and pollen-associated food allergy syndrome (PFAS) (N=5). The reported sensitivity ranged from 77 to 98 percent and specificity from 75 to 100 percent. In some studies BAT was more accurate than SPT or

sIgE. In a series of peanut allergy studies from one research group, which included a validation substudy, the BAT significantly improved diagnosis over SPT and sIgE, reducing the number of OFCs required for diagnosis (Santos et al., 2014) and provided predictive value for severity and threshold of reactivity (Santos et al., 2015). The position paper also reviewed the use of BAT to predict development of tolerance in food allergic children (N=4 studies), and to monitor responses to immunomodulatory therapy (N=11 studies). Overall, while the test is not available for widespread use, the potential utility is recognized and will require additional validation and standardization.

NONSTANDARDIZED AND UNPROVEN PROCEDURES

A number of tests have been referred to as "unproven," "unconventional," or "nonstandardized and unproven" by guidelines and are not recommended for food allergy diagnosis (Boyce et al., 2010; Muraro et al., 2014; Sampson et al., 2014). These tests or procedures include: allergen-specific IgA, IgG or IgG_4, provocation neutralization, immune complexes, HLA screening, lymphocyte stimulation, facial thermography, gastric juice analysis, endoscopic allergen provocation, hair analysis, applied kinesiology, cytotoxic assays, electrodermal testing, mediator release assays, bioresonance, and iridology. The rationale for not recommending these tests or procedures is the lack of evidence demonstrating the value of each method in diagnosis of food allergy. There is a concern that use of these methods may result in false positive or false negative diagnoses that may lead to unnecessary dietary restriction or may delay appropriate diagnostic evaluations.

For example, IgG_4 testing against foods as a diagnostic modality was reviewed in the 2008 EAACI Task Force report (Stapel et al., 2008). Many serum samples have positive IgG_4 results without corresponding clinical symptoms. The report noted a lack of convincing evidence for histamine-releasing properties of IgG_4, and a lack of controlled studies to determine diagnostic value. Conversely, evidence suggests that food-specific IgG_4 reflects exposure, and may indicate a state of immunological tolerance. The task force concluded that testing of IgG_4 to foods is irrelevant to the laboratory work-up for diagnosis of food allergy. It should be noted, however, that food-specific IgG and IgG_4 responses, when monitored during immune therapy with allergen exposure, is associated with clinical improvement in threshold. Thus, IgG and IgG_4 may be markers or mechanisms of desensitization and may have some role in diagnosis, especially during treatments, when considered along with other measurements, such as sIgE. Studies have begun to evaluate the diagnostic or prognostic potential of the IgE/IgG ratio or antibody classes. More studies are needed to validate these approaches,

as currently available data are conflicting (Ahrens et al., 2010; Caubet et al., 2012; Dannaeus and Inganas, 1981; Okamoto et al., 2012; Savilahti et al., 2012, 2014; Sverremark-Ekström et al., 2012; Tomicic et al., 2009).

PREDICTION OF SEVERITY OR THRESHOLD OF REACTIONS

Severity of an allergy is typically defined by symptoms triggered during an allergic reaction, and threshold of exposure for a reaction refers to the dose of allergen that triggers symptoms. There is strong interest in, and need for, a test for severity or threshold. Dosing during OFC is generally stopped before severe symptoms, limiting the ability of this study design to predict severe reactions (Wainstein et al., 2010). No comprehensive reviews have been published on the prediction of severity or on simple tests to diagnose the severity of a reaction. One might surmise that increasing sIgE concentrations correlate with severity because they correlate with risk of clinical reactivity. Although a number of studies suggest this correlation, it has not been universally substantiated (Benhamou et al., 2008; Blumchen et al., 2014; Clark and Ewan, 2003; Neuman-Sunshine et al., 2012; Rolinck-Werninghaus et al., 2012; Summers et al., 2008; Ta et al., 2011; van der Zee et al., 2011; Wainstein et al., 2010). In addition, CRD could be considered a means to possibly diagnose severity of a reaction because, for example, isolated binding to Ara h 8 is associated with no or mild allergy (oral-pharyngeal symptoms, related to PFAS) while binding to Ara h 2 is associated with systemic peanut allergy. However, on an individual patient or research study participant basis, degree of binding to Ara h 2 does not appear to accurately predict severity (Astier et al., 2006; Klemans et al., 2013a,b; Leo et al., 2015; Peeters et al., 2007). Studies have suggested that modalities such as BAT (Homsak et al., 2013; Santos et al., 2015; Song et al., 2015) or analysis of epitope[3] binding patterns (Flinterman et al., 2008; Shreffler et al., 2004) may hold promise for determining severity. Disparities in prediction of severity based on testing may have many methodological reasons, but on an individual basis, outside of studies that control for such variables, the tests may not or do not currently consider specific patient-circumstance variables, such as whether the individual with food allergy has asthma, is currently ill, exercising, or experiencing other factors that may cause increased sensitivity (i.e., eliciting factors, other factors regarding physiologic responses) (Summers et al., 2008; Vadas et al., 2008). A recent paper describes the lack of predictability, perceptions about severity, and the types of factors that may affect the severity of a reaction, including those related to a person's behaviors (e.g., exercise) and other factors (e.g., infections) (Turner et al., 2016).

[3] Epitopes are segments of a protein that are recognized by antibodies.

PROGNOSIS AND DISEASE MONITORING

The rate of allergy resolution varies based on the food, patient's age, pathophysiology of the allergy, and other factors (Boyce et al., 2010; Sampson et al., 2014). Table 4-3 summarizes resolution rates of common food allergies (Savage et al., 2016). Most children with allergies to cow milk, egg, soy, and wheat will develop tolerance by adulthood, whereas resolution of peanut, tree nut, and seafood allergies is less likely (less than or equal to 20 percent) (Boyce et al., 2010; Sampson et al., 2014). Adults with food allergies may have experienced persistence from childhood or may have a new onset in adulthood, and these allergies tend to persist. The natural course of food allergy is not known for most foods. Periodic re-evaluation with testing is recommended and can be individualized based on patient characteristics, the food, and underlying food allergic disorder (Boyce et al., 2010; Sampson et al., 2014). In general, periodic re-evaluation is undertaken with history, SPT, sIgE, and OFC depending on the specific results of each test and history. This testing might be performed more frequently (e.g., yearly) for a young child with food allergies, and less frequently (e.g., every few years) for an adult with allergies to foods such as peanut, tree nuts, and seafood.

Unfortunately, no simple accurate prognostic tests exist. Having tests that could be performed early in life that reflect prognosis would be helpful in selecting the best periodicity of retesting, providing anticipatory guidance, and identifying which patients might benefit from interventional treatments (as these become available). Studies have suggested that higher compared to lower concentrations of sIgE or skin test size are a poor prognostic marker (Ho et al., 2008; Keet et al., 2009; Peters et al., 2013, 2015; Savage et al., 2007, 2010; Sicherer et al., 2014; Skripak et al., 2007; Wood et al., 2013). However, additional clinical factors are associated with prognosis, including severity of symptoms, threshold dose, family history, change in sIgE over time, ability to tolerate milk or egg in baked goods (for cow milk and egg allergy), comorbid asthma, and comorbid atopic dermatitis (including severity), and other factors (Cantani and Micera, 2004; Elizur et al., 2012; Ho et al., 2008; Peters et al., 2013, 2014, 2015; Savage et al., 2007; Shek et al., 2004; Sicherer et al., 2014; Skripak et al., 2007; Wood et al., 2013). Studies have used multivariate analysis to create predictive models using the variables with the greatest impact (especially sIgE levels), but validation is needed (Sicherer et al., 2014; Wood et al., 2013). Studies using newer in vitro tests, such as CRD and BAT, have not been extensively applied to develop prognostic algorithms. A 2013 systematic search and review on this topic identified 26 articles, noting heterogeneity and biases in the studies, and concluded that population-based, prospective studies are needed that use OFC—without bias of test results—to diagnose food allergy

TABLE 4-3 Natural Course of Food Allergy

Food	Resolution Likely
Milk, egg, wheat, soy	Early-late childhood (~>70-80%)
Peanut	Childhood (~20%)
Tree nut	Childhood (~10%)
Fish, shellfish, seeds	Less certain but likely similar to tree nuts

SOURCE: Savage et al., 2016.

at baseline and then to follow up to develop thresholds for SPT and sIgE that predict the course of food allergy (Peters et al., 2013). Little is known about food allergy prognosis after diagnosis in adulthood.

Many of the modalities discussed here also have been evaluated during treatment studies, to identify markers that may indicate desensitization or tolerance of food(s) to which individuals are initially allergic, including sIgE, SPT, CRD, BAT, sIgE/total IgE ratio, $sIgG_4$, and ratio of sIgE to $sIgG_4$ (Nozawa et al., 2014; Savilahti et al., 2014; Thyagarajan et al., 2012; Vickery et al., 2013, 2014). Additional markers have been followed, including cytokines, regulatory T cells, T cell number and function, and B cell activity (Bedoret et al., 2012; Hoh et al., 2016; Syed et al., 2014; Varshney et al., 2011). However, biomarkers to confirm desensitization and tolerance without OFC remain to be found.

GENERAL DIAGNOSTIC ALGORITHMS

Guidelines and reviews have suggested general algorithms (i.e., panels) for diagnostic approaches (Greenhawt et al., 2013; Muraro et al., 2014; Sicherer, 2002; Urisu et al., 2014; Venter et al., 2013). Approaches typically begin with a medical history to identify the nature of the symptoms (whether likely reflecting food allergy or another disorder), the pathophysiology (IgE mediated or not), and the potential food triggers. Testing based on the initial impressions is conducted and interpreted based on the results of the history and suspected foods and related pathophysiology. This may include tests for IgE, elimination diets and/or OFCs, depending on the circumstances.

Different algorithms may fit specific disorders. For example, evaluation of food allergy in acute anaphylaxis, where symptoms come on quickly and are associated with sIgE antibodies, differs from evaluation of the role of food allergy in atopic dermatitis or EoE (Greenhawt et al., 2013; Sicherer,

2002; Urisu et al., 2014; Venter et al., 2013). No overarching approach has been universally accepted. However, because the sensitivity and specificity of individual tests are generally not 100 percent, using pretest probability obtained from one test (e.g., the medical history) is recognized as beneficial for interpreting the post-test probability of allergy following a second test (Muraro et al., 2014). Indiscriminately performing multiple tests is not recommended (Boyce et al., 2010), but a case can be made for using more than one test when additional diagnostic value may be obtained. Specific algorithms may, for example, consider diagnostic values of several tests performed in series to improve accuracy (Ben-Shoshan et al., 2010; Dang et al., 2012). Additionally, it may be possible to isolate a number of factors from the medical history and simple diagnostic tests to estimate the risk of an allergy, using a standardized approach, but this also needs validation (DunnGalvin et al., 2011). In summary, although no evidence-based, universally accepted overarching diagnostic algorithm exists, guidelines promote step-wise evaluations rather than solely depending upon single tests to conclude a diagnosis of food allergy in children (Boyce et al., 2010; Muraro et al., 2014; Sampson et al., 2014). Information on adults is limited.

TESTING FOR SPECIFIC DISEASE STATES OTHER THAN ANAPHYLAXIS AND ATOPIC DERMATITIS

As indicated above, diagnostic approaches may vary depending upon the pathophysiology, epidemiology, and clinical characteristics of particular food-allergic disorders (Greenhawt et al., 2013; Muraro et al., 2014; Sicherer, 2002; Urisu et al., 2014; Venter et al., 2013).

Food Protein–Induced Enterocolitis Syndrome

FPIES and food protein-induced allergic proctocolitis are non-IgE-mediated disorders that lack current means of simple laboratory testing to identify causal foods or to confirm the diagnosis. Guidelines suggest using the medical history, resolution of symptoms during dietary elimination, and recurrence of symptoms upon exposure; for example, during a food challenge (although not typically necessary for proctocolitis), as a means of diagnosis (Boyce et al., 2010; Muraro et al., 2014; Sampson et al., 2014). For FPIES, guidelines indicate that factors in the history may be so suggestive of the diagnosis that an OFC is not needed. For example, a patient may have experienced repeated reactions with typical symptoms or severe symptoms (Boyce et al., 2010; Sampson et al., 2014). It also is recognized that a subset of children may develop IgE antibodies (especially for cow milk) signifying prolonged course and possibly anaphylactic symptoms that can warrant periodic testing before using an OFC to evaluate for resolution

(Caubet et al., 2014; Sampson et al., 2014). The APT does not appear to be useful for diagnosing FPIES (Jarvinen et al., 2012; Ruffner et al., 2013). Endoscopy and biopsies are not typically needed for diagnosis (Boyce et al., 2010; Muraro et al., 2014). The OFC for evaluation of FPIES could induce severe symptoms (e.g., hypotension, methemoglobinemia [unexpected], acidemia) and requires caution.

Eosinophilic Gastrointestinal Diseases

Eosinophilic gastrointestinal diseases may have both a cellular and IgE antibody component. No specific diagnostic strategies other than elimination and OFC have been proposed for identifying the food-specific triggers in eosinophilic gastroenteritis, and no biomarkers to identify responses are currently available, making repeated endoscopy/biopsy necessary to identify responses to treatment. Guidelines suggest considering tests for food-specific IgE and APT to help identify causal foods, specifically for evaluating EoE (Boyce et al., 2010; Sampson et al., 2014). Testing for food-specific sIgE also derives from the observation that 15 to 43 percent of patients are diagnosed with typical IgE-mediated food allergies and up to 80 percent are sensitized to aeroallergens (Muraro et al., 2014). However, these tests are not to be depended on to identify causal foods, and the diagnosis of EoE also requires a trial of proton pump inhibitors, and evaluations to identify characteristic biopsy results for diagnosis (and to exclude other diagnoses) (Boyce et al., 2010; Muraro et al., 2014; Sampson et al., 2014). Ultimately, trial elimination diets are needed, with follow-up biopsy to assess resolution of inflammation.

Pollen-Associated Food Allergy Syndrome

The best approaches for diagnostic testing for PFAS have not been systematically evaluated. A number of recommendations have been published (Sampson et al., 2014). The detailed medical history is important because the diagnosis should be considered in patients experiencing limited oropharyngeal symptoms when eating foods (raw) that have cross-reacting proteins with pollens; it may be noted that symptoms are increased during and just following the pollen season. Testing for sIgE to pollens is suggested, and performing SPT with fresh food (sometimes termed "prick-prick" testing which may be performed by pricking the raw fruit or some of its extracted juice with the skin test device and then pricking the skin) can also be used to aid diagnosis (Begin et al., 2011; Vlieg-Boerstra et al., 2013). Such testing is not standardized. The use of commercial extracts may be less useful because the responsible proteins are labile and may not be present. It is not understood why only some persons with pollen aller-

gies experience reactions, or why people with similar pollen allergies may have different patterns of reactions to different fruits and vegetables. Simple diagnostic tests lack the ability to differentiate or predict these variations (Crespo et al., 2002; Pastorello et al., 1994; Rodriguez et al., 2000; Ta et al., 2015). Variations in reactivity are noted even among cultivars of the same fruit, or with ripening or storage (Carnes et al., 2006; Sancho et al., 2006). Systemic reactions to the same foods that trigger PFAS can occur. The reason for systemic reactions could be explained by having reactivity to a higher dose of the labile allergen, a greater sensitivity to that allergen (possibly varying with cofactors such as exercise or illness), or having an immune response to proteins that are not labile (e.g., lipid transfer proteins) (Cudowska et al., 2008; Gomez et al., 2014; Pascal et al., 2012; Zuidmeer and van Ree, 2007). It is possible that CRD or BAT represent a means to evaluate this difference in risk, but studies have had mixed results (Asero, 2014; Ebo et al., 2010; Erdmann et al., 2005; Gamboa et al., 2009; Guhsl et al., 2015; Hofmann et al., 2013; Tolkki et al., 2013).

COMMON PITFALLS AND MISCONCEPTIONS IN DIAGNOSTICS

As indicated previously, diagnostic and monitoring tests have a variety of limitations that, if not appreciated, can result in over- or underdiagnosing food allergy in patients. Table 4-4 summarizes common misconceptions.

Sensitization Is Not Diagnostic of Clinical Allergy

Key among potential pitfalls is the fact that sensitization (demonstrated by a positive test) is not a sole indication for a diagnosis. Testing with panels (i.e., preselected lists) of foods without a consideration of the medical history can result in unnecessary concerns and is not recommended (Bernstein et al., 2008; Cox et al., 2008; Sampson et al., 2014; Sicherer and Wood, 2012). Physicians may not appreciate this test limitation (Gupta et al., 2010) and, as reviewed above, patients and clinicians may misinterpret test results with low values versus higher values as reflecting severity of the allergy.

Clinically Relevant and Nonrelevant Cross Reactivity

Another potential pitfall is recognizing the difference between cross reactivity identified on testing (sIgE or SPT) that may or may not be clinically relevant (Sampson et al., 2014; Sicherer, 2001). When food allergens share sufficient homology, antibodies may be detected to multiple allergen proteins, but the clinical relevance of the test finding can vary. For example, a large proportion of individuals with peanut allergy will test positive to

TABLE 4-4 Common Misconceptions About Food Allergy and Testing

Misconception	Reality
It is possible to do a comprehensive test that finds which foods should be avoided to stop the symptoms.	No comprehensive test exists to identify all food allergies. Diagnosis requires a careful medical history and thoughtful selection of tests. Doing evaluative "panels" of preselected tests/foods can be misleading.
A positive skin or blood test identifies an allergy.	Many people "test positive" to foods that they can eat without any symptoms. For example, about 8 percent of people test positive to peanut, but can eat it without symptoms.
A negative allergy test means that a food is safe to eat.	Although this is often true, with some types of food allergies, or circumstances, the test can be negative despite a true allergy.
The level on a blood test or the size of a skin test indicates the severity of a reaction.	The severity of a reaction is not well reflected by the tests, because underlying asthma, individual sensitivity, and other factors, such as how much of the allergen is eaten, may influence severity. However, the stronger a positive test, the more likely a true allergy exists.
Allergy to one type of food means the person will have allergy to related foods.	This is not a general rule. For example, allergy to peanut, a bean, does not necessarily mean the person will have allergy to other beans.
Food allergy and food intolerance are the same.	A food can make a person ill in many ways. Allergic reactions involve the immune system and can be severe or fatal. Intolerance, such as lactose intolerance, does not involve the immune system and is not life-threatening.

other legumes, such as soy (up to 79 percent), but only a small proportion of patients (up to 5 percent) will experience allergic reactions to them. Although the test rate of cross reactivity is higher than the observed rate of clinical cross reactivity, studies on this topic are limited and likely reflect results that vary depending upon methodology, patient selection, and geographic influences, including pollen sensitization. Estimated rates of clinical cross reactivity among crustacean shellfish is 38 percent, among fish 30 to 75 percent, among tree nuts 12 to 37 percent (varies depending on the nuts; for example, walnut and pecan are more similar, cashew and pistachio are more similar), and between wheat and other grains 21 percent. An OFC is often needed to confirm tolerance if a potentially cross reactive food has not

already been tolerated in the diet. A serious pitfall can occur if a food tests positive in panels (and the patient removes it from the diet) when tolerance has already been proven by inclusion of the food in the diet.

Delayed Anaphylaxis Associated with Mammalian Meats

Although most pitfalls in food allergy diagnosis may occur from overdiagnosis related to misunderstanding of pathophysiology and test utility, a special case of under- or misdiagnosis involves mammalian meat allergy (beef, pork, lamb) attributed to sIgE antibodies against a sugar moiety, galactose-alpha-1,3-galactose (alpha-gal) (Commins et al., 2011, 2014; Hamsten et al., 2013; Kennedy et al., 2013). The syndrome is likely associated with initial sensitization to allergen in tick bites. In contrast to typical food anaphylaxis that occurs within minutes to 2 hours following ingestion of the trigger food, alpha-gal-related reactions to mammalian meat, with the same allergic symptoms, occur 3 to 6 hours after ingestion. Skin testing to the trigger foods may not be strongly positive but in vitro sIgE testing to alpha-gal is commercially available and can be used to confirm the diagnosis. The reason for the delay in onset of anaphylactic symptoms is not known with certainty.

ROLE OF ELICITING FACTORS

Eliciting factors, also referred to as cofactors and augmentation factors, are circumstances or ingestants that can alter threshold or severity of an allergy, resulting in more serious reactions or allowing clinical expression of a food allergic response to an otherwise tolerated food (Boyce et al., 2010; Muraro et al., 2014; Sampson et al., 2014). These factors can include exercise, nonsteroidal anti-inflammatory drug (NSAID) agents, alcohol, body temperature, menstruation, infections, stress, and antacid medications (Niggemann and Beyer, 2014). These factors may influence absorption or immune responses. The best described entity is food-associated (dependent), exercise-induced anaphylaxis, where the food is tolerated when exercise does not occur, but reactions may occur when the food is ingested before exercise. Common food allergenic foods that trigger a reaction with exercise are wheat, shrimp, and celery, but numerous triggers have been reported (Romano et al., 2001).

The possibility that a cofactor is responsible for the expression of a food allergy is assessed by history, and assessment may include evaluation by SPT or sIgE of foods ingested before exercise or concomitant ingestion of alcohol or NSAIDs. A case can be made for evaluating specific allergens associated with these syndromes, such as gliadin and lipid transfer proteins in some settings, but the diagnostic utility is not fully understood (Muraro

et al., 2014; Romano et al., 2012; Urisu et al., 2014). The history and supporting test evidence may warrant the diagnosis, but OFC with exposure to the eliciting factor may be needed. The reliability of such testing is variable, and the symptoms can recur despite an OFC not triggering reactions. Many factors may confuse the diagnostic approach, such as the need for multiple different or a combination of augmenting factors to result in a reaction, various degrees of the factor (amount of food, exercise, alcohol), and testing methodology (Asaumi et al., 2016; Brockow et al., 2015; Jo et al., 2012; Medrala et al., 2014; Niggemann and Beyer, 2014).

FUTURE DIAGNOSTIC MODALITIES

Food allergy guidelines have recognized a large number of approaches under investigation to improve diagnosis and provide insights on prognosis and severity (Boyce et al., 2010; Muraro et al., 2014; Sampson et al., 2014). Many of these approaches have been reviewed above (CRD, BAT, and others). The diagnostic value of determining the pattern of IgE binding to synthetic sequential epitopes (binding segments) of allergens has been evaluated, with results suggesting that this testing can provide information on phenotype (i.e., ability to tolerate extensively heated milk in those with cow milk allergy), prognosis, and severity (e.g., diversity of binding associated with severity of reactions) (Cerecedo et al., 2008; Flinterman et al., 2008; Jarvinen et al, 2001, 2002; Lin et al., 2012; Shreffler et al., 2004; Wang et al., 2010).

As reviewed above, a number of cellular markers are being evaluated to improve diagnosis and prognosis, including cytokines, regulatory T cells, T cell number and function, B cell activity, and epitope binding (Bedoret et al., 2012; Hoh et al., 2016; Syed et al., 2014; Varshney et al., 2011). One study suggests value in determining deoxyribonucleic acid (DNA) methylation signatures (Martino et al., 2015). Martino et al. performed genome-wide DNA methylation profiling on subjects who had undergone OFC, concurrent SPTs, and specific IgE tests (Martino et al., 2015). Fifty-eight were food-sensitized patients (ages 11 to 15 months), half of whom were clinically reactive, and 13 were nonallergic control subjects. Reproducibility was assessed in another 48 samples from an independent population of patients with food allergy. This study revealed a methylation signature consisting of 96 CpG sites that predict clinical outcomes. This methylation signature was superior to allergen-specific IgE and SPTs for predicting OFC outcomes. Therefore, in addition to elucidating mechanisms involved in the epigenetic regulation of food allergies and the interplay between genetic and environment, this evidence can be used to develop novel, practical, and improved diagnostic assays. Bioinformatics approaches that take into consideration multiple variables should support improved diagnostics (Lin

et al., 2012). These approaches, which could include data from numerous biologic markers such as genomic, transcriptomic, proteomic, metabolomics, microbiome, and various laboratory tests, will allow for assessment of billions of variables (Chen et al., 2012).

OVERALL CONCLUSIONS

Currently, no simple diagnostic tests exist for food allergy. Selection and interpretation of tests depend on the disorder being considered (epidemiology, pathophysiology) and the individual medical history. A common pitfall in diagnosis results from performing tests for sIgE without considering the medical history, resulting in unnecessary avoidance or removal of tolerated foods from the diet (a positive test alone may not indicate a clinical allergy). The gold standard test, the OFC, carries risk and expense, and is underused. The history and available test results can often suggest a likelihood of a food allergy, presenting a reasonable pretest probability for deciding upon the need for an OFC. Understanding how the size of skin tests, concentration of sIgE, and the clinical history can provide pretest probability estimations for providing a diagnosis at this point or proceeding to other tests, including the OFC is key. CRD is currently providing improved diagnosis in some circumstances. Developing "calculators" that evaluate these currently available parameters is promising. The BAT shows promising preliminary data, but validation and commercialization are needed. Sorely missing are simple tests that would indicate, for an individual with current possible allergy symptoms, degree of severity or threshold or both, as well as prognosis.

As reviewed in the discussion above, food allergy testing strategies (history, diagnostic elimination diet, OFC, SPT, sIgE, CRD, APT) are generally not well standardized, including the various factors involved with the history, elimination diets, and food challenge. Many methodologic issues are involved in evaluating test utility, and comparisons of diagnostic utility of specific tests among different populations often show some level of disparity. Regarding SPTs, extracts are not uniformly standardized and the individual allergenic protein content may vary (Hefle et al., 1995). The FDA has approved three automated systems to determine sIgE. Each system uses slightly different methods and results from one system are not directly comparable to others (Hamilton and Williams, 2010; Hamilton et al., 2011; Wang et al., 2008). The manner of reporting SPT skin test sizes varies (e.g., reporting greatest wheal diameter, mean wheal diameter, size in relation to controls), as does the representation of sIgE levels from serum tests (e.g., classes versus concentration, kU_A/L). Different OFC regimens have been proposed in the literature as well as different means to report

results. Attention to these issues affects research approaches as well as clinical care. Studies are under way to improve standardization.

Additional standardization and validation would require extensive study in different patient populations (e.g., ages, illnesses, geographic regions) and consideration of the role of eliciting factors, and circumstances where interventions are being applied to the patient (immunotherapeutic strategies as they become available). This is similarly the case for emerging diagnostics, such as epitope analysis.

Education is needed for patients and physicians to understand the meaning and limitations of commonly used food allergy test results, to know about unconventional and unproven tests, and to understand how to effectively use existing tests (or when to refer from primary care to specialist care). No comprehensive studies on the cost effectiveness of testing and misdiagnosis have been conducted. Studies on diagnostics have been primarily focused on children, and more studies of adults or comparison of adults and children are needed. Numerous potential diagnostic tests are in development. At this point, they are labor-intensive or expensive, but they may identify novel factors of use in the future.

RECOMMENDATIONS

The committee recommends that physicians use evidence-based, standardized procedures as the basis for food allergy diagnosis and avoid nonstandardized and unproven procedures (e.g., applied kinesiology, immunoglobulin G panels, electrodermal testing). When food allergy is suspected, a patient should be evaluated by a physician who has the training and experience to select and interpret appropriate diagnostic tests.

Although this process often may include an initial evaluation by a primary physician, it is important that those with suspected food allergy be diagnosed appropriately, which is likely to involve referral to or consultation with a physician specialist who can diagnose, comprehensively evaluate, and manage the food allergy.

Food allergy evaluation procedures include a medical history and physical examination, and also may include food-specific skin prick test, food-specific serum immunoglobulin E test, diagnostic food elimination diet, and oral food challenge (OFC). Selection of the specific tests needs to be individualized based on the medical history of each patient. Health care providers trained in food allergy, leaders of health care facilities, and health care payor groups can facilitate the appropriate use of OFCs, including personnel, facilities, and safety guards, so that physicians are not

deterred from performing the types of diagnostic testing that are appropriate for the patient's diagnosis and care.

RESEARCH NEEDS

Diagnosis of food allergy is complex, currently requiring expertise in assessing the medical history, understanding allergen cross-reactivity, understanding eliciting factors that may alter reactivity, selecting and interpreting imperfect tests, and possibly conducting a medically supervised OFC test. The OFC is currently the best diagnostic test to confirm an allergy, but it is time consuming, expensive, carries risks (e.g., the risk of triggering an allergic reaction), and is often deferred due to patient and physician concerns. Therefore, the OFC is underused. In addition, commonly available simple allergy tests (sIgE antibody tests or SPT) have limitations that can result in misdiagnosis, primarily overdiagnosis, requiring procedures such as OFCs to confirm a proper diagnosis. For example, currently available, simple diagnostic tests that are often used to diagnose IgE-mediated food allergies, the sIgE test and SPT, actually diagnose sensitization, not food allergy. A variety of diagnostic tests, such as CRD, the basophil activation test, and many others, are emerging or under study and may better inform diagnosis, prognosis, severity, and threshold.

To fill gaps in knowledge in this area, studies should be conducted to accomplish the following objectives:

- Optimize the currently available diagnostic tests and validate methods, such as OFC (including in special contexts, such as OFC in infants and young children), as well as pursue additional novel tests to improve diagnosis, prognosis, determination of severity of disease, and assessment of antigen thresholds, and to monitor host responses. These tests will be valuable in assessing the effectiveness and durability of interventions, such as immunotherapy. These studies should include all affected patient populations (ages, sexes, ethnicities, co-morbidities, socioeconomic strata, should consider the role of eliciting factors (such as exercise and infections), and also should be assessed in those circumstances where interventions are being applied to the patient (immunotherapeutic strategies as they become available).
- Comprehensively examine the utility, cost-effectiveness of, and barriers to testing, especially regarding the OFC, with a goal of maximizing the use of appropriate tests.
- Examine and assess educational approaches and tools to improve physician and health care provider education about both the natu-

ral history of food allergies and the appropriate approaches to use to diagnose food allergies.

- Study the utility of emerging technologies in the area of "omics" methodologies (e.g., genomics, epigenomics, metabolomics). In particular, identify reliable and clinically useful biomarkers for the following important goals:
  - Assessing the severity of a food allergy (e.g., to identify those at high risk for anaphylaxis),
  - Evaluating and monitoring responses to therapy (e.g., immunotherapy),
  - Predicting prognosis (e.g., predicting severity),
  - Identifying populations at risk of developing a food allergy so that they can be included when conducting research on prevention and management strategies and on public health guidelines, and
  - Diagnosing food allergy in individuals and populations (e.g., for collecting data on prevalence).

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5

Potential Genetic and Environmental Determinants of Food Allergy Risk and Possible Prevention Strategies

The increase in food allergy has captured the attention of the medical and research communities and the general public. Although the extent of the increase and the most affected countries are not accurately known, there is little doubt that immunoglobulin E (IgE)-mediated food allergy and anaphylaxis were rarely reported 50 years ago but are now commonly described (see Chapter 3). The prevalence of allergenic reactions to foods might differ by region of the world in part because of differences in exposures to specific foods. However, the drivers for this modern day epidemic in food allergy are poorly understood. It is not clear whether this phenomenon is part of the global rise in all allergic diseases at the end of the 20th century, or is due to a new set of unique factors, or to a combination of both.

Like other complex diseases, food allergy is thought to be caused by a combination of genetic and environmental factors. This chapter describes the state of the scientific evidence related to what are currently thought to be the most relevant genetic and environmental risk factors as well as genome-environment (GxE) interactions. The chapter starts with a discussion of the application of the developmental/ecological model (see Chapter 1) to food allergy risk factors. To that effect, a brief summary of the parallel development of the immune system of the child is included. The concept of atopic march[1] is briefly introduced as potentially important when considering prevention strategies. Although other immune-related diseases, such as eczema

[1] The atopic march refers to the idea that atopic disorders progress over time from eczema (i.e., atopic dermatitis) to asthma (see Box 5-2 and Figure 5-1).

(also known as "atopic dermatitis"), are often components of the atopic march that includes food allergy, not all people with eczema develop food allergy. Consequently, preventing eczema might not always decrease the risk of developing food allergy. Therefore, the committee decided to focus only on the relevant literature directly linked to the development of food allergy and findings associated with eczema alone are not included in this report. Also, the chapter concentrates on food allergy as an outcome except for a few risk determinants for which there are no data on food allergies. In these cases, the committee explored food sensitization[2] as a potential surrogate outcome. Although food sensitization is on the causal pathway for IgE-mediated food allergy, care should be taken in interpreting these results because food sensitization may be a nonspecific marker predisposition to atopy in general, not to food allergy in particular.

To provide context for the current scientific evidence on risk determinants, the methodological limitations of studies to date are explained. The pre- and postnatal environmental risk factors that might explain the development of food allergies have been grouped into emerging hypotheses: (1) microbial hypotheses (hygiene and old friends); (2) allergen avoidance hypothesis; (3) dual allergen exposure hypothesis; (4) nutritional immunomodulation hypothesis; and (5) other hypotheses. Each section on a specific determinant factor ends with a conclusion statement about the evidence supporting the link between exposure to the considered determinant and food allergies. At the end of the chapter, the committee provides their overall conclusions, recommendations, and research needs about strategies for preventing food allergies.

FINDING PREVENTIVE MEASURES: A DEVELOPMENTAL/ECOLOGICAL APPROACH

As described in Chapter 1, the committee approached its task from a developmental/ecological perspective. From the developmental perspective, the committee emphasizes the importance of *developmental timing* for exposures and for safety. In considering the risk determinants for developing food allergies, the committee focused on the different developmental periods—prenatal, early childhood, primary school-age, adolescence, adulthood, and elder years. In the prenatal period and first year of life, a fetus and infant's gut goes through substantial microbiome and immune developmental changes (see Box 5-1). This key period presents a window of opportunity to modify health outcomes at a time when infants are ready to

[2] Sensitization is a condition where an individual produces detectable immunoglobulin E (IgE) to a particular allergen. It can precede a food allergy reaction, but not all individuals with detectable IgE to a food allergen will experience a food allergy reaction.

BOX 5-1
Highlights of Early Development: The Microbiome, the Immune System, and the Gastrointestinal Barrier

Humans acquire their genes from their parents and when infants are born, they acquire their microbiome primarily from their mothers but also from medical staff, family members, and others. After birth, microbes colonize every epithelial surface of the baby and the microbiome matures until adulthood. The gut has specific receptors that are required to be present in order for microbes to be able to colonize the human host and in that way the microbiome and the immune system co-develop; some microbes play a critical role in maturation of the immune system as they induce pro-inflammatory or anti-inflammatory responses to maintain homeostasis of the immune system.

Although the immune system begins to develop through transfer of maternal immunoglobulins across the placenta, data suggest that immune dysregulation can occur at birth (Zhang et al., 2016) and that immune responsiveness can be detected as early as 22 weeks of gestation (Jones et al., 1996; Prescott et al., 1998). Another method of transfer of bioactive compounds from the mother to the child is through consumption of breast milk. A multitude of hormones, growth factors, neuropeptides, and anti-inflammatory and immunomodulatory agents can influence gut colonization by microorganisms (Goldman, 2000). At the same time, the microbiome produces signaling molecules that interact with the host. The baby also produces antibodies.

Infant feeding practices (i.e., use of formula versus breast milk) influence the succession of microbiota colonization (Adlerberth and Wold, 2009). During their first year, infants transition to solid food, which happens concurrently with a number of factors, such as an increasing ability to chew. Over the same period, oral immune tolerance (a state of systemic immune unresponsiveness to ingested allergens) ordinarily is acquired (Pabst and Mowat, 2012). A substantial increase in oral immune tolerance to food has been hypothesized to occur at the time of weaning (Prescott et al., 2008), possibly in relation to changes in microbial constitution and developmental maturation of the mucosal immune system (i.e., gut-associated lymphoid tissues, or GALTs).

The largest interface between the environment and the individual is the intestinal epithelium. Molecules can either be absorbed or secreted through this barrier. In a healthy state, it is necessary for the host to develop immune homeostasis in order to balance the need to respond to pathogens while maintaining suppressed responses against commensal microbial antigens and food antigens. For example, the epithelium and dendritic cells in the GALT have receptors that recognize specific molecular patterns on pathogens. Also, tight junctions between cells lining the small intestine appear to play a significant role in regulating epithelial permeability and are dynamic, in that they are able to adapt to a variety of developmental, physiological, and pathological circumstances. This is likely controlled through the first year of life in response to dietary and developmental changes (Fasano, 2000) and also is facilitated by the commensal intestinal microbiota, which is essential for the normal development of the GALT and maintenance of immune homeostasis (Hansen et al., 2012; Sudo et al., 1997).

begin eating solid foods. Due to the importance of this period in establishing the onset of food allergies, the scientific literature on food allergy risk factors has focused more on these early life stages and less on those changes that may occur in older children, adolescents, or adults. Therefore, while the committee's conclusions and recommendations were crafted through a developmental lens, they are limited by the preponderance of scientific literature on these early ages.

Food Allergies and the Atopic March

Within the developmental perspective, the committee considered the concept of the atopic march (see Box 5-2) in their deliberations. The atopic march refers to the idea that atopic disorders progress over time from eczema to asthma (see Figure 5-1). In fact, in some publications, eczema is viewed as a proxy for food allergies because eczema frequently precedes the development of food allergies. In fact, eczema and food allergies are distinct conditions with different etiologies and it is not appropriate to assume that eczema is a surrogate for food allergy. Although the concept of the atopic march is generally accepted, the interplay of the various related immune conditions is still being studied and, therefore, it would be premature to adopt the general idea that strategies to prevent atopic disorders that typically occur earlier in a child's development necessarily would also prevent the onset of food allergy. Additional prospective cohort studies with the appropriate methodologies are needed, particularly to understand the relationship between other allergic disorders and food allergy. Thus, the committee did not include other allergic disorders (i.e., wheeze, asthma, eczema, or allergic rhinitis) or their risk factors in their review of the evidence of potential determinants of food allergy.

METHODOLOGICAL LIMITATIONS

Current evidence about the risk factors associated with food allergy or sensitization is derived primarily from epidemiological (observational or ecological) studies. In addition to potential limitations in any research study—such as lack of generalizability, small number of samples, and inaccurate outcomes measurements—epidemiological studies need to be interpreted appropriately, with particular consideration to potential confounding factors and their careful adjustment. For instance, being at high risk of allergic disease could be a confounder when exploring the effects of breastfeeding in food allergies because high-risk families are more likely to follow guidelines, which might inform them about the putative protective effects of breastfeeding. If researchers do not adjust their analysis for family history of allergy (the main risk of allergy development), breast-

BOX 5-2
The Atopic March

A food allergy can coexist with a variety of other allergic conditions that share the same signs and symptoms. A systematic review reported that in individuals with food allergy, 35 to 71 percent also had evidence of atopic dermatitis, 33 to 40 percent also had evidence of allergic rhinitis, and 34 to 49 percent had evidence of asthma (Boyce et al., 2010). A food allergy also can be part of the temporal pattern in which an individual develops multiple allergic disorders. This pattern, called the atopic march, describes a process in which atopic disorders progress over time from eczema (i.e., atopic dermatitis) to asthma (see Figure 5-1).

In the context of risk determinants and prevention strategies, understanding the mechanisms that underlie the atopic march from infancy to adulthood (including whether the allergic disorders have a cause-and-effect relationship or simply share similar environmental and genetic causes) would be important when considering prevention options or when identifying individuals at risk. For example, if eczema early in life (age 0 to 12 months) is a risk factor for developing peanut and milk allergy as a child, health care providers might consider this when designing effective prevention strategies.

One hypothesis that might explain the atopic march is the dual allergen exposure hypothesis. This hypothesis identifies the epithelium of the skin, airways, and digestive system as the primary location where both allergic sensitization and (later) allergic reactions are initiated. The hypothesis proposes that genetically determined or environmentally induced abnormalities affecting the epithelium could be a common factor in the development of allergic diseases. For example, certain mutations in the gene that codes for filaggrin, a protein essential in maintaining epidermal homeostasis in the skin, result in an impairment of epidermal barrier function that predisposes to allergic diseases not only in the skin (i.e., atopic dermatitis) but also to allergies affecting other anatomical sites, namely, allergic rhinitis, atopic asthma, food sensitization, and possibly food allergy.

Although the concept of atopic march is widely accepted, the questions about the nature of the relationships continue to be the subject of many investigations and much debate. For example, the authors of a systematic review on the causal relationship between eczema and subsequent allergic disorders concluded that atopic dermatitis might contribute to the development of allergic rhinitis. However, they could not reach a similar conclusion for the relationship between atopic dermatitis and food allergies (Dharmage et al., 2014). Also, a recent review of systematic reviews of birth cohort studies was not conclusive on whether early life food sensitization leads to eczema and other allergic disorders (i.e., wheeze, asthma, or allergic rhinitis) (Alduraywish et al., 2016). In the opinion of the authors of that report, the main reason for this was the lack of studies in which confounding factors (early life eczema and wheeze) had been considered.

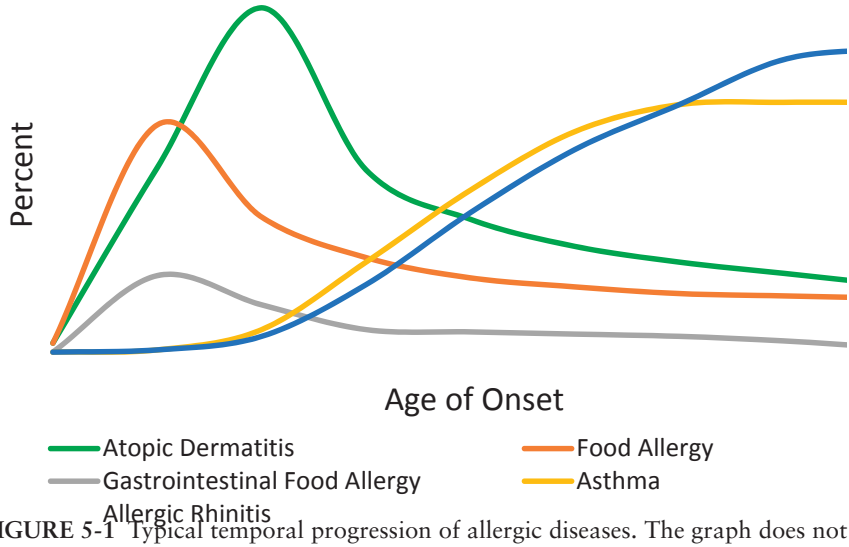

FIGURE 5-1 Typical temporal progression of allergic diseases. The graph does not include specific ages or percents on the x- and y-axis because it was not constructed from empirical data on the progression of immune-related diseases but from the concept of the atopic march, which needs to be studied further.

feeding can be misinterpreted as increasing the risk of allergic disease. This phenomenon is called "reverse causation" and is one of the reasons why randomized controlled trials (RCTs) are required to provide strong evidence that a factor is indeed causally related. Even with the best intentions, observational studies can be undermined by unmeasured confounders (i.e., residual confounding). High-quality data demonstrating causation should exist before recommendations are incorporated into public health guidelines. In most cases, this would mean RCTs. However, when evidence is not strong or trials are ethically difficult to mount (such as is the case for breastfeeding where randomization to a nonbreastfeeding arm would be unethical), clinicians need to interpret emerging or less robust evidence and provide carefully framed information to individual patients and their families to inform health decisions.

Until recently, food allergy has been less common than other allergic diseases. Therefore earlier allergy studies generally did not focus on food allergy as an outcome. It is only recently, as food allergy prevalence has increased, that attempts have been made to more precisely define and measure food allergy. Measurement methods have evolved from often inaccurate

self- or parent-reported data to better methods, such as the results of oral food challenges (OFCs). Recent literature, particularly after 2010, has more consistently reported food allergy outcomes using what is now regarded as the gold standard measurement—double-blind, placebo-controlled oral food challenge (DBPCOFC), in which the food is disguised so that neither parent nor health care professional knows whether the food or a placebo is being offered. Some experts have recommended that for children younger than 2 years, open OFC, in which foods in their natural state are offered (versus DBPCOFC) also can be included in the definition of gold standard because, in this age group, subjective symptoms do not complicate medical history and objective signs can be reliably used as endpoints.

Even DBPCOFC are limited by methodologic differences among studies (see Chapter 4). In addition, criteria for defining a positive oral challenge (i.e., a food allergic reaction) have not been formalized until recently (Koplin et al., 2012b; Sampson et al., 2012; see Chapter 4). Although most protocols state that a positive challenge is evidenced by an immediate reaction consistent with IgE-mediated food allergy, such as urticaria (hives), angioedema, or anaphylaxis, interpretation of more subjective symptoms, such as abdominal pain or nausea, or the more ubiquitous and less clearly defined sign of an eczema flare, remains difficult. Differences in criteria for defining a positive OFC across different studies and research centers hinders the ability to compare food allergy prevalence estimates among studies, to identify risk factors (because phenotypes might vary across different study cohorts), and to assess the success of different treatment strategies (including oral immunotherapy).

It should be noted, however, that performing large-scale OFCs is not always possible because of issues with compliance, risk to participants, and cost. As stated in Chapter 2, many population-based studies have relied on the detection of food-specific serum IgE (sIgE) antibodies as an indirect marker of food allergy, either alone or in conjunction with reported symptoms on ingestion of the food. These studies do provide insights into the temporal trend changes in food allergy prevalence, but should be viewed with caution when assessing risk factors for predicting food allergy owing to the high false positive rate and low specificity of this method. Self-reported measures tend to overreport food allergy due to the inability of individuals to distinguish between symptoms of food intolerance and food allergy. It is also not possible to employ reports from parents to determine allergic status to foods that have not yet been introduced into an infant's diet (see Chapters 3 and 4).

These methodological limitations, and specifically the outcome used to define the food allergy, and their implications for the interpretation of the studies reviewed herein, are noted in conjunction with the specific studies described in this chapter.

APPROACH TO LITERATURE REVIEW

Literature Search Strategy and Study Selection

Electronic literature searches of published systematic reviews (from 2010 to September 2015) and primary studies (from 2012 to September 2015) indexed in Medline, Cochrane Database of Systematic Reviews, EMBASE, and ISI Web of Science were conducted. The complete literature search and screening strategies, study selection flow, and study eligibility criteria are described in Appendix C. The committee based its literature search strategies on the systematic reviews by Marrs et al. and de Silva et al. and on selected individual papers published after those reviews (2012 and beyond) to develop its conclusions (de Silva et al., 2014; Marrs et al., 2013). Where appropriate, other systematic reviews also were considered.

Summary tables for all systematic reviews and studies conducted after 2012 are included in Appendix C. Ongoing trials of risk determinants of food allergy for which results were not available at the time of this publication are summarized in Table 5-1. Selected public health guidelines from various countries are listed in Table 5-2.

Grading the Evidence

For each factor described, the committee made a final conclusion statement considering the preponderance of the evidence collected, as described above. The committee used the approach taken by the 2015 Dietary Guidelines Advisory Committee to grade as strong, moderate, limited, or no grade (DGAC, 2015) (see Table 5-3).

GENETIC AND EPIGENETIC RISK FACTORS

The rise in the prevalence of allergic diseases has occurred more rapidly than can be accounted for by changes in genetic sequence (Tan et al., 2012b). Therefore, similar to other complex diseases, the rising prevalence of allergic diseases is likely due to environmental factors (i.e., the exposome).[3] In this way, the rise may be primarily occurring in those who are both genetically predisposed and exposed to the allergenic environment, as well as in those at risk through a heritable epigenetic mechanism from events that occurred when the parents of current children were in utero. Environmental exposures, including lifestyle and diet, interact[4] with genetic

[3] The exposome refers to all life course environmental exposures (including factors related to lifestyle, such as smoking or diet) from the prenatal period onward.

[4] An interaction is indicated when the simultaneous influence of two or more factors on a phenotype is not additive.

predisposition to modify the risk of disease. For example, the influence of the C-159 T polymorphism on the cluster of differentiation 14 (CD14) gene may be dependent on microbial stimulation from the environment (Lau et al., 2014), with individuals who carry the TT genotype demonstrating increased protection from eczema with exposure to dogs (Myers et al., 2010).

The concept of the epigenome,[5] which regulates gene expression and is largely established in utero, is relevant to early life origins of allergic disease. In contrast to deoxyribonucleic acid (DNA) sequences, which are relatively stable, the epigenome can be altered throughout the lifespan, but is particularly sensitive to environmental factors during early life periods (see Figure 5-2). Environmental factors that have often been considered in interaction with genetic risk factors include vitamin D (Koplin et al., 2016; Liu et al., 2011), smoking, air pollution, and microbial exposures (Tan et al., 2012b). Epigenetic considerations for other environmental factors, for which there is evidence of involvement in allergic diseases, have not yet been considered. It also would be useful to consider putative causative factors for food allergy, such as diet and food supplements, in relation to well-known genetic risks, such as filaggrin mutations.

A further consideration is the fact that these environmental risk factors may operate differentially based on the underlying risk category of the individual (i.e., genetic risk or family history, the more traditional form of risk stratification). As discussed below, evidence already exists of different responses to some environmental factors (e.g., vitamin D) based on a genetic risk factor (vitamin D receptor binding protein) (Koplin et al., 2016). In addition to biological variations, risk factors also may affect behavioral patterns, as has been described by Tey et al. (2014). The authors found that those with a family history of allergy were less likely to respond appropriately to guidelines revisions to introduce allergenic solids earlier in the diet of an infant. Future clinical practice guidelines and public health policy may need to take into account the way that a risk factor may differentially affect not only risk of disease, but also the behavior of the individual with a food allergy and/or their caregivers.

This section describes studies on the genetic and epigenetic factors that might affect food allergy outcomes.

[5] Epigenome refers to the chemical changes to the deoxyribonucleic acid and histone proteins (e.g., methylation) of an organism that occur through life and can result in changes to the structure of chromatin and to the function of the genome. These changes can be inherited through transgenerational epigenetic inheritance.

TABLE 5-1 Registered Randomized Controlled Clinical Trials and Observational Studies on Prevention

Study	Study Design, Country	Population	N	Age When Outcome Is Ascertained	Food Allergy Outcome Definition	Exposure	Question to Answer
BEAT (Beating Egg Allergy)	RCT, Australia	Infants with high risk of atopy, 4-6 mo		8 and 12 mo	Egg allergy assessment	Egg introduction versus placebo	What is the effect of early introduction of egg into the diet of infants at high risk of atopy and subsequent egg allergy?
CoFAR2	Observational, US	Children with egg and/or milk allergy, 3-15 mo	515	After 3 years of age	Peanut allergy		What is the development of peanut allergy in infants (3 to 15 months in age) with known milk or egg allergy?
EAT (Enquiring about Tolerance)	RCT, UK	Infants 3 mo	1,306	3 years		Early introduction of 6 allergenic foods together with breastfeeding versus standard introduction (6 months)	Does introducing certain foods early in a child's diet along with continued breastfeeding stop infants from developing food allergy?
STEP (Starting Time for Egg Protein)	RCT, Australia	Infants 4-6 mo without eczema but atopic mothers	1,500			Egg introduction versus placebo	

HEAP	Germany	Infants 4-6 mo	800	12 mo	Egg allergy	Egg introduction versus placebo	
PreventADALL (Preventing Atopic Dermatitis and Allergies in Children)	RCT, Norway	Infants		6, 12, 36, and 48 mo	Early food introduction by 3-4 mo	Food allergy to any intervention allergen (cow milk, peanut, wheat, egg)	Is primary prevention of allergic diseases possible by skin care and early food introduction?
PIFA (Pertussis Immunisation and Food Allergy)	Observational (case-control), Australia	Children 14-18 years		14-18 years	History of consistent clinical symptoms following ingestion of an implicated food and evidence of sensitization to that food by laboratory testing	Whole cell versus acellular pertussis vaccine	What is the possible food allergy-preventive benefit of using whole cell pertussis vaccination compared with acelluar pertussis vaccine for whooping cough vaccination in childhood?
VITALITY	RCT, Australia	Infants 6-8 weeks		12 months	Challenge-proven food allergy in study participants with positive SPT	Vitamin D (400 IU/day) versus placebo for 10 months	Can vitamin D supplementation in infants prevent food allergy in the first year of life?

continued

TABLE 5-1 Continued

Study	Study Design, Country	Population	N	Age When Outcome Is Ascertained	Food Allergy Outcome Definition	Exposure	Question to Answer
Early Life Origins of the Food Allergy Epidemic	Observational, Canada	Peanut-sensitized children, 4-10 years		5 years	DBPCOFC to peanut	Eating versus avoiding peanut	Does avoidance of peanut by children with positive SPT to peanut in the first 5 years of life increase the likelihood of developing a persistent peanut allergy by age 5 years?
The Cork BASELINE Birth Cohort Study (BASELINE)	Observational, Ireland	Infants		2 years		Incidence and prevalence of food allergy	What are the early life factors, including parental allergy, genetic susceptibility measured using fillagrin mutational status, skin barrier function, and vitamin D status and their effect on risk of eczema and food allergy in the first 2 years of life?

Probiotic Supplementation in Breastfed Newborn Infants	RCT, US	Infants, 1-7 days old, with intent to be exclusively breastfed for a minimum of 6 months	First 78 weeks of life	Levels of serum FABPs and glutathione-S-transferase (alpha-GST) will be measured as markers of GI permeability and potential food allergy; parental report of feeding intolerance	Probiotic supplementation versus placebo	What is the dose of a probiotic supplement (Bifidobacterium longum subsp. infantis) required to achieve predominant gut colonization in healthy newborn, breastfed infants? Does supplementation with this probiotic reduce the chance of developing eczema and food allergies in enrolled infants?
PROOM-3	RCT, Sweden	Pregnant women with at least one parent or a sibling with clinical symptoms or history of allergic disease and their newborn infants	6 and 12 months	IgE-associated disease measured by SPT (milk, egg, wheat, peanut)	Dietary supplementation with L. reuteri and omega-3 PUFA during pregnancy and postnatally versus placebo	Can supplementation with Lactobacillus reuteri and omega-3 fatty acids during pregnancy and lactation reduce the risk of allergic disease in infancy?

continued

TABLE 5-1 Continued

Study	Study Design, Country	Population	N	Age When Outcome Is Ascertained	Food Allergy Outcome Definition	Exposure	Question to Answer
Mis-BAIR (Melbourne Infant Study-BCG for Allergy and Infection Reduction)	RCT, Australia	Infants, younger than 10 days old		1 year	SPT and challenge-proven food allergy	BCG immunization for TB versus no immunization	Does BCG immunization at birth, compared to no BCG immunization, lead to a reduction in measures of allergy and infection in the first 12 months of life?
Molecular Basis of Food Allergy	Observational, US	Food allergic individuals ages 4 months to 75 years		Various			What is the molecular basis of food allergy? What are the genetic factors that lead to the development of food allergy?

NOTE: AU = Australia; DBPCOFC = double-blind, placebo-controlled oral food challenge; FABP = fatty acid binding protein; GI = gastrointestinal; IgE = immunoglobulin E; sIgE = food-specific serum IgE; SPT = skin prick test; TB = tuberculosis; UK = United Kingdom; US = United States.

Genetics

The role of genetics in food allergies was initially supported by its familial aggregation (Tsai et al., 2009) and heritability estimates derived from twin studies (Liu et al., 2009; Sicherer et al., 2000). Later, the ability to explore the genome opened the possibility to examine the involvement of specific candidate genes. More recently the potential for discovery of new loci has expanded with the use of genome-wide association studies (GWASs)[6] (Hong et al., 2015). However, unlike other diseases and phenotypes, for which hundreds of loci have been identified, the number of loci that have been tentatively associated with food allergies is still rather small.

As expected, most of these candidate genes encode products influencing immune mechanisms, including antigen presentation or a shift of the immune system toward a Th2 response. The hypothesis is that genetic predispositions may result in dysregulation of the immune system and, in the context of specific environmental factors, lead to food allergy. However, the association studies performed to date that have aimed to uncover the genetic architecture of food allergies have faced similar challenges as for other complex human diseases to date. Specifically, the identified loci can explain only a very small fraction of the phenotypic variance and few of the loci examined have provided conclusive and consistent findings across populations (see Table 5-4).

Only one GWAS has been reported in relation to food allergies (peanut, milk, and egg) (Hong et al., 2015). Two single nucleotide polymorphisms (SNPs) showed an association with peanut allergy that was above the GWAS threshold for significance, both of them in the human leucocyte antigen (HLA)[7] system. The first one, rs7192, is in the HLA-DR region and the second one, rs9275596, is located in the HLA-DQ region. Most interesting, both loci are also associated with differential DNA methylation. Therefore, these results support the relevance of the HLA system as well as epigenetic modifications in the predisposition to peanut allergy. In this study, though, the food allergy outcome was defined based on a convincing history of clinical allergic reaction on ingestion of a specified food and evidence of

[6] Genome-wide association studies (GWASs) examine many common genetic variants in different individuals to see if any variant is associated with a trait. GWASs typically focus on associations between single-nucleotide polymorphisms (SNPs) and traits like major diseases (Gottgens, 2012).

[7] The human leukocyte antigen (HLA) system is a gene complex located in chromosome 6p21 that encodes the major histocompatibility complex (MHC) proteins, which are cell proteins responsible for the regulation of the immune system. MHC class I, II, and III have different functions. MCH class I present peptides from inside the cell, MHC class II present antigens from outside of the cell to T-lymphocytes and stimulate the multiplication of T-helper cells. MHC class III are components of the complement system.

TABLE 5-2 Current Guidelines on Food Allergy Prevention

Guideline (reference)	Year	Country	Breastfeeding
Interim Guidance Regarding Peanut Introduction from the American Academy of Pediatrics; American Academy of Allergy, Asthma & Immunology; American College of Allergy, Asthma & Immunology; and others[a] (Fleischer et al., 2015)	2015	US, Australia, Japan, European Union (EU)	

Early Introduction of Foods	Infant Formula	Diet of Mother	Prebiotics or Probiotics
Introduce peanut-containing products into the diets of "high-risk" infants early on in life (between 4 and 11 months of age) in countries where peanut allergy is prevalent. Infants with early-onset atopic disease, such as severe eczema, or egg allergy in the first 4 to 6 months of life (LEAP criteria) might benefit from evaluation by an allergist or physician to diagnose any food allergy and assist in implementing these suggestions of early peanut introduction.			

continued

TABLE 5-2 Continued

Guideline (reference)	Year	Country	Breastfeeding
NIAID/NIH-supported Guidelines (Boyce et al., 2010)	2010	US	Recommends that all infants be exclusively breastfed until 4 to 6 months of age, unless breastfeeding is contraindicated for medical reasons.
2016 Addendum to the NIAID/NIH-supported Guidelines (Togias et al., 2017)	2016	US	
World Health Organization and World Allergy Organization (WHO, 2003)	2003	Worldwide	Breastfeed exclusively until 6 months.

Early Introduction of Foods	Infant Formula	Diet of Mother	Prebiotics or Probiotics
	Does *not* recommend using soy infant formula instead of cow milk infant formula as a strategy for preventing the development of food allergy or modifying its clinical course in at-risk infants. Suggests that the use of hydrolyzed infant formulas, as opposed to cow milk formula, may be considered as a strategy for preventing the development of food allergy in at-risk infants who are not exclusively breastfed.	Does *not* recommend restricting maternal diet during pregnancy or lactation as a strategy for preventing the development or clinical course of food allergy.	
Suggests that the introduction of solid foods should *not* be delayed beyond 4 to 6 months of age. Potentially allergenic foods may be introduced at this time as well.			
	Infants with cow milk allergy should avoid cow milk proteins; if a supplement is needed, use hypoallergenic formula, if available, and affordable to improve symptom control.	No special diet for the lactating mother.	

continued

TABLE 5-2 Continued

Guideline (reference)	Year	Country	Breastfeeding
American Academy of Allergy, Asthma & Immunology (Fleischer et al., 2013)	2013	US	Exclusive breastfeeding for at least 4 and up to 6 months is endorsed.
European Academy of Allergy & Clinical Immunology Guidelines (Muraro et al., 2014)	2014	EU	Exclusive breastfeeding for at least the first 4-6 months of life is recommended.

Early Introduction of Foods	Infant Formula	Diet of Mother	Prebiotics or Probiotics
Complementary foods can be introduced between 4 and 6 months of age. Highly allergenic foods can be given as complementary foods once a few complementary foods have been tolerated first and should initially be given at home first rather than at day care or a restaurant.	For high-risk infants who cannot be exclusively breastfed, hydrolyzed formula appears to offer advantages to prevent allergic disease and cow milk allergy.	Avoidance diets during pregnancy and lactation are not recommended at this time, but more research is necessary for peanut. This recommendation does not apply to infants who manifest signs of allergic disease shortly after birth, because treatment may, in some cases, involve dietary interventions during lactation.	
Introduction of complementary foods after the age of 4 months according to normal standard weaning practices and nutrition recommendations, for all children irrespective of atopic heredity.	For high-risk infants: If a supplement is needed during the first 4 months, a documented hypoallergenic formula is recommended.	No special diet during pregnancy or for the lactating mother.	

continued

TABLE 5-2 Continued

Guideline (reference)	Year	Country	Breastfeeding
European Society of Pediatric Allergy and Clinical Immunology and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition Committee on Nutrition (Agostoni et al., 2008)	2008	Europe	Exclusive or full breastfeeding for about 6 months is a desirable goal.

Early Introduction of Foods	Infant Formula	Diet of Mother	Prebiotics or Probiotics
There is no convincing scientific evidence that avoidance or delayed introduction of potentially allergenic foods, such as fish and eggs, reduces allergies, either in infants considered at increased risk for the development of allergy or in those not considered to be at increased risk. Complementary foods should not be introduced before 17 weeks and foods should be added one at a time to allow detection of reactions to individual components. It is prudent to avoid both early (<4 months) and late (>7 months) introduction of gluten and to introduce gluten gradually while the infant is still breastfed because this may reduce the risk of wheat allergy.			

continued

TABLE 5-2 Continued

Guideline (reference)	Year	Country	Breastfeeding
American Academy of Pediatrics (Greer et al., 2008)	2008	US	For infants at high risk of developing atopic disease, evidence suggests that exclusive breastfeeding for at least 4 months compared with feeding intact cow milk protein formula decreases the cumulative incidence of atopic dermatitis and cow milk allergy in the first 2 years of life.

Early Introduction of Foods	Infant Formula	Diet of Mother	Prebiotics or Probiotics
Although solid foods should not be introduced before 4 to 6 months of age, there is no current convincing evidence that delaying their introduction beyond this period has a significant protective effect on the development of atopic disease regardless of whether infants are fed cow milk protein formula or human milk. This includes delaying the introduction of foods that are considered to be highly allergic, such as fish, eggs, and foods containing peanut protein. For infants after 4 to 6 months of age, there are insufficient data to support a protective effect of any dietary intervention for the development of atopic disease.	In studies of infants at high risk of developing atopic disease who are not breastfed exclusively for 4 to 6 months or are formula fed, there is modest evidence that atopic dermatitis may be delayed or prevented by the use of extensively or partially hydrolyzed formulas, compared with cow milk formula, in early childhood. Extensively hydrolyzed formulas may be more effective than partially hydrolyzed in the prevention of atopic disease. There is no convincing evidence for the use of soy-based infant formula for the purpose of allergy prevention.	Current evidence does not support a major role for maternal dietary restrictions during pregnancy or lactation.	

continued

TABLE 5-2 Continued

Guideline (reference)	Year	Country	Breastfeeding
National Health Service (NHS, 2015b)	2015	UK	Breast milk or first infant formula for first 6 months.
National Health and Medical Research Council (NHMRC, 2013)	2012	Australia	Exclusive breastfeeding until around 6 months of age. For infants with a family history of allergy, continue breastfeeding while introducing solid foods.

Early Introduction of Foods	Infant Formula	Diet of Mother	Prebiotics or Probiotics
Introduce cow milk, eggs, wheat, gluten, nuts, peanuts, peanut products, seeds, fish and shellfish one at a time and not before 6 months.	Infant formula made from cow or goat milk is the only suitable alternative to breast milk in the first 12 months. Only use soy-based infant formula if advised by health care provider. Follow-on milks are available for babies older than 6 months, but there is no need to change over to these. If child has an allergy or intolerance to milk, health care provider can advise on suitable milk alternatives.		
For infants with a family history of allergy, solid foods should be introduced at about 6 months of age.	If breastfeeding is discontinued for any reason, there is no advantage in using special formulas, except under medical supervision. Soy-based formulas do not prevent or reduce the risk of developing allergies and are not a suitable alternative to cow milk–based formulas.	Dietary elimination of potential allergens during pregnancy is not recommended for preventing childhood allergy.	The evidence on probiotics or prebiotics in infant formula to prevent atopic disease varies.

continued

TABLE 5-2 Continued

Guideline (reference)	Year	Country	Breastfeeding
Australasian Society of Clinical Immunology and Allergy (ASCIA, 2016a,b)	2016	Australia	Breastfeeding is recommended for at least 6 months.[b]
Academy of Nutrition and Dietetics (AND, 2015)	2015	US	Exclusive breastfeeding provides optimal nutrition and health protection for the first 6 months of life and breastfeeding with complementary foods from 6 months until at least 12 months of age is the ideal feeding pattern for infants. Breastfeeding should be supported and preserved even under adverse or challenging conditions, such as prematurity, allergies, chronic illness, and multiple births.

NOTE: UK = United Kingdom; US = United States.

[a] Australasian Society of Clinical Immunology and Allergy, Canadian Society of Allergy and Clinical Immunology, European Academy of Allergy & Clinical Immunology, Israel Association of Allergy and Clinical Immunology, Japanese Society for Allergology, Society for Pediatric Dermatology, and World Allergy Organization.

[b] For all infants (not as a prevention for allergic diseases).

Early Introduction of Foods	Infant Formula	Diet of Mother	Prebiotics or Probiotics
Recommends the introduction of complementary "solid" foods within the window of 4-6 months and preferably while breastfeeding, regardless of whether the food is considered to be a common food allergen.	In children with confirmed cow milk and soy allergy, appropriate formula is available on prescription. There is no consistent convincing evidence to support a protective role for partially hydrolysed formulas or extensively hydrolyzed formulas for the prevention of food allergy in infants or children.	Exclusion of any particular foods (including foods considered to be highly allergenic) from the maternal diet during pregnancy or breastfeeding is not recommended.	Recommendations about probiotic supplements cannot currently be made.

TABLE 5-3 Evidence-Based Review Grading System Used by the Committee to Evaluate the Association Between Potential Risk Determinants and Food Allergies

Strong	The conclusion statement is substantiated by a large, high quality, and/or consistent body of evidence that directly addresses the question. There is a high level of certainty that the conclusion is generalizable to the population of interest, and it is unlikely to change if new evidence emerges.
Moderate	The conclusion statement is substantiated by sufficient evidence, but the level of certainty is restricted by limitations in the evidence, such as the amount of evidence available, inconsistencies in findings, or methodological or generalizability concerns. If new evidence emerges, there could be modifications to the conclusion statement.
Limited	The conclusion statement is substantiated by insufficient evidence, and the level of certainty is seriously restricted by limitations in the evidence, such as the amount of evidence available, inconsistencies in findings, or methodological or generalizability concerns. If new evidence emerges, there could likely be modifications to the conclusion statement.
Grade not assignable	A conclusion statement cannot be drawn due to a lack of evidence, or the availability of evidence has serious methodological concerns.

SOURCE: DGAC, 2015.

sensitization to the same food measured by sIgE and/or a positive skin prick test (SPT) to this specified food, not by OFC.

Overall, evidence exists of genetic predisposition for food allergy based on family aggregation (Tsai et al., 2009) and heritability studies (Liu et al., 2009; Sicherer et al., 2000), the latter showing a wide range of values between 0.15 and 0.88. However, as with other complex diseases that are polygenic, challenges remain to identify what contribute to the "missing heritability."

The committee concludes that although some evidence from various lines of investigation suggests that genetics contribute to the development of food allergies, none of the studies on the association of food allergy with specific loci examined to date has provided conclusive and consistent findings across populations.

Interaction Between Genetics and Environment: Migration Studies

As mentioned above, environmental exposures, including lifestyle and diet, interact with genetic predisposition to modify the risk of disease. The

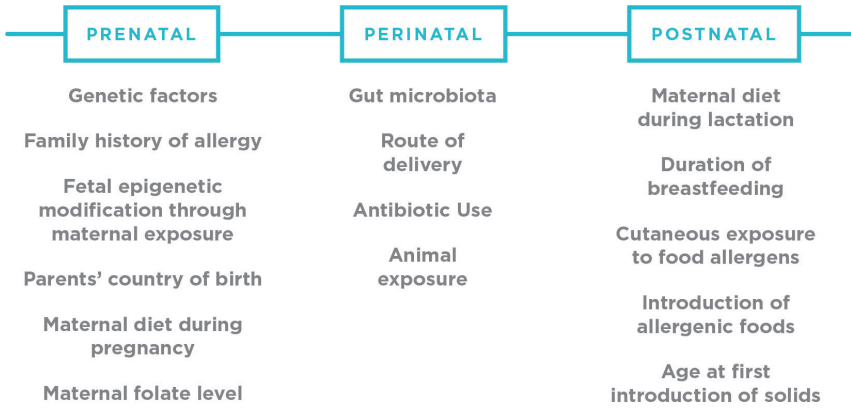

FIGURE 5-2 Major genetic and environmental determinants of food allergy risk.

"natural experiment" of migration has provided an opportunity to postulate a possible protective effect of the Asian environment on Asian children that is removed on migration to a developed country such as the United States or Australia, where risk of allergic disease rises. In HealthNuts, challenge-confirmed peanut allergy was about three times more common in infants whose parents were born in East Asia compared to those with parents born in Australia (Koplin et al., 2014). Similar effects were seen for other food sensitizations and food allergies and for eczema. This increased risk appears to have occurred in a single generation and to be specific to infants of Asian parents. This effect was not seen among infants whose parents were born in the United Kingdom or Europe.

More recently in a large cohort of more than 65,000 children whose parents undertook a survey as their children entered primary school (age 5 years), the finding of increased rates of nut allergy in Asian children born in Australia was replicated. However the most intriguing observation in this study was the finding that children born in Asia who subsequently migrated to Australia before the age of 5 years were protected from the development of food allergy (Panjari et al., 2016).

Migration may be associated with changes to a number of factors (some of which were not measured in HealthNuts) that might be inter-related (Allen and Koplin, 2015) (see Figure 5-3). These include humidity (and its impact on skin barrier function), microbial exposure (hygiene hypothesis), and dietary changes and changes in latitude (vitamin D). For example, changes to the skin barrier function and risk of eczema as an early risk factor of food allergy may result from higher humidity in Asia than Australia

TABLE 5-4 Summary of Studies Associating Specific Genes with Food Allergy

Author, Year	Study Design, Country	Population	N	Candidate Gene	Outcome	Summary
Senechal et al., 1999	Observational, Europe	European-born white adults	42 atopic 42 healthy	HLA	Apple allergy	Association with the HLA-DRB1*07 allele
Hand et al., 2004	Observational, UK	Allergy clinic patients: ages 3-56 years; 81 white 3 mixed race 40 male 44 female Atopic controls: ages 16-61 years; 31 male 51 female	84 nut-allergic patients 82 atopic non-nut-allergic patients 1,798 random blood donors	HLA	Nut allergy (peanut, Brazil nut, hazelnut, walnut, cashew, almond, and pecan)	Increased for HLA-beta*07 and HLA-DRB1*11, HLA-DRB*13, and HLA-DQB1*06 alleles
Madore et al., 2013	Observational, Canada	Peanut-allergic Caucasian children, mean age 11 years Controls: mean age 4 years	590 cases 332 controls	HLA	Peanut allergy	HLA-DQB1*02 and HLA-DQB1*06:03P associated with peanut allergy
Hong et al., 2015	Observational, US	Participants in the Chicago Food Allergy Study	1,315 children 1,444 parents	HLA	Peanut allergy	HLA-DR and -DQ gene region at 6p21.32, tagged by rs7192 and rs9275596

Woo et al., 2003	Observational, US	Food allergic patients, mean age 5.2 years, 74% male, 83% white Non-atopic, non-asthmatic adult controls	77 cases 61 controls	CD14	Food allergy	The C-159T SNP associated with food allergy
Campos et al., 2007	Observational, Japan	Food-allergic children, mean age 7.1 years Non-food-allergic controls, mean age 9.45 years	88 cases 101 controls	CD14	Food Allergy	No association with the C-159T or the C-550T
Torgerson et al., 2007	Case series, France	Index case with IPEX syndrome and other family members	11	FOXP3	Severe food allergy	1300-bp deletion could cause severe food allergy
Siegel et al., 2013	Observational, US	Atopic patients: 40% female, mean age 14.8 years Controls: 61% female, mean age 34.5 years	65 patients with severe atopic disease 41 healthy controls	STAT3	Food allergies (egg, milk, or peanut)	Complex association between this locus and allergic phenotypes

continued

TABLE 5-4 Continued

Author, Year	Study Design, Country	Population	N	Candidate Gene	Outcome	Summary
Amoli et al., 2002	Observational, UK	Nut-allergic, Caucasian patients, mean age 10 years Healthy atopic, non-allergic controls UK Caucasian blood donors	71 patients 45 controls 184 blood donors	STAT6	Nut-allergy (peanut, cashew, Brazil nut, pecan, almond, hazelnut, or walnut)	The G allele at the G2964A SNP increased in nut-allergic patients.
Negoro et al., 2006	Observational, Japan	Allergic children	220	STAT6	Food allergy	No association of G2964A and severity of food allergy
Kusunoki et al., 2005	Observational, Japan	Children with atopic dermatitis, >5 years of age	118	SPINK5	Food allergy	The 1258AA or 1258AG carriers have higher prevalence of food allergy
Negoro et al., 2006	Observational, Japan	Allergic children, mean age 7.3 years	220	IL10	Food allergy	No association with the C-627A SNP
Campos et al., 2008	Observational, Japan	Food-allergic children, mean age 7.6 years, 63% male Atopic control children without food allergy, mean age 8.2 years, 64% male	111 cases 115 controls	IL10	Food allergy	No association with the C-627A SNP; but the -1082AA genotype was associated with higher risk

Chen et al., 2012	Observational, Taiwan	Food-allergic patients, age range 1-32 years; 62% male Non-food-allergic controls, age range 1-59 years, 40% male	37 cases 52 controls	IL10	Food allergy	Both the -1082A/G and the -592A/C SNPs were associated with food allergies
Liu et al., 2004	Observational, Germany	German children who participated in the German Multicenter Allergy Study	823	IL13	Food sensitization	C-1055T higher risk
Gaudieri et al., 2012	Observational, Australia	Children recruited antenatally from healthy pregnant mothers; followed from birth to age 5 years	35 allergic 35 non-allergic	IL28B	Food allergy	The rs12979860 SNP associated positively with food allergy
Venkataraman et al., 2014	Observational, UK	Isle of Wight birth cohort; children ages 1-18 years	1,456	FLG	Food allergy	FLG LOF mutations associated with food allergy.
Tan et al., 2012a	Observational, Australia	HealthNuts Cohort study participants; white infants, age 1 year	700	FLG	Food sensitization/ allergy	FLG LOF mutations do not increase the risk of food allergies beyond that of food sensitization

continued

TABLE 5-4 Continued

Author, Year	Study Design, Country	Population	N	Candidate Gene	Outcome	Summary
Brough et al., 2014	Observational, UK	Birth cohort of the Manchester Asthma and Allergy Study, children ages 1-11 years	1,184	FLG	Peanut allergy	Positive association with peanut allergy
Li et al., 2012	Observational, China	Atopic dermatitis outpatients, mean age 3.5 years, 64.3% male	249	FLG	Food sensitization	Interaction of K4671X mutation and the combined mutations in FLG related to sensitization to peanut allergens in patients with atopic dermatitis
Oxelius et al., 2015	Observational, Germany	Children from the German Multicenter Allergy Study, Caucasian, age 1 year or 10 years	194	IGHG genes	Food sensitization	The IGHG*bfn haplotype (B*bfn cells) and increased innate IgG2*n levels are predictive factors for IgE food sensitization in childhood

NOTE: FLG = filaggrin; HLA = human leukocyte antigen; IGHG = immunoglobulin heavy locus gene; IL = interleukin; LOF = loss of function; UK = United Kingdom; US = United States.

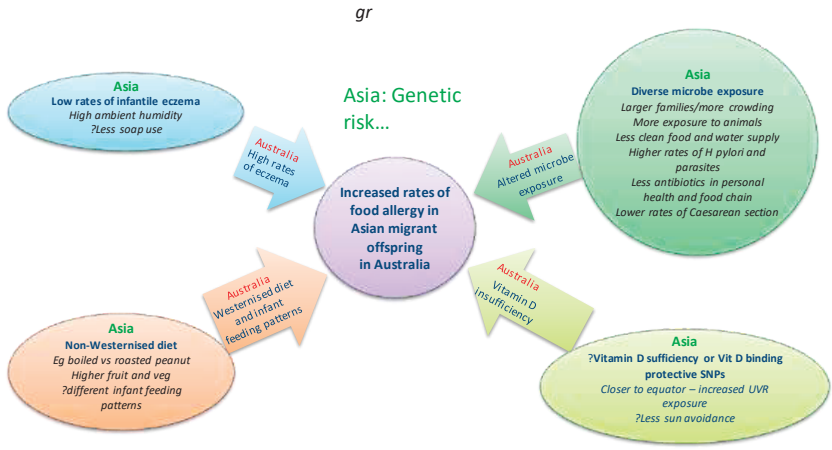

FIGURE 5-3 Modifiable lifestyle risk factors that could explain the rise in food allergy risk in offspring of Asian migrants in Australia.
NOTE: SNP = single nucleotide polymorphism; UVR = ultraviolet radiation.
SOURCE: Allen and Koplin, 2015. Reprinted with permission from Elsevier.

but equally may result from differences in infant washing practices (types of soap and water composition) that occur in each country and may exert an effect through the hygiene hypothesis. Microbial exposure factors that differ not only include variations in the quality of water supply (and differences in risk of waterborne gastrointestinal infections) but also differences in microbes that are a part of the food chain supply (for example, in unwashed vegetables or higher use of antibiotics in the food chain supply of meat-producing animals), number of children in a family, and issues of crowding and exposure to pets, farm animals, and stray animals (which may have higher rates of parasites), and variations in overprescribing of antibiotics in each region. Dietary differences are multiple (e.g., higher use of herbicides and pesticides that might affect the microbial load of food and increased sterilization; use of plastic in developed countries; cooking practices that may alter the allergenicity of food; different vitamin D status).

Epigenetics

The contribution of epigenetics has been more extensively studied for other allergic diseases, including asthma, eczema, and allergic rhinitis, as reviewed by Hong and Wang (2014), than for food allergies. In light of the

atopic march and common comorbidities between food allergies and these other allergic diseases, one may speculate that a link between epigenetic changes and the development of food allergies is possible, but at this time the evidence is quite limited and comes from indirect studies such as the migration studies described above.

Direct evidence to establish the relevance of epigenetic changes as a mediator of genetic susceptibility to food allergies is very limited. The most up-to-date knowledge about the role of epigenetics in food allergy has been summarized in a recent review by Neeland et al. (2015). In their epigenome-wide association study (EWAS) of food allergies,[8] Martino et al. measured genome-wide DNA methylation profiles from CD4+ T-cells (see Chapter 2) on a birth cohort of 12 children with IgE-mediated food allergy diagnosed at 12 months; 12 individuals with no food allergies were controls (Martino et al., 2014). A number of statistically significant differentially methylated probes (DMPs) were identified from DNA obtained from samples taken at birth and at 12 months of age. Of interest is the finding of 96 allergy-associated non-SNP DMPs that were present at time of birth before the expression of the disease. These could be causally related to its expression, including several mitogen-activated protein kinase (MAPK) signaling molecules. Therefore, the authors concluded that "dysregulation of DNA methylation at MAPK signaling-associated genes during early CD4+ T-cell development may contribute to suboptimal T-lymphocyte responses in early childhood" that could influence the development of food allergy (Martino et al., 2014). However, this is a small study and, therefore, its findings need independent validation in larger studies and other populations.

Support for a role of epigenetics in food allergies is provided by the results from a food allergy GWAS carried out in 2,759 U.S. participants (1,315 children and 1,444 parents) from the Chicago Food Allergy Study (Hong et al., 2015). In a recent study in the Chicago cohort, Hong et al. conducted an EWAS of cow milk allergy using a two-stage approach (Hong et al., 2016). During the discovery stage, DNA methylation was measured at 485,512 genomic loci in whole blood samples from 106 Caucasian children with cow milk allergy (cases) and 76 nonallergic and nonatopic Caucasian children (controls) using the Illumina HumanMethylation450 arrays. The findings were confirmed in a small replication sample (5 cases and 20 controls). The researchers demonstrated that altered DNA methylation in genes involved in the Th1-Th2 pathways and some novel candidate genes are associated with cow milk allergy.

[8] Epigenome-wide association studies (EWASs) are large-scale, systematic studies that explore the association between the epigenetic variations and diseases, equivalent to genome-wide association studies (GWASs).

The committee concludes that relative to other immune-related diseases, only a few studies have been conducted that directly support a contribution of epigenetic factors to the development of food allergies. Limited evidence from ecological studies and studies on methylation signatures of participants with food allergies suggest that gene-environment interactions and underlying epigenetic mechanisms need to be taken into account when exploring potential pre- and postnatal risk factors for food allergy.

ENVIRONMENTAL RISK FACTORS

Microbial Exposure Hypotheses

As mentioned in Box 5-1, evidence increasingly suggests that the interaction between the host microbiome and the immune system is essential to the development of immune regulation and oral tolerance (Martin et al., 2010). Exposure to microbes after birth prompts the maturation of the mucosal immune system (Kelly et al., 2007). The composition and timing of exposure to gut microbiota, and their possible role in disease development or prevention have been considered as explanations for the development of food allergy (Li et al., 2014; McLoughlin and Mills, 2011; Prince et al., 2015). The microbial hypothesis proposes that a decrease in early childhood exposure to microbes or their products may hinder the normal development of early immunoregulatory responses. This leaves the immune system more susceptible to inappropriate reactivity to innocuous antigens, resulting in the development of "allergic" diseases.

The overall microbial hypothesis encompasses two different concepts—the "Hygiene Hypothesis" and the "Old Friends Hypothesis." The Hygiene Hypothesis, originally explained in the landmark paper by David Strachan in 1989, described a protective effect of an increasing number of siblings in a household on the risk of developing allergic rhinitis (Strachan, 1989). This was thought to potentially relate to the shared exposure to common childhood infections transmitted through direct contact with older siblings or by maternal contact with her older children prenatally. Although a protective sibling effect has been confirmed for challenge-proven food allergy outcomes (Koplin et al., 2012a) and for various food sensitization and allergy outcomes (Marrs et al., 2013), the mechanism(s) underlying this phenomenon is not clear. Although the finding is interesting and reproducible, changes to postwar houses and sanitation, and sizes of families, as well as the emergence of national immunization programs with high uptakes, also should be considered in attempting to identify the mechanisms underlying the protective effects of siblings.

Second, evidence of a protective effect of dog ownership on food allergy risk may point to the benefit of sharing of microbes or even parasites, the

latter underpinning the idea of the Old Friends hypothesis. Although this hypothesis was predicated on the assumption that IgE antibody–associated immune responses developed in part as a mechanism of host defense against parasite infestation, recent evidence indicates that, at least in mice, IgE antibody–associated immune response also can confer increased acquired resistance to the morbidity and mortality induced by arthropod and reptile venoms (Galli et al., 2016; Marichal et al., 2013; Palm et al., 2013; Starkl et al., 2016). Speaking more broadly, early evidence suggests a difference between the prevalence of food allergy in rural versus urban environments that appears to be reflected in rising rates of food allergy described in cities in China undergoing rapid urbanization (Hu et. al., 2010).

The main environmental factors contributing to the microbial exposure hypothesis include route of delivery at birth, antibiotic use, exposure to pets/animals, and immunization. Breastfeeding has been linked to infant immune development (Praveen et al., 2015) and the composition of the microbiota (Azad et al., 2016). It would therefore be plausible that a mechanism linking food allergy risk and breastfeeding could be mediated through microbiome modulation (Fooladi et al., 2013). However, no published studies to date have investigated this hypothesis, and the data linking breastfeeding and food allergy are inconclusive, potentially due to reverse causality and the inability to randomize infants for breast- versus formula-feeding. Therefore breastfeeding will not be included in this section; instead the effect of breastfeeding is included as part of the "Allergen Avoidance Hypothesis" (see p. 185). The ingestion of prebiotics and probiotics could modify the gut microbiota in a way to change immune system functionality and atopic diseases. Therefore, their use as potential risk factor for food allergies also is included.

A systematic review of the evidence linking microbial exposure and food allergy was published by Marrs et al. (Marrs et al., 2013). The authors reviewed scientific publications available in Medline between 1948 and July 2012. The key findings of this review will be briefly summarized below, but the focus will be on reviewing the findings of papers published since July 2012.

Gut Microbiota and the Use of Probiotics and Prebiotics

Data on microbial profiling and its relationship to disease are still not sufficiently detailed to consider specific microbiota modifications as a food allergy prevention strategy. However, some emerging data suggest that changes in microbiota could influence food allergies, offering further support for the microbial exposure hypothesis (West et al., 2015).

Marrs et al. included five studies in their systematic review that investigated characteristics of gut microbiota, two of which used food challenge

outcomes and three that used food sensitization parameters (Marrs et al., 2013). The two manuscripts that ranked highest in quality and measured food allergy were from the same study of Spanish infants who were diagnosed with IgE-mediated cow milk allergy by milk challenge at a tertiary referral center. Differences in microbiota were identified but unfortunately none of the results was adjusted for diet. The Marrs review also included 11 RCTs in which microbial supplementation was the intervention as a potential prevention or treatment of food allergies or sensitization. Although the quality varied, the two highest quality studies that measured food allergy by OFC to assess whether microbial supplementation may be used to prevent or treat food allergies or sensitization found no benefit.

More recent data originate from the Canadian Synergy in Microbiota (SyMBIOTA) study, part of a larger Canadian research effort on the microbiota. This large 6-year longitudinal study is using metadata and samples from the Canadian Healthy Infant Longitudinal cohort to discern relationships between infant fecal microbiota and each of a group of factors, including antibiotic use, pets, and food sensitization (Kozyrskyj, 2015). Their data suggest that lower species richness in microbiota of infants (N=166, ages 3 and 12 months) might be a predictor of food (i.e., for egg, milk, and peanut) sensitization (SPT at age 12 months), even when adjusting for birth delivery mode, antibiotic use, or breastfeeding (Azad et al., 2015). Their research also revealed that sensitization occurred after the changes in microbiota diversity and richness, two commonly used indexes. Therefore, this ratio could potentially be used as a predictor of food sensitization, a potential surrogate for food allergies. Each quartile increase in richness at 3 months was associated with a 55 percent reduction in risk for food sensitization by 1 year (adjusted odds ratio [aOR] 0.45; 95% confidence interval [CI]: 0.23-0.87).

One meta-analysis of 10 RCTs (Kong et al., 2014) reported no significant difference in the incidence of food allergies comparing prenatal and postnatal probiotics supplementation with placebo or control. However, the food allergy assessments were not described in the meta-analysis. The World Allergy Organization (WAO) has recently conducted a systematic review on the relationship between supplementing the diet of pregnant or lactating women or infants with probiotics and allergy diseases. Six trials explored the relationship with food allergies but none of them made the direct comparison of probiotics versus no probiotics in pregnant women or in breastfeeding women for prevention of allergy in their children. None of the trials found differences in food allergy with probiotic supplementation (Cuello-Garcia et al., 2015). Two additional observational studies found during the committees' evidence-based search did not find an association between the addition of probiotics to infants' diets (Loo et al., 2014; West et al., 2013). The most recent work on the effect of prebiotics in

food allergy, also conducted by the WAO (Cuello-Garcia et al., 2016), is a guideline that seems to be based on a systematic review. The methods of systematic review, however, were not fully reported and no other source or citation to the systematic review was found. The guideline is based on studies investigating the relationship between prebiotics consumption by women during pregnancy or lactation and by healthy infants for preventing various allergic symptoms, including food allergy. Only one intervention study assessed the risk of developing food allergy in infants consuming an infant formula containing oligosacharides (Ivakhnenko and Nyankovskyy, 2013). That study (N=240) found that infants who had been fed with breast milk or oligosaccharide-supplemented infant formula had significantly fewer allergic reactions to food products compared to the infants fed the standard formula (3.92 percent and 4.84 percent versus 16.98 percent, respectively; $P<0.05$).

The committee concludes that, at this time, only a few studies have been conducted on the relationship between changes in the microbiota and food sensitization and, therefore, the evidence supporting this relationship is limited. RCTs on probiotic and prebiotics supplementation are few and have methodological limitations. Therefore, the committee concludes that the evidence is limited and does not yet support a decrease in food allergy risk from the use of probiotics or prebiotics by pregnant and lactating women or by infants. Additional research would be needed before recommending the use of prebiotics or probiotics to prevent the onset of food allergies.

Route of Delivery

The composition of the gut microbiota is influenced by route of delivery. Vaginally-delivered infants harbor bacterial communities resembling their mother's vaginal microbiota. In contrast, infants delivered by cesarean section have bacterial communities similar to those found on the skin surface (Dominguez-Bello et al., 2010). In light of the fact that the gut microbiome plays a central role in the development of immune regulation and oral tolerance, it is not surprising that investigators have examined the question of whether caesarean delivery increased the risk of food allergy.

In their systematic review, Marrs et al. identified 13 publications. Of these, five identified food allergy through OFCs. All 13 publications, except for the study of lowest quality, reported an increased risk of developing food allergy or food sensitization in children delivered by cesarean section (Marrs et al., 2013). Six of these associations were significant. However, only two included clinical food allergy diagnoses. Of the studies included for review, these two studies yielded the highest quality data. The studies used 2,803 consecutive mother-infant pairs from a Norwegian birth

cohort surveyed at 12, 18, and 24 months. When children were challenged with food orally using open or double-blind protocols, cesarean section was associated with a significantly higher risk for cow milk allergy. This occurred only in the subgroup of children with atopic mothers, however (aOR: 9.6 [95% CI: 1.8-52.4]) (Eggesbo et al., 2005). They also observed a nonsignificant 60 percent increase in egg allergy risk up to age 2 years (Eggesbo et al., 2003).

The Marrs review also included a prospective nested case-control study of 16,237 infants in Finland, ages 0 to 2 years (Metsala et al., 2010). Infants whose parents had received a reimbursement for the cost of specialized formula based on diagnosis of cow milk allergy were recruited, and the allergy was certified by a pediatrician using clinical exam, symptoms, elimination diet, SPT, and elevated sIgE or open challenge test (Metsala et al., 2010). Controls were randomly selected infants who were matched for age, sex, and delivery hospital. A significant relationship between cesarean delivery and cow milk allergy was observed (aOR: 1.18; 95% CI: 1.10-1.27).

Lodge et al. conducted a more recent review of systematic reviews and found two systematic reviews that included six original studies (Lodge et al., 2013). An association between cesarean section delivery and increase in food allergy is seen in only the three smallest studies. Two of these studies used specific IgE to food allergens as the outcome measurement. No conclusion was reached by the authors due to methodological flaws (i.e., small size studies or inaccurate food allergy measurement).

Since the Marrs' systematic review, six prospective cohort studies investigating associations between cesarean delivery and allergy risk have been published. They include studies conducted in Australia (Peters et al., 2014), France (Pele et al., 2013), the United Kingdom (Grimshaw et al., 2014), the United States (Luccioli et al., 2014; McGowan et al., 2015), and a five-country study (Depner et al., 2013) totaling 25,688 cases and controls. Overall, these studies found no significant associations between cesarean delivery and a variety of food allergies. The age of the children in the studies ranged from 0 to 5 years, and most included physician-diagnosed food allergy. Minimum criteria for diagnosis were sIgE to food allergen or a positive SPT. However, Luccioli et al. used physician diagnosis based on parental report (Luccioli et al., 2014). The largest study was the Australian HealthNuts Study (Peters et al., 2014), which recruited 5,276 infants at immunization clinics. These infants (2,848 of the total recruited) were investigated for open challenge-proven egg, peanut, and sesame allergy. However, no significant association was demonstrated with mode of delivery (Peters et al., 2014). Two retrospective case-control studies from Finland (N=3,181) (Pyrhonen et al., 2013) and the United States (N=291) (Dowhower Karpa et al., 2012) also did not show an association between cesarean delivery and food allergy.

The variation in association between mode of delivery and risk of food allergy may be partly explained by the fact that some studies have been unable to distinguish between whether cesarean delivery had been done on an elective or emergency basis (e.g., Koplin et al., 2012a; Peters et al., 2014). Emergency cesarean delivery is generally associated with rupture of membranes. As a result, the baby has some exposure to vaginal commensal bacteria during labor. However, the exposure is not usually to the same extent as vaginal delivery. However, because the proportion of emergency cesarean deliveries is usually relatively small compared to elective cesarean deliveries, we would still expect to see some association between mode of delivery and food allergy. This would be true even in those studies that could not differentiate emergency from elective cesarean deliveries, particularly in the larger and better powered studies. It also should be noted that the association between cesarean delivery and allergic risk could be misinterpreted due to the potential for reverse causation similar to breastfeeding.

Only a few observational studies have been conducted on the relationship between food sensitization or food allergy and cesarean delivery. The studies have methodological limitations. Therefore, the committee concludes that, at this time, evidence to support an increased risk for food sensitization or food allergy due to giving birth by cesarean delivery is limited. Strong evidence is unlikely to be forthcoming because of the ethical inability to randomize a population to deliver a baby by cesarean section. However, additional prospective research studies are needed.

Antibiotic Use

Antibiotics are known to cause short-term and, in some cases, lasting alterations in the microbiota (Faa et al., 2013). Infants can be exposed to antibiotics pre-, peri-, or postnatally as individual exposures or multiple exposures across this time, when the microbiome is not well established and is more susceptible to perturbations. The Marrs et al. systematic review reported no relationship between antenatal or postnatal antibiotic exposure and increased risk of food allergy (Marrs et al., 2013).

Since 2012, two prospective cohort studies of food allergic children have been published that were not included in the Marrs systematic review (Marrs et al., 2013). Studies in Finland (Metsala et al., 2013) and the United Kingdom (Grimshaw et al., 2014) and one retrospective case control study from the United States (Dowhower-Karpa et al., 2012) investigated associations between antibiotic exposure and food allergy risk. In those infants whose mother used antibiotics before or during pregnancy, respectively, the Finnish prospective, nested case-control study (N=16,237) reported a statistically significant 26 percent (aOR: 1.26; 95% CI: 1.20-1.33) and 21

percent (aOR: 1.21; 95% CI: 1.14-1.28) increased risk for cow milk allergy (determined by OFC) (Metsala et al., 2013). An even greater risk of cow milk allergy (aOR: 1.71; 95% CI: 1.59-1.84) was reported in infants who were treated with antibiotics between birth and 1 month of age (Metsala et al., 2013).

However, two other studies described below showed no statistically significant association. Cases (N=41) and controls (N=82) in the UK study were drawn from the Prevalence of Infant Food Allergy (PIFA) study (Grimshaw et al., 2014). Children in this study were part of the larger EuroPrevall birth cohort. Food allergy was diagnosed using SPT, physical exam, clinical history, sIgE, and DBPCOFC. Maternal antibiotic use during or after pregnancy or during breastfeeding was not associated with increased risk of food allergy in the infant. However, administration of the antibiotic to the infant was not assessed (Grimshaw et al., 2014). In a retrospective case (N=99) control (N=192) design, Dowhower Karpa et al. found no association between peripartum or neonatal antibiotic exposure and food allergy, diagnosed by positive sIgE or SPT (Dowhower Karpa et al., 2012).

Thus, taking together the results of the Marrs systematic review (Marrs et al., 2013) and the three studies published since, only one study (Metsala et al., 2013) has reported a link between antibiotic use and food allergy. The strengths of that study is the large sample size (more than 16,000 children) and the prospective design. However, additional studies are needed to conclusively demonstrate a link between antibiotic use in early life and food allergy risk.

Only a few studies have explored the relationship between food allergies and antibiotic use. The committee concludes that evidence from observational studies suggesting a link between antibiotic use in early life and food allergies is limited. Additional studies with information on the type and dose of antibiotic, the timing of exposure along the perinatal continuum, and whether the infant is repeatedly exposed are needed to conclusively demonstrate a link with food allergies.

Animal Exposure

As noted above, the premise of the "Hygiene" and "Old Friends" hypotheses is based on the concept that the lack of early childhood exposure to infectious agents, symbiotic microorganisms, and/or parasites increases susceptibility to allergic diseases and asthma by suppressing the natural development of the immune system (Strachan, 1989).

The Marrs review reported on four studies investigating associations between farm and animal exposure and food allergy (Marrs et al., 2013). In their review, only the HealthNuts Study supported the microbial hypothesis. The study reported data on risk of pets and siblings for the develop-

ment of challenge-proven egg allergy (Koplin et al., 2012a). It also assessed the role of these factors on any food allergy using latent class analysis, a sophisticated analytical epidemiological method (Peters et al., 2015). Marrs et al. also reported findings from the European Protection against Allergy Study in Rural Environments (PASTURE), which described a cohort of families living in proximity to farm animals in rural settings (Marrs et al., 2013). This study showed significantly less food sensitization in the cord blood of mothers who consumed raw cow milk (versus boiled milk) in the perinatal period. However, the authors applied a lower cutoff for sIgE concentration than is conventionally used (>0.2 versus 0.35 IU/ml), which may have overestimated the incidence of food sensitization (Ege et al., 2008).

Since 2012, several prospective cohort studies have investigated whether exposure to farm animals (Depner et al., 2013; Pele et al., 2013) or pets (Goldberg al., 2013; Grimshaw et al., 2014; Martin et al., 2015; Peters et al., 2015; Stelmach et al., 2014) influenced the risk of food allergy or food sensitization. Depner et al. performed an additional analysis of data from 686 children in the rural European PASTURE cohort (Depner et al., 2013). Again using sIgE as their diagnostic criterion for food sensitization, they explored the more traditionally used sIgE cutoff of 0.35 IU/ml compared to 0.2 IU/ml in their previous study by Ege et al. (2008). They found that allergen-specific IgE levels rarely exceeded 0.35 IU/mL (<3% of all children) at age 1 year and the 95th percentiles at 1 year were consistently less than 0.7 IU/mL (RAST class 2) for any IgE. The only exception was cat (1.3 IU/mL) (Depner et al., 2013). They also found that early life exposure to farm animals, such as sheep, goats, and rabbits, did not confer protection against food allergen sensitization. However, exposure to farming increased (P=0.0015) the risk of food allergen sensitization (aOR: 2.11; 95% CI: 1.33-3.34). A total of 793 (378 farm and 415 nonfarm) children were included in the analyses. Pele et al. also reported no effect of farm animal contact on food allergy incidence in more than 1,400 children participating in the PELAGIE mother–child cohort. However, mold or dampness in the home increased (P≤0.001) the incidence of food allergy (23.9% versus 8.8%, yes versus no) in this cohort, as measured by parent report (Pele et al., 2013).

All other prospective cohort studies published since 2012 investigated exposure to pets. Two studies with a total of 350 children reported no association between pets in the home (Israel) and food sensitization (measured by specific IgE to cow milk) (Goldberg et al., 2013) nor an association of pet ownership (United Kingdom) with food allergy risk (measured by DBPCOFC or convincing history of anaphylaxis) (Grimshaw et al., 2014). In contrast, Stelmach et al. reported an increased risk of food allergy based on diagnosis by a doctor following international guidelines (aOR: 1.48; 95% CI: 1.02-2.16) associated with pets in the home during pregnancy in

a cohort of 501 children from the Polish Mother and Child Cohort Study (REPRO_PL cohort) (Stelmach et al., 2014).

Two studies from the HealthNuts cohort, a prospective, population-based cohort of 5,276 infants age 12 months in Melbourne, Australia, investigated whether direct exposure to pets (Koplin et al., 2012a; Peters et al., 2015) or the co-incidence of eczema (Martin et al., 2015) moderated the effect of pets on food allergy risk. Koplin et al. examined the relationship between environmental and demographic factors and egg allergy, the most common food allergy in infants and young children (Koplin et al., 2012a). Using SPT to egg white and oral food challenge at 12 months revealed that children with a pet dog at home (dog ownership ascertained by questionnaire) were less likely to develop egg allergy than those without a pet dog at home (aOR: 0.72; 95% CI: 0.52-0.99). Peters et al. observed that, compared to not having a dog in the home, having a dog significantly reduced the risk of multiple food allergies (including peanut) by 60 percent (aOR: 0.4; 95% CI: 0.21-0.73), whereas having a dog that was kept outside only (versus no dog) provided no protection. In this latter scenario, a significantly increased risk in egg allergy was actually observed (aOR: 1.56; 95% CI: 1.1-2.21) (Peters et al., 2015). Within the same cohort, Martin et al. compared the effect of dog or cat exposure on infants with (N=2,795) or without (N=1,903) eczema (Martin et al., 2015). Having a dog reduced the risk of food allergy in infants with eczema (aOR: 0.7; 95% CI: 0.5-0.9), but not in infants without eczema. A similar effect on food allergies was observed for infants with (aOR: 0.6; 95% CI: 0.4-0.9) or without eczema in homes with cats (Martin et al., 2015).

Results from studies exploring the relationship between animal exposures and food allergies are inconsistent. The few observational studies related to living on a farm found that exposure to farm animals offers no protection against food allergies. Also, from observational studies, the committee concludes that evidence is limited regarding the potential for a close interaction with a pet being more protective against a food allergy than pet ownership in general or having a pet who is restricted to outside the home. Further studies should be conducted on the nature of the association between exposure to farm animals or pet ownership and food allergies.

Allergen Avoidance Hypothesis

As mentioned in the introduction of this chapter, in considering the risk determinants for developing food allergies, the committee focused on the prenatal and early childhood developmental periods. In that vein, this section focuses on allergen exposure beginning at conception. The allergen avoidance hypothesis was predicated on the basis of the concept that

avoiding common food allergens early in life when the immune system is developing would prevent the onset of food allergies.

Exposure to Antigen Through Maternal Diet During Pregnancy or Lactation

Maternal diet during pregnancy and lactation has been of great interest in understanding the etiology of food allergies in offspring. The fetal programming hypothesis supports the idea that the maternal diet has long-term influence on children's health (Barker, 1990; Langley-Evans, 1997). Its application to food allergies would suggest that consuming specific allergenic foods during this critical period might be associated with the development of the immune system in utero that may later manifest itself as food allergies over the life course, given specific childhood exposures. Results from two prospective cohort studies (Bunyavanich et al., 2014; Frazier et al., 2014) (total N=9,482 mother–child pairs) show that a higher consumption of allergenic foods before or during pregnancy (e.g., peanut), as measured by a food frequency questionnaire, was associated with a reduced risk of having a child with food allergies. This finding supports the fetal programming hypothesis. The HealthNuts Study also assessed the role of allergen avoidance in pregnancy and lactation and the risk of challenge-proven egg allergy and found no association (Koplin et al., 2010). Another recent prospective cohort study (Pele et al., 2013) reported an association between maternal pre-pregnancy consumption of shellfish and food allergy (1.62; 95% CI: 1.11-2.37). However, this study assessed food allergy by parental report. Randomized studies on this subject have involved the elimination of certain allergenic foods as opposed to increasing their consumption among primarily high-risk families. Kramer and Kakuma conducted a high-quality systematic review that included three RCTs of foods avoided during pregnancy and/or lactation and the outcomes of egg and milk sensitization (but not food allergy itself) among women at high risk of having an atopic offspring (Kramer and Kakuma, 2012). In two of the RCTs (Falth-Mangnusson and Kjellman, 1987; Lilja et al., 1988) (total N=334), women either avoided or decreased their intake of cow milk and eggs beginning in the third trimester of pregnancy and this was associated with a nonsignificant reduction of egg sensitization in their infants at 6 months, but not at 18 months. Sensitization for cow milk allergy was not reduced at either time point. The remaining RCT (Appelt et al., 2004) (total N=497) had women totally avoid peanuts, nuts, and fish as well as decrease their intake of cow milk and eggs beginning in the third trimester through 1 year postpartum. This study found no significant associations with milk or peanut sensitization in offspring at age 1, 2, or 7 years. However, for egg sensitization, an increased risk was seen at age 2 years only (1.91; 95% CI:

1.03-3.5). This trial is published in abstract form only, with no details on the randomization being available.

Another recent systematic review by de Silva et al. found seven high-quality studies on maternal diets and also concluded that "overall, the evidence is not strong enough to recommend changing the diet or supplements of pregnant or breastfeeding women" to prevent food allergies in infants at normal or high risk of food allergies (de Silva et al., 2014).

The committee concludes that, to date, study findings provide limited evidence to support or discourage eliminating allergenic foods from the diet of pregnant or lactating women at high risk of having a child with allergies. Because the evidence about the benefits of consuming or eliminating allergenic foods during pregnancy and lactation is not clear, additional RCTs are warranted before providing advice in this regard. Studies exploring the effect on the development of food allergies in children of intake of allergens by the mother are in progress.

Breastfeeding

Breastfeeding is an important early life factor that determines an individual's gut microbiota and likely indirectly modulates immune responses. In addition, breastfeeding transfers bioactive compounds from the mother to the child that can also influence immune responses. However, the evidence assessing any potential link between breastfeeding and food allergies risk is not clear. Systematic analysis of observational studies on the protective effect of breastfeeding have shown conflicting results, and many of the studies included were conducted decades ago when food allergy was uncommon and methods of assessment were limited (Grimshaw et al., 2009). Most systematic reviews have failed to find a specific beneficial effect of breastfeeding on food allergy or food sensitization (de Silva et al., 2014; Kramer and Kakuma, 2012). Moreover, two cohort studies reviewed in de Silva et al. (2014) suggested that exclusive breastfeeding for 8 weeks did not reduce the risk of cow milk allergy (measured by parents report followed by SPT and oral food challenge) (Saarinen et al., 1999) and breastfeeding for 5 months or more may increase the likelihood of sensitization to egg in infants at high risk of atopy, although food allergy was not assessed (Wetzig et al., 2000). Importantly, the apparent negative effects of extensive breastfeeding may relate to the delayed introduction of first complementary foods rather than the effects of breast milk per se (see the section "Dual Allergen Exposure Hypotheses" in this chapter). Alternatively, these recent findings of increased risk of breastfeeding may simply be a misinterpretation of the data related to the reverse causation phenomenon (see the section "Methodological Limitations" in this chapter). One study found that the effects

of breastfeeding on food sensitization can be modified by genetic variants relevant to allergic diseases (Hong et al., 2011).

Lodge et al. undertook a systematic review to assess the role of breastfeeding in food allergy (Lodge et al., 2015). The review included nine cohort and four cross-sectional studies. The numbers of participants ranged from 163 to 21,766 (cohort studies) and from 1,278 to 13,110 (cross-sectional studies). No association with food allergy was found for more versus less[9] breastfeeding in the pooled estimate (6 cohort and 6 cross-sectional), although study heterogeneity was high. Various sub-analyses failed to find any protective association of breastfeeding for food allergy. The primary issue concerning the quality of these studies was the poor accuracy of outcome assessment. Only two studies used OFCs, the recognized gold standard for food allergy diagnosis; most studies relied on parental report of symptoms or on physician diagnosis.

The committee's review of the evidence found eight studies (seven cohort and one cross-sectional) that explored breastfeeding as a food allergy risk determinant. Although Ivakhnenko and Nyankovskyy showed that infants (N=240) who were breastfed had significant risk of developing an allergy to cow milk protein and had gastrointestinal symptoms of food allergy by age 18 months compared with those who were fed standard infant formula, the risk of bias of this trial was high due to unclear definitions and diagnoses of food allergy outcomes and high dropout rates (Ivakhnenko and Nyankovskyy, 2013). Two studies performed only unadjusted analyses so the results (mostly no significant associations) are likely to be confounded (Grimshaw et al., 2014; McGowan et al., 2015). The other four cohort studies showed associations between longer duration of breastfeeding (any or exclusive) and a lower risk of developing cow milk sensitization (Liao et al., 2014; N=258), food allergy (Stelmach et al., 2014; N=501; aOR: 0.88; 95% CI: 0.82-0.95), or multiple food allergy (predominantly egg) (Peters et al., 2015; N=5276; aOR: 1.17; 95% CI: 1.09-1.24) after adjusting for potential confounders. The single cross-sectional study did not find a significant association between exclusive breastfeeding (poorly defined) and food allergies among children (N=386) ages 0 to 18 years with atopic dermatitis. Luccioli et al. collected data from prospective cohort of children (N=1,363) who participated in the Infant Feeding Practices Study (IFPS) II and also found no significant relationship between breastfeeding for various periods and food allergies (Luccioli et al., 2014). Only some studies used OFC as an outcome measure (Grimshaw et al., 2014; Peters et al., 2015). The single

[9] More or Less: The authors included all studies. When multiple odds ratios were available for a single study, the authors preferentially selected estimates for exclusive breastfeeding, then longest duration versus shortest. When multiple ages of outcome were available, the authors chose the oldest up to 18 years.

cross-sectional study did not find a significant association between exclusive breastfeeding (poorly defined) and food allergies among children, ages 0 to 18 years, with atopic dermatitis (Mailhol et al., 2014).

As mentioned above, investigation of the role of breastfeeding in allergic disease is particularly prone to confounder bias because families who are at high risk of allergy are more likely to breastfeed, as recommended by some guidelines. In addition, the composition of human milk changes from colostrum to late lactation and throughout the day, and differs from mother to mother (Ballard and Morrow, 2013) and could therefore affect health outcomes of the child. Compounding the difficulties in this area is the inability to randomize to a nonbreastfeeding arm, as this would be unethical given the many well-established benefits of breastfeeding, such as protection against some chronic diseases, obesity, and infections.

The committee concludes that due to inconsistencies in results from prospective studies, the evidence that breastfeeding is protective against food allergies is limited. Strong evidence is unlikely to be forthcoming because of the ethical inability to randomize a population to breastfeeding alternatives. However, additional well-designed prospective research studies in infants at low and high risk for food allergy are needed.

Types of Infant Formula

Significant interest has been expressed in the use of modified infant formulas—especially partially hydrolyzed formulas (PHF), which include longer cow milk peptides, and extensively hydrolyzed cow's milk formulas (EHF), which include di- and tri-peptides derived from cow milk protein—as a way to avoid allergen exposure and prevent early childhood allergic disease. As a result of demand from families with a history of allergy seeking readily available primary prevention interventions, industry has responded with the development of a variety of "allergy prevention" formulae, and expert bodies have provided recommendations regarding their use for preventing allergies. Some infant feeding guidelines have recommended that hydrolyzed formula can be considered as primary prevention therapy for some allergic diseases. In the United States, a policy statement from the American Academy of Pediatrics indicated that in studies of infants at high risk of atopy, modest evidence supports the delay or prevention of onset atopic dermatitis by the use of hydrolyzed, and particularly extensively hydrolyzed, formulas (Greer et al., 2008). In Australia, the Australasian Society of Clinical Immunology and Allergy *Guidelines: Infant Feeding and Allergy Prevention* no longer recommends hydrolyzed formulas as primary prevention therapy for allergic diseases. The guidelines now state, "Based on a recently published review of studies (Boyle et al., 2016), no consistent convincing evidence supports a protective role for partially hydrolyzed for-

mulas (usually labelled 'HA' or Hypoallergenic) or extensively hydrolyzed formulas for the prevention of eczema, food allergy, asthma or allergic rhinitis in infants or children" (ASCIA, 2016b).

A Cochrane review supports the use of hydrolyzed formula to prevent allergy in high-risk infants who are unable to be completely breastfed but not for those infants who can breastfed (Osborn and Sinn, 2006, 2009). Critics of this Cochrane review have pointed out that it suffers from small-study publication bias (i.e., scarcity of small negative studies) (Lowe et al., 2013) and thus the beneficial effect of PHF was likely overestimated. Due to the methodological concerns and inconsistency of the findings of the studies included in the review, the authors themselves recommend that further larger trials be conducted. Subsequently, new evidence from a large intervention trial of 620 high-risk infants (the Melbourne Atopic Cohort Study) has emerged. Findings from this trial challenge the effectiveness of PHF (Lowe et al., 2011).

The German Infant Nutritional Intervention (GINI) study was a trial aimed at exploring the effect of hydrolyzed formulas (compared to cow milk formula) in preventing allergic diseases in infants at high risk of atopy. Infants (N=2,252) were randomly assigned at birth to receive partially or extensively hydrolyzed whey formula, extensively hydrolyzed casein formula, or cow milk formula as milk substitute for the first 4 months when breastfeeding was insufficient. In a follow up until the children were age 6 years, hydrolyzed infant formulas prevented eczema and allergic manifestation (atopic dermatitis, food allergy, allergic urticaria, asthma, and hay fever/allergic rhinitis) (von Berg et. al., 2008). However, subsequent results showed little evidence of an ongoing preventive effect between the ages of 7 and 10 years (von Berg et al., 2013a). These more recent findings have not yet been incorporated into the Cochrane review. Likewise, the European Academy of Allergy & Clinical Immunology (EAACI) systematic review included both the Cochrane review and the Melbourne Atopic Cohort Study as well as the preliminary GINI results but did not include the latest results from the GINI study. Therefore, their conclusion supported the protective effect for PHF. Interestingly, the most recent findings from the GINI study suggest that casein-predominant EHF might be expected to have a greater biological effect than PHF because the formula is more extensively modified (von Berg et al., 2013a,b). However, most infant feeding guideline recommendations are based on the reality that PHF is both cheaper and more palatable than EHF and therefore should be considered instead of EHF. Additionally, in some countries EHF is only available with a prescription, which significantly increases costs to the health care system.

Most recently, Boyle et al. conducted a systematic review and meta-analysis of studies to determine whether feeding infants with hydrolyzed formulas reduces their risk of allergic disease (Boyle et al., 2016). Their

search yielded 37 intervention trials of more than 19,000 participants, although few studies included in the meta-analysis were published in the past 10 years. For the majority of studies, infants were considered to be at high risk of allergy because a first degree relative had a history of allergic disease. Overall, the pooled data showed no significant reduction in risk of any food allergy in infants ages 0 to 4 years when they were fed EHF or PHF compared to standard cow milk formula. On concluding the review, the authors found that previous studies suffered from unclear or high risk of bias. The review also showed evidence of conflict of interest and had inadequate methods of randomization and treatment allocation (selection bias). The authors recommended that international infant guidelines should be revised to remove the recommendation that hydrolyzed formula protects against allergic disease. In addition, a review of systematic reviews also stated that evidence is insufficient to conclude that the use of hydrolyzed formulas may reduce food allergy or sensitization when compared with standard formula in children with high atopy risk, and no evidence supports hydrolyzed formulas over breast milk for prevention of food sensitization or food allergy (Lodge et al., 2013).

The committee concludes that the studies on the effects of PHF or EHF for preventing food allergies have methodological flaws and their findings are inconsistent. Therefore, evidence on the effect of PHF or EHF for the prevention of food allergies is limited. If this area were to be investigated, high-quality RCT studies on the effects of PHF and EHF to determine whether hydrolyzed infant formulas influence the onset of food allergies would be needed before the use of these formulas could be recommended for prevention.

Dual Allergen Exposure Hypothesis

The "Dual Allergen Exposure" hypothesis proposes that allergic sensitization to foods may occur through exposure to low doses of allergen through the skin due to food allergens in the environment being absorbed through a damaged skin barrier (such as in eczema or presence of filaggrin loss-of-function mutations). This hypothesis also proposes that oral exposure to these allergens through consumption of allergenic foods early in infancy, before skin sensitization, leads to lasting oral tolerance and prevents the development of sensitization and allergy even with subsequent skin exposure (Du Toit et al., 2016; Lack, 2012; Lack et al., 2003) (see Figure 5-4).

Mechanistic evidence supporting this hypothesis comes from mouse models (Strid et al., 2005). Recent studies suggest that the activation of innate immune pathways in the skin through thymic stromal lymphopoietin, an interleukin (IL)-7-like cytokine associated with atopic dermatitis

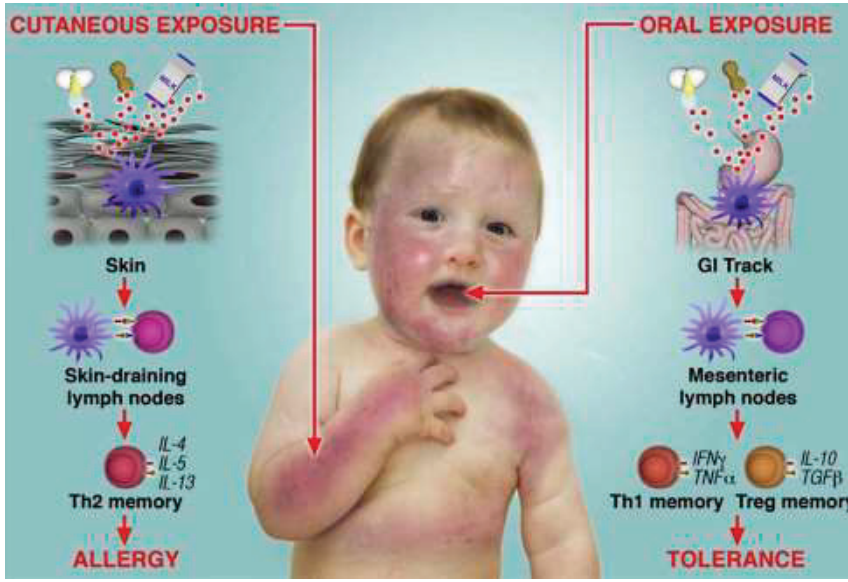

FIGURE 5-4 Dual-allergen exposure hypothesis for the pathogenesis of food allergy. Allergic sensitization can result from cutaneous exposure and tolerance is favored as a result of oral exposure to food.
NOTE: GI = gastrointestinal, Treg = T regulatory.
SOURCE: Lack, 2012. Reprinted with permission from Elsevier.

and asthma, and basophil activation may play a key role in development of food allergy secondary to cutaneous sensitization in animal models (Muto et al., 2014; Noti et al., 2014).

Studies of human populations to date have primarily focused on peanut allergy. One human study demonstrated that peanut allergens can be found in the household environment and that higher exposure to environmental peanut antigens appears to increase the risk of peanut allergy in children with either filaggrin loss-of-function mutations or atopic dermatitis (Brough et al., 2014).

Other contextual factors support this hypothesis. Weaning practices in developed countries, coupled with high eczema rates may contribute to the high prevalence of food allergy. In the Western world, eczema prevalence is as high as 25 percent by age 1 year (Martin et al., 2013). (As noted previously, eczema frequently co-associates with food allergy, with 50 percent of those with early onset, moderately severe eczema developing food allergy by age 1 year [Martin et al., 2015].) This, coupled with recommendations

in the late 1990s and early 2000s to delay allergenic solids (e.g., egg until age 24 months and peanut until age 3 years) provide the correct temporal framework for this practice to have had a potential effect on the epidemic (Koplin and Allen, 2013). The following section presents the evidence on the main factors related to this hypothesis, namely skin barrier function and timing of introduction of foods. The section also includes the results from recent studies on introduction of diet diversity in early life.

Adequate Early Life Skin Barrier Function

It is important to note that mutations leading to filaggrin loss-of-function appear to be equally common among individuals with asymptomatic food sensitization and those with true food allergy (Tan et al., 2012a), suggesting that filaggrin confers a risk for food sensitization—the first step to food allergy—but not for food allergy itself. Previous studies reporting an association with food allergy were not designed to untangle any differential effect between sensitized tolerant and sensitized allergic individuals (Brown et al., 2011). Recent data from the Isle of Wight birth cohort used path analysis to demonstrate that the effect of filaggrin loss-of-function mutations on food allergy at age 10 years occurred indirectly through an effect on eczema and food sensitization in early childhood (Venkataraman et al., 2014). Together, these findings suggest that skin barrier function plays a role in sensitization status but not in food allergy or tolerance.

Two recent RCTs have investigated the application of daily moisturizer from birth in an attempt to reduce infantile eczema. Although the studies are small in size, the results support the idea that the integrity of the skin barrier is related to preventing food allergy. One RCT in the United States and the United Kingdom (N=124) examined the effects of an intervention that consisted of the use of an emollient at least once per day on neonates at risk of atopic dermatitis (Simpson et al., 2014). Atopic dermatitis was measured at 6 months. The results demonstrated a significant protective effect against atopic dermatitis (relative risk [RR]: 0.50; 95% CI: 0.28-0.9; P=0.017). The second trial examined the effect of using a moisturizer from the first week of life on eczema as a primary outcome and egg sensitization (but not allergy) as a secondary outcome in a group of 118 neonates at high risk of atopic dermatitis (Horimukai et al., 2014). At 32 weeks postnatal age, application of moisturizer to neonates was effective at preventing atopic dermatitis after 32 weeks, but unfortunately the trial showed no evidence of a reduction in sensitization to egg white in this relatively small study of 118 infants. However, a higher proportion of infants with atopic dermatitis showed egg sensitization compared with infants without atopic dermatitis.

The committee concludes that limited but consistent evidence on mutations on the filaggrin gene and on preventing eczema at early age suggests that impairment of skin barrier function plays a role in sensitization status as the first step on the path to food allergy.

Timing of Introduction of Solids and Infant Feeding

The dual antigen exposure hypothesis states that the second factor in the two steps to food allergy is the delay in oral allergen exposure. Until recently, delayed introduction of solids and particularly allergenic solids into the infant's diet was a strategy adopted in many countries with the aim of reducing or preventing food allergies. Although exclusive breastfeeding for the first 6 months of life has been universally recommended in all countries to promote its health benefits (WHO, 2016), as described above, no evidence indicates that exclusive breastfeeding prevents the development of food allergies.

In 2008 and 2009, specific dietary advice to avoid peanuts in the United Kingdom and the United States, respectively, was rescinded (Greer et al., 2008; NHS, 2015a) based largely on the premise that evidence was insufficient to promote avoidance as a strategy to prevent food allergies. More recent advice does not state whether infants should actively receive allergenic foods, and if so at what age. Indeed, a recent nationwide UK dietary survey showed that only 8 percent of children younger than age 1 year had consumed any foods containing peanut (McAndrew et al., 2012).

The EAACI systematic review includes three cohort studies that found that the concept of delaying solid foods or cow milk consumption until 4 months of age does not appear to confer any benefit in terms of food allergies (de Silva et al., 2014). Most recently, evidence has been accumulating about the benefits of introducing allergens early. This section will focus on the most recent RCTs that evaluate the benefits of introducing allergens early in life.

In 2008, Du Toit et al. found that the level of peanut allergy in Jewish children in the United Kingdom was 10-fold higher than that of Jewish children in Israel and that median consumption of peanut protein was 0 g per month in the United Kingdom versus 7.1 g per month in Israel[10] (Du Toit et al., 2008). Based on these results, Du Toit et al. conducted a large RCT to formally assess whether early introduction of peanut prevented the development of peanut allergy at age 5 years (Du Toit et al., 2015). The LEAP (Learning Early about Peanut Allergy) study randomized 640 highly

[10] At the time, it was common practice in Israel to introduce a peanut snack (Bamba) as a weaning food into the diet of infants around the age of 4 to 6 months. In contrast, UK guidelines at the time recommended that children avoid peanut until after age 3 years.

atopic children with severe eczema and/or egg allergy to either consumption or avoidance of peanut at ages 4 to 11 months and the intervention continued until the children were age 5 years. The results showed that early consumption of peanut reduced the prevalence of peanut allergy (diagnosed by DBPCOFC) at age 5 years by more than 80 percent. The reduction was effective in children who were either SPT negative or SPT positive to peanut (wheals of 1, 2, 3, or 4 mm). As 17 percent of the LEAP cohort had peanut-specific IgE ≥0.35 at entry into the study and 27 percent had detectable IgE (≥0.1 kU_A/L), prevention of peanut allergy was occurring for the majority of children after IgE sensitization had occurred; this represents secondary prevention (Du Toit et al., 2013). However, for infants in the group who were SPT negative at enrollment and who had no detectable IgE, early consumption of peanut also reduced the prevalence of peanut allergy (6 percent and 1 percent in the peanut avoidance group and in the peanut consuming group, respectively). This primary prevention strategy also was effective in a secondary analysis in children of different races.

As reviewed in Chapter 4, at the moment, we do not have definitive biomarkers to define tolerance. It is of interest that during the LEAP study, an early rise in peanut-specific IgG4 and peanut-specific IgG4/IgE ratio occurred in the peanut-consuming group (Du Toit et al., 2015). A high peanut-specific IgG4/IgE ratio was associated with protection against peanut allergy. Although the peanut-specific IgG4/IgE ratio decreased in the original peanut-consuming group during the period of peanut avoidance in the follow-up LEAP-On Study (Du Toit et al., 2016), it remained significantly higher than in the original peanut avoidance group. Interestingly in LEAP, peanut-specific IgE was not significantly different between the original peanut consuming and peanut avoidance groups throughout the study. However, peanut-specific IgE to Ara h 2 started to decline in the original peanut consuming group after 2.5 years of consumption, and continued to decline despite 1 year of peanut avoidance in that group between ages 5 and 6 years (Du Toit et al., 2016). This suggests potentially that high production of allergen-specific IgG4 may be important in the initiation of tolerance and that inhibition of IgE synthesis may be important in long-lived tolerance.

In order to determine whether early introduction of peanut was effective at preventing peanut allergy in the absence of ongoing peanut consumption, the LEAP-On Study was designed (Du Toit et al., 2016). Children (N=566) from the original LEAP cohort, irrespective of whether they were in the original peanut consumer or avoidant group, were asked to completely avoid peanut consumption for 1 year and then their peanut allergy status was determined by OFC, SPT, and specific IgE. Despite high adherence to this protocol of avoidance, the protective effects of early consumption remained and the original peanut consuming group had a 74 percent reduction in peanut allergy at age 6 years compared to the original peanut avoid-

ant group. Another follow-up study, the LEAP Adlib Study, is currently being designed. In this trial the original LEAP participants will continue to be followed up for a 4-year period of ad libitum consumption of peanut to determine whether the effects of early introduction remain protective.

In regard to other foods, observational studies suggest that delayed introduction of egg (Koplin et al., 2010), cow milk (Katz et al., 2010), and wheat (Poole et al., 2006) are associated with an increased risk of those respective food allergies. Various trials are in progress to confirm or refute these observations (see Table 5-1). Early evidence from Koplin and Allen (2013, p. 830) "suggests that if a window of opportunity for promoting tolerance exists, it may be different for each food" (Koplin and Allen, 2013, p. 830). However, further investigation is required. In the large HealthNuts study, where egg allergy was determined by challenge (among other food allergens), it was found that early introduction (age 4 to 6 months) of hen egg in the infant's diet protected against the development of egg allergy, but introduction after 6 months of age was associated with significantly increased risk of developing egg allergy and even more so if introduced after age 9 months (Koplin et al., 2010). The results from the LEAP study (Du Toit et al., 2015) also are supported by data from the Solids Timing for Allergy Research (STAR) trial, which randomized 86 infants with eczema to egg avoidance or early regular egg consumption from age 4 months. The study found a lower, nonsignificant prevalence of egg allergy by 12 months in the intervention group (33% versus 51%; P=0.11) (Palmer et al., 2013). In a large birth cohort study conducted in Israel, IgE-mediated cow milk allergy did not occur in infants (N=13,019) who had received cow milk–based formula regularly in the first 2 weeks of life. In contrast, children who had formula milk introduced at age 3 to 4 months had the highest rate of cow milk allergy (Katz et al., 2010).

The EAT (Enquiring about Tolerance) intervention trial, which has recently been published, also examined the effects of early introduction of common allergenic foods. Unfortunately, compliance with intervention in this trial was low and the intention to treat analysis did not reveal a protective effect from early introduction of solids. In contrast, the per protocol analysis did suggest that early introduction of other common allergenic foods into the diet of infants may protect against the development of food allergies in general (Perkin et al., 2016). In the EAT study, exclusively breastfed infants (N=1,303) were recruited in the general population and randomly assigned at age 3 months to either introduction of six allergenic foods (cooked egg, peanut, cow milk, sesame, white fish, and wheat) (Early Introduction Group) or to the current recommended practice of exclusive breastfeeding until approximately 6 months of age (Standard Introduction Group). The primary outcome was determined to be food allergy between 1 and 3 years of age determined in nearly all participants by DBPCOFC.

The study showed a modest and nonsignificant 20 percent overall decrease in the rate of food allergies in the Early Introduction Group (5.6 percent compared to 7.1 percent in the Standard Introduction Group). However, in a per protocol analysis, the prevalence of any food allergy was significantly lower in the Early Introduction Group compared to the Standard Introduction Group (2.4 percent versus 7.3 percent; P=0.01) representing a 66 percent reduction in the prevalence of overall food allergy. The effects were most apparent for peanut allergy in the per protocol analysis (0 percent in the Early Introduction Group versus 2.5 percent in the Standard Introduction Group; P=0.003) and for egg allergy (1.4 percent versus 5.5 percent; P=0.009). These changes also were accompanied by decreases in SPT to the foods in the Early Introduction Group. A dose–response analysis revealed that 2 g of peanut protein or egg white protein per week appeared to be most protective against these food allergies. Interestingly 2 g of peanut protein per week is the dose that was observed in the Du Toit et al. study in Israel where children appeared to be protected against peanut allergy (Du Toit et al., 2008).

The EAT study shows that early introduction of foods was safe, as the intervention group did not experience an increased number of reactions compared to the controls. However, it is difficult to make any certain conclusions from the EAT study about the efficacy of early introduction of foods, given that efficacy was seen only in the per protocol group. Although careful analysis did not show any evidence of bias that could account for these results, it is not possible to completely exclude unmeasured bias.

A number of factors appeared to be associated with nonadherence to early introduction of foods relating to atopic predisposition. These include ethnicity, family life, readiness to eat solid foods, and parental perception of possible food allergic reactions (IgE- or non-IgE-mediated). The EAT study therefore suggests that if early introduction of allergenic foods from 3 months of age is to be adopted as a prevention strategy, numerous potential obstacles must be overcome with respect to implementation of adherence. Importantly, early introduction of allergens in the LEAP study or the EAT study did not reduce duration of breastfeeding (Feeney et al., 2016). It is noteworthy, however, that the participants in the EAT study are from the general population rather than a high-risk population and therefore any effect size may be less pronounced compared to the LEAP study. Furthermore, the intervention was more complex because it involved six foods, not one.

Diet diversity Two studies have examined the role of diversity of early life food exposures, which may be one factor that coincides temporally with the rise in food allergy, in the development of food sensitization and food allergy. A prospective birth cohort study of 856 children found that

increased diversity of complementary foods introduced in the first year of life was associated with a reduced risk of food allergy (Roduit et al., 2014). In another prospective longitudinal study of 123 participants, the authors found that dietary patterns in the first year of life consisting of more fresh fruit and vegetables and home-prepared meals were associated with less challenge-proven food allergy by the age of 2 years (Grimshaw et al., 2014).

The committee concludes that results of the LEAP trial provide strong evidence that early introduction of peanut (between 4 and 11 months) is protective against peanut allergy in infants who are at high risk (as defined by early onset eczema or coexistent egg allergy). Limited evidence from observational studies also suggests that delaying the introduction of egg, cow milk, and wheat to decrease risk of those food allergies has no benefits. Results from one RCT show a not significant decrease in food allergy if allergenic foods (i.e., cooked egg, peanut, cow milk, sesame, white fish, and wheat) are introduced starting at 3 months of age. More studies are necessary to assess whether early introduction of other allergenic foods, in addition to peanut, affect food allergy.

Nutritional Immunomodulation Hypothesis

Proper functioning of the immune system is crucial to health, and diet is a major and common exogenous factor modulating immunocompetence. Thus, nutrition research has focused on the role of foods or specific food components in enhancing immune system responsiveness to challenges and thus improving health and reducing disease risks (Albers et al., 2005). Along these lines, evidence supports the notion that sensitization or expression of food allergies does not depend exclusively on the food allergens per se, but on the exposure to other immunomodulatory exposures, such as other dietary factors, during specific critical periods. This section provides an overview of the immunomodulatory capacities of selected food components, including vitamin D, selected fatty acids, and folate. Better knowledge of these interactions should provide additional avenues for preventing and/or ameliorating food allergies.

Vitamin D

Vitamin D has become increasingly recognized as an important regulator of immune response (Adams and Hewison, 2008). $1,25(OH)_2D$ can be converted from 25(OH)D locally based on widespread expression of vitamin D activating enzyme CP27B in a broad spectrum of cells involved in immune response, such as macrophages, B cells, and T cells. This active form of vitamin D exerts its function through interaction with the vitamin D receptor (VDR), which is also present in the above immune cells. Vitamin

D has been demonstrated to inhibit the differentiation of B lymphocytes to plasma cells and suppress immunoglobulin production (Chen et al., 2007). However, the effects of vitamin D on T lymphocytes are more complicated. Vitamin D has been shown to inhibit T cell proliferation and production of Th1 cytokines, which induces a shift in the balance between Th1 and Th2-type cytokines toward Th2 dominance (Cantorna et al., 2004; Iho et al., 1985; Reichel et al., 1987). In contrast, in CD4+ and CD8+ T-cells from human cord blood, vitamin D inhibits IL-12-generated interferon (IFN)-γ production and IL-4 production, as well as IL-4-induced expression of IL-13.

It has been hypothesized that in the presence of vitamin D, T regulatory cells function normally to suppress inappropriate Th1 and Th2 responses to environmental exposures leading to disease (Litonjua and Weiss, 2007). Research suggests that vitamin D deficiency might impair epithelial barrier integrity, which would in turn result in increased and inappropriate mucosal exposure to food antigens and also a pro-sensitization immune imbalance that compromises immunological tolerance (Roider et al., 2013).

Two opposing hypotheses have been proposed regarding the connection between vitamin D and allergic disease in general. In 1999, Wjst postulated that excess vitamin D might be associated with an increased risk of allergic disease based on its effects on the shift in the T-cell phenotype from a balance on Th1/Th2 to aTh2 dominance, and parallel patterns of increased oral vitamin D supplementation with a "Western lifestyle" (Wjst, 2008; Wjst and Dold, 1999). In contrast, Litonjua and Weiss raised an opposite hypothesis, suggesting that vitamin D might protect against asthma and allergies (Litonjua and Weiss, 2007, 2008). They believed that the immune effects of vitamin D are probably found on dendritic cells and Treg cells, and that these effects may differ depending on the stage of human development.

Two lines of ecological enquiry support the more recent hypothesis that low vitamin D may increase the risk of food allergy. First, countries further from the Equator (and thus receiving lower ambient ultraviolet radiation) have recorded more pediatric admissions to the hospital for food allergy–related events, and more prescriptions of hypoallergenic formulas for the treatment of cow milk allergy and adrenaline auto injectors for the treatment of anaphylaxis in children, compared to countries closer to the Equator (Camargo et al., 2007; Mullins et al., 2009, 2010; Rudders et al., 2010). These findings appear to be independent of longitude, socioeconomic status, or physician density. Second, children receiving care at a large medical center in Boston for food-related acute allergic reactions were more likely to be born in autumn/winter than in spring/summer (Vassallo et al., 2010). Similar relationships of food allergy to birth seasonality have been reported in the Southern hemisphere (Mullins

et al., 2011). Furthermore, children residing in Australia's southern states have twice the odds (95% CI: 1.2-5.0) of peanut allergy at age 4 to 5 years and three times (95% CI: 1.0-9.0) the odds of egg allergy than children in the northern states (Osborne et al., 2012). A recent study from Australia described that infants with vitamin D insufficiency were three times more likely to have egg allergy than those who had adequate stores of the vitamin, with the odds increasing to 10-fold among those with two or more food allergies. Furthermore, among food-sensitized infants, those with vitamin D insufficiency were six times more likely to be food allergic than tolerant (Allen et al., 2013). These effects were observed among infants with Australian-born parents but not those with parents born outside Australia. Genetic polymorphisms contribute to variation in vitamin D binding protein levels, explaining almost 80 percent of variation in levels (Koplin et al., 2016). Binding protein levels in turn alter the biological availability of serum vitamin D, with lower levels increasing the availability of serum vitamin D ($25OHD_3$). It was recently described that polymorphisms resulting in lower VDR levels appeared to compensate for adverse effects of low serum vitamin D on food allergy risk (Koplin et al., 2016), presumably by increasing the ability to use available vitamin D. These findings suggest that references ranges for optimal levels of serum vitamin D may need to take into account differences in VDR level.

A few studies have been published on the effect of maternal vitamin D status during pregnancy and the development of food allergy in offspring. A follow-up study from an RCT (N=164) reported that Vitamin D supplementation of the mothers during lactation may increase the risk of later food allergy up to 2 years of age (unadjusted analysis), although the authors reported high loss in subjects in the follow-up (Norizoe et al., 2014). However, results from cross-sectional studies (Allen et al., 2013) suggest that vitamin D sufficiency in infants age 1 year may be an important protective factor for food allergy at that age. Another cross-sectional study that followed a German birth cohort for 10 years reported that specific IgE for food allergens (OR: 1.07; 95% CI: 1.02-1.11) at age 10, as well as lifetime prevalence were significantly related to the vitamin D status (Wawro et al., 2014). Conversely, a study in Korea (N=226) showed that vitamin D deficiency increased the risk of sensitization to food allergens (Baek et al., 2014). In a longitudinal study (N=231), Jones et al. showed that maternal intake of supplemental vitamin D was significantly correlated with cord blood $25(OH)D_3$ concentration (Jones et al., 2012). However, the associations between cord blood $25(OH)D_3$ concentration and allergen sensitization, IgE-mediated food allergy, or eczema severity were not significant. Another prospective birth cohort study (N=378) in Germany reported that maternal and cord blood $25(OH)D_3$ was positively associated with

children's risk for food allergy within the first 2 years of life (Weisse et al., 2013).

Liu et al. reported that the combination of persistently low vitamin D status at birth and in early childhood (ages 1 to 3 years) increased the risk of food sensitization (defined as specific IgE ≥0.35 kUA/L to any common food allergen, that is, egg white, milk, peanut, walnut, soy, shrimp, cod fish, and wheat) (aOR: 2.03; 95% CI: 1.02-4.04); the risk was particularly higher among children carrying the C allele of rs2243250 (aOR: 3.23; 95% CI: 1.37-7.60) (N=460) (Liu et al., 2013).

Multiple genes are known to be involved in 25(OH)D_3 metabolism and regulatory pathways: genes encoding the molecules to convert 25(OH)D_3 into its bioactive form 1,25(OH)2D (i.e., *CYP27B1*) and then a water-soluble metabolite (i.e., calcitroic acid; *CYP24A1*), as well as the receptor complex of vitamin D (i.e., *VDR*, *RXRA*, *RXRB*) and vitamin D binding protein (i.e., *GC*). Liu et al. evaluated children in the Boston Birth Cohort (N=649) and did not find an association between vitamin D levels in cord blood and sensitization to food allergens in early childhood (Liu et al., 2011). However, when examined with candidate gene single nucleotide polymorphisms, a significant interaction was identified for an IL-4 gene polymorphism and three other genes, indicating a risk for sensitization. In an Australian study, Koplin et al. investigated whether polymorphisms in a VDR-binding protein gene (low, the GT/TT genotype; high, the GG genotype) could modify the relationship between serum vitamin D and food allergy (Koplin et al., 2016). The study (N=5,276) found that low serum 25(OH)D_3 levels (≤50 nM/L) at age 1 year had a modest association with food allergy, particularly among infants with the GG genotype (aOR: 6.0; 95% CI: 0.9-38.9) but the CI was wide. There was no association with food allergy in children with those with low serum 25(OH)D_3 levels and GT/TT genotypes (aOR: 0.7; 95% CI: 0.2-2.0; P interaction=0.014).

The committee concludes that the quantity of evidence on the role of vitamin D in the development of food allergy during critical developmental windows (in utero, infancy, and early childhood) is limited. Further research is needed to confirm or refute this relationship.

Lipids/Omega-3 Fatty Acids

Dietary fat consumption has been hypothesized to influence atopy development by modulation of IgE production (Black and Sharpe, 1997). Among the different dietary fats, the ones that have been studied most extensively are the omega-3 fatty acids. Omega-3 fatty acids are known to have anti-inflammatory and immune modulator properties (Wall et al., 2010). Current evidence suggests that the intake of omega-3 fatty acids has decreased from ancestral times, whereas the consumption of omega-6 has

probably increased. Consequently, the dietary ratios of omega-6 to omega-3 fatty acids have changed over time from approximately 1:1 to almost 17:1 in certain industrialized societies (Simopoulos, 2002). The parallel increases in this ratio and in the prevalence of allergic disease, as well as information from experimental models, have elicited the hypothesis that dietary omega-3 fatty acids in early life may influence immune system development and immune cell function (Calder, 2013; Shek et al., 2012).

This hypothesis has been tested using a variety of experimental models, and the results of individual studies have been the focus of several reviews and meta-analyses that reveal the uncertainties that currently afflict this area of knowledge. Contributing to the current controversies are (1) the different experimental designs (observational versus RCTs), (2) the times of intervention and follow up, (3) the usually small size of the populations studied, (4) the different approaches to supplying the omega-3 fatty acids and the doses used, (5) the different periods investigated (fetal life, infancy, childhood), (6) the different outcomes examined, and (7) the potential confounder introduced by the wide-ranging presence of pro-allergenic pollutants and contaminants in fish, the major source of dietary omega-3.

The systematic review of Klemens et al., which reviewed the literature from 1950-2010, is considered to be of medium quality (Klemens et al., 2011). The review included three RCTs (Dunstan et al., 2003; Furuhjelm et al., 2009; Lauritzen et al., 2005; total N=264) of omega-3 fatty acids supplementation compared to olive or soy oil during pregnancy and/or lactation in a high-risk population for outcomes of food allergy, as defined by SPT and clinical diagnosis. When supplementation started during pregnancy egg sensitization decreased at 12 months of age (OR: 0.33; 95% CI: 0.16-0.70). Receiving the supplementation during pregnancy and/or lactation and food allergy at age 12 months were not significantly associated.

A recent Cochrane review, which included manuscripts published until August 2014, assessed the effect of omega-3 supplementation in pregnant and/or breastfeeding women on allergy outcomes (food allergy, atopic dermatitis, allergic rhinitis, and asthma/wheeze) in their children (Gunaratne et al., 2015). Overall, the results showed little reduction of allergic disease in the children resulting from maternal omega-3 supplementation during pregnancy and/or breastfeeding. Five trials reported food allergy outcomes (Dunstan et al., 2003; Furuhjelm et al., 2009; Lauritzen et al., 2005; Makrides et al., 2009, 2010). There was only one study where omega-3 supplementation reduced the incidence of IgE-mediated food allergies in children up to 12 months of age (Furuhjelm et al., 2009) (N=117; RR: 0.13; 95% CI: 0.02-0.95). Similarly, another recent review identified three RCTs (Dunstan et al., 2003; Furuhjelm et al., 2009; Palmer et al., 2012) and two follow-up studies (Furuhjelm et al., 2011; Palmer et al., 2013) with pregnant women whose infants were at high risk of atopy. After adjusting for

potential confounders or after long-term follow-up only one study showed an association between maternal omega-3 fatty acid supplementation and lower risk of food sensitization (Newberry et al., 2016).

The committee concludes that the current evidence does not support a link between increased maternal omega-3 intake and a protective effect on childhood food allergy.

Folate

Emerging interest in the role of folate in immune development and allergic disease has been driven by the recent understanding that folate, a dietary methyl donor, can affect immune function and alter gene expression through epigenetic mechanisms (Brown et al., 2014). Concerns have been raised about whether folic acid supplementation during pregnancy and/or early childhood is a potential risk factor for the development of atopic diseases in children. As animal models have demonstrated, maternal supplementation with dietary methyl donors during pregnancy induces hypermethylation of key regulatory genes in lung tissue, resulting in subsequent allergic airway disease in offspring (Hollingsworth et al., 2008). Exposure to folate in utero can affect DNA methylation during fetal development in humans (Amarasekera et al., 2014), which can influence transcriptional activity. For example, hypermethylation can silence the expression of genes. During polarization of naive T helper cells to Th2 cells, methylation of the promoter region of the IFN-γ gene blocks transcription factor binding and thus expression of the IFN-γ gene (Jones and Chen, 2006). Consequently, increased folic acid intake could influence the expression of genes that may be involved in T-cell differentiation during gestation. In turn, this may influence the allergic predisposition in the neonate.

To date, most human studies on this topic have focused on asthma, with very limited number of studies specific to food allergy or food sensitization. An Australian study (N=484) assessed maternal folic acid intake and serum folate levels during the third trimester, and cord blood folate status at birth (N=285), and allergic outcomes at age 12 months, including IgE-mediated food allergy, eczema, and asthma, in offspring (Dunstan et al., 2012, p. 51). In their study, food allergy was defined as "a history of immediate symptoms following contact and/or ingestion and a positive SPT to the implicated food."

However, maternal serum folate status and allergic outcomes were not associated (Dunstan et al., 2012). In a study of 2,834 Dutch children, maternal folic acid supplement intake across the whole pregnancy, and intracellular folate status (measured in the third trimester of pregnancy in 837 [29.5%] participants) was not significantly associated with specific

IgE against hen egg, cow milk, peanut, and aeroallergens at age 2 years or eczema until age 6 to 7 years (Magdelijns et al., 2011).

A recent study that measured serum folate (at ages 2, 4, 6, and 8 years) in 138 U.S. children found that increased serum folate levels at or before age 6 years were significantly associated with increased incidence of sensitization to both food and aeroallergens, but not with serum total IgE, asthma, or wheezing at ages 6 or 9 years (Okupa et al., 2013). In the National Health and Nutrition Examination Survey (NHANES) (which covers ages 2 to 85 years), a cross-sectional study, serum folate levels were inversely associated with atopy, wheeze, and elevated total IgE levels (Matsui and Matsui, 2009).

Of note, the inconsistent results of previous studies are likely due to many reasons, including differences in sample size, participants' ages, clinical characteristics, allergic outcomes, methods used for measurement of folate status, and statistical methods used in the analysis.

The committee concludes that evidence to assess the causal association between folate and the development or prevention of food allergy is lacking. Further research to study this potential association is needed.

Other Nutrients

A prospective cohort study assessed the relationship between maternal dietary antioxidant intake (B carotene, vitamins C and E, copper, and zinc) during pregnancy and food allergy of the child at age 12 months among families at high risk (West et al., 2012). This study of 300 mother-infant dyads found a protective effect of vitamin C intake on food allergy, with higher intakes that were limited to one quartile of vitamin C intake. For copper, intake in the highest quartile also showed a protective effect. However, as previously noted, observational studies suffer from inherent methodological flaws. Thus, proper RCTs are required to determine the causal effect of the maternal diet on the etiology of food allergies in offspring.

The committee concludes that evidence to assess the causal association between other nutrients and the development or prevention of food allergy is lacking.

Other Hypotheses

Do the Obesity and Diabetes Epidemics Have a Role in the Rise of Food Allergy?

The parallel increase in the prevalence of obesity and type 2 diabetes and allergic diseases raises the question of whether these conditions may be linked. Obesity is known to induce systemic inflammation, which

might adversely influence the immature immune system and atopic outcomes. Increased adipose tissue also could lead to reduced adiponectin levels, which in turn down-regulates the secretion of IL-10 and decreases regulatory T cells (Hersoug and Linneberg, 2007). Although the precise mechanism underlying the link between obesity and allergic disease including food allergies remains to be elucidated, the hypothesis is biologically plausible.

Very limited data are available on the association between having overweight or obesity and food allergy. Observational studies have shown that obesity is associated with a higher risk of atopy (elevated specific IgE to allergen) (Ouyang et al., 2009; Visness et al., 2009; Xu et al., 2000). For example, data from the 2005-2006 NHANES demonstrated that children with overweight or obesity had a higher geometric mean of total IgE levels and were at a higher risk of atopy than children with normal weight. This association was driven largely by allergic sensitization to food allergens, and systemic inflammation (measured as serum c-reactive protein) in children with obesity may play a role in the development of allergy (Visness et al., 2009). In contrast, ample studies show the association between overweight and obesity and asthma in both children and adults (Baumann and Lorentz, 2013; Granell et al., 2014).

The role of maternal overweight and obesity and diabetes on the developing fetus and the subsequent risk of allergic diseases has not been well studied but deserve attention. In the prospective Boston Birth cohort, Kumar et al. reported that in term births, gestational diabetes was significantly associated with allergen sensitization in the child, and such association was also driven by food sensitization (Kumar et al., 2009). In contrast, others reported no associations between obesity measures and atopy (Jarvis et al., 2002; Ma et al., 2010), or inverse associations (Van Gysel et al., 2009).

Other Unsubstantiated Hypothesis for the Rise in Food Allergy

Media interest in food allergies has become significant and sustained as food allergies have become more common. As such, public conjectures about potential causes for the rise are widespread. In particular, awareness about unfortunate cases of food-induced anaphylaxis is high. Added to that is the increased awareness by various community or commercial organizations (such as schools, restaurants, airlines, and sporting clubs) of their need to be careful about how they provide foods for food allergic individuals. As a result, communities are greatly interested in why the prevalence of food allergy appears to be rising.

One of the most widely held theories, among the many that abound, as to why food allergy is on the rise holds that it is due to the increasing

consumption of processed foods and food additives. Unfortunately, to date no significant research has been conducted on this issue. Websites and blogs tout the dangers of processed foods and food additives, and evidence from clinical observation suggests that some parents believe that food additives aggravate a range of clinical symptoms and signs, from difficult behavior and autism to gastrointestinal reactions. Clinically, the best way to understand whether a food is aggravating symptoms is to eliminate that food and later challenge with it—provided the risk of anaphylaxis has been excluded. However, the role of additives and preservatives in the development of food allergy in the first place has never been examined at the ecological or epidemiological level. In addition to understanding whether preservatives or additives have a direct toxicological effect on the developing immune system, it would be valuable to assess whether these substances actually influence the composition of the gastrointestinal microbiome.

Concerns over genetically modified crops (Nordlee et al., 1996) has resulted in consideration of the role that such foods may play in aggravating food allergy and in a requirement to assess the potential allergenicity of genetically modified crops (CAC, 2009; FAO/WHO, 2001). Although an online tool recently has been developed to help assess the role a novel protein may play in cross-reactivity (Goodman et al., 2016) based on criteria from the Codex Alimentarius Commission (CAC, 2009), current methodologies are considered inadequate to predict de novo allergenicity. Little or no research exists on whether the increased use of genetically modified crops could be linked to the rise in food allergy.

Numerous lay books and review articles argue that the increased consumption of fast food in the Westernized diet may have a significant impact on immunity (Myles, 2014). Although emerging indirect evidence suggests that fresh fruit and vegetables and food diversity might be important for an optimal and healthy start to life, to date little work has been done on their role specifically in preventing food allergy. Some of the first emerging evidence of diet diversity and its impact on food allergy development has been generated by the EuroPrevall study (Grimshaw et al., 2014). In a nested case-control within-cohort study of 41 infants using gold standard food challenge outcomes and 82 age-matched controls, the authors found that an infant diet with high levels of fruits, vegetables, and home-prepared foods is associated with less food allergy by 2 years of age. As an observational study, these results are subject to confounding but they generate a hypothesis worth testing in systematic trials.

The committee concludes that speculation abounds regarding why food allergy is on the rise. Although some ideas are based in appropriate theoretical frameworks, the absence of RCTs prevents firm conclusions to be drawn on their validity.

OVERALL CONCLUSIONS

The development of food allergies, like other complex diseases, might be regulated by the epigenome and in that way be caused by a genetic predisposition interacting with environmental exposures. The epigenome can be altered throughout the lifespan, but is particularly sensitive to environmental factors during early life periods. There appears to be a window of opportunity in the perinatal and early childhood period that may modulate the functionality of the immune system and related health conditions, specifically food allergies.

Many factors have been postulated to contribute to the onset of sensitization and to food allergies. A few of them have been extensively researched and sufficient evidence exists to support guidelines or to continue research to gain more insights (e.g., about the optimal timing and dosing of early introduction of foods). For other factors, either evidence is lacking about their association with food allergy but the association is biologically plausible (e.g., folate) or limited evidence exists about their association (e.g., vitamin D or fatty acids). For these, a recommendation based on their association with food allergy development cannot be made at this time and more research is needed. For other factors, direct or indirect evidence is lacking, but myths continue to prevail among the public (e.g., food additives).

For some factors (e.g., breastfeeding or vaginal delivery), although the evidence is inconsistent, it would be unethical to pursue RCTs; therefore, the evidence about their contribution to food allergies is derived solely from epidemiological studies. The review of the evidence by the committee neither confirmed nor rebutted current hypotheses related to any association between these factors and the increase in the prevalence of food allergies. The most recent research on the effects of allergen exposure at early age, however, strongly supports the dual allergen exposure hypothesis. The strongest data on potential prevention practices derives from a large RCT supporting the hypothesis that delaying the introduction of peanuts, coupled with high eczema rates, may have contributed to the high prevalence of peanut allergy in the Western world. Similar trials are being conducted for other allergenic foods and some of them are still being analyzed and interpreted (see Table 5-1). The LEAP study found that within a very narrow time range (ages 4 to 11 months), early introduction of peanut is protective against peanut allergy in infants who are at high risk (as defined by early onset eczema or coexistent egg allergy). Other studies have found that delaying introduction of other allergenic foods (cooked egg, cow milk, and wheat) has no benefits.

The lack of strong evidence for a link between most of the potential risk determinants and food allergy has created inconsistencies in public health

advice among different guidelines (see Table 5-2) and corresponding confusion among physicians, patients, and their families. Consensus of infant feeding guidelines to prevent food allergy across different public health authorities is needed for health care providers to counsel patients and their caregivers with consistent recommendations. Moreover, future clinical practice guidelines and public health policy should take into account the way in which a risk factor may differentially affect the risk of disease as well as the behavior of individuals with food allergy or their caregivers.

RECOMMENDATIONS

The committee recommends that public health authorities and clinical practice guidelines include consistent, clear, and evidence-based advice for families and health care providers, including dietitians, about the potential benefits of introducing allergenic foods (e.g., peanut products, egg, dairy, and wheat) in the first year of life to infants, when an infant is developmentally ready (around 6 months of age), but not before 4 months of age, particularly to those at high risk of allergy. Guidelines also should include information about the circumstances in which health care providers should advise their patients about the safest way to introduce in their diet peanut products (and/or other foods, as determined by the results of ongoing research).

In addition, as mentioned in Chapter 6, the committee recommends that public health authorities regularly update food allergy guidelines on diagnosis, prevention, and management based on strong scientific evidence. For example, current evidence is insufficient to associate any of the following behaviors with prevention of food allergy: food allergen avoidance diets for pregnant or lactating women, prolonged allergen avoidance in infancy, vaginal delivery, breastfeeding, infant formulas containing extensively or partially hydrolyzed protein, and supplementation with specific nutrients (e.g., vitamin D, folate, fatty acids) in children or adults.

RESEARCH NEEDS

Considerations for Study Designs

Studies on the etiological factors associated with food allergies frequently present methodological flaws due to various reasons, including lack of accounting for confounding factors (e.g., breastfeeding), use of inaccurate food allergy measures (e.g., self-reporting), or disregard for the

fact that different populations (e.g., those at high risk of developing a food allergy) might respond differently to the various risk factors. For example, due to a variety of differential gene-environment factors (e.g., genetics, epigenetics, microbiomes, and other pre- and postnatal environmental factors), populations will respond differently to interventions. Also, the etiology and early life onset of food allergy seems to be multifactorial, and collecting specimen for future analyses would be advantageous. Future research design on etiological determinants should consider the following:

- Conduct longitudinal birth cohort studies that explore the effects of environmental factors during critical developmental windows (in utero, infancy, and early childhood) on food allergy.
- Couple relevant prenatal, perinatal, and early childhood epidemiological and clinical data with appropriate biospecimen collections (e.g., serum, cord blood, breast milk) for current and future biomarker analyses.
- Design studies so that the responses to various exposures of individuals and populations at high risk and low risk of developing food allergy can be differentiated.
- Use the currently accepted gold standard—double-blind, placebo-controlled oral food challenges (employing standard dosing protocols and scoring systems, so that the results of various studies can better be compared)—as the food allergy outcome in research intervention studies until a simpler reliable method to measure food allergy is identified and validated.
- Account for the potential influence of confounding factors, in addition to age, sex, and geography, such as breastfeeding, composition of breast milk, dietary intake, other allergic disorders in the patient or family history (particularly atopic dermatitis), genetic susceptibility, presence of dogs or cats in the household, number of siblings, history of antibiotic usage, and exposure to agents or practices that might impair skin barrier function.
- Engage patients or groups representing patients so that research designs may take into consideration potential socio-psychological, cultural, and behavioral considerations.

Overall Research Needs

Many genetic and environmental factors could contribute to the onset of sensitization and to food allergy. For the majority of factors reviewed by the committee, some, but largely insufficient or inconsistent, evidence exists at this time about their association with sensitization or food allergy. Nev-

ertheless, health care providers, patients, and their caregivers still need clear prevention approaches and authoritative and clear public health guidelines. Therefore, research needs to continue to support or refute the contribution of these factors to food sensitization or food allergy. The committee recognizes, though, that for other factors direct or indirect evidence is lacking and research is not currently warranted (e.g., food additives). Although some public health guidelines have been developed to guide practices of health care providers and individuals, efforts have not been undertaken to assess the impact of such public health guidelines on practices related to food allergy and on prevalence of food allergy. Prospective studies and behavioral research should be conducted to accomplish the following objectives:

- Examine risk factors for food allergies in all populations (ages, sex, ethnicities, comorbidities, socioeconomic strata), especially in those populations that might have been underrepresented in past research.
- Gain insights about the behaviors of those with (or at risk of) food allergy and their caregivers as well as about the impact of public health guidelines on health care providers and individuals' practices.
- Examine the etiology of the rising prevalence of food allergy within the past two decades, which could identify new targets for allergy prevention and treatment. For example, what changes have occurred in food preparation and consumption behavior in communities and what is their potential relationship to the increase in food allergies? What changes may have occurred in the use of agents (such as detergents) or practices (such as in personal hygiene) that might contribute to impaired skin barrier function?
- Elucidate, through prospective studies, the role of environmental factors and gene-environment interactions in the atopic march and the development of food allergy. For example, do specific factors increase the risk of an individual progressing from eczema to food allergy?
- Explore potentially unidentified risk factors that may influence food allergy. For example, although the data available to date have not shown evidence of a relationship, it is plausible that maternal and early childhood adiposity and metabolic disorders could be risk factors for food allergy development.
- Using prospective birth cohort studies, evaluate the effects of multiple early life factors (individually and in combination) and of possible gene-environmental interactions in the development and

prevention of food allergy in order to inform the design of specific RCTs.
- Identify best practices to engage patients and their families in the planning stages of research studies so that patients' and families' concerns are considered, and assess the value of using these approaches.

Specific Research Needs

In addition, high-quality prospective studies and RCTs are needed on specific risk determinants for which some evidence exists about their effect on food allergy related to the most plausible hypotheses to make meaningful conclusions. These studies should be conducted to accomplish the following objectives:

The Microbial Hypothesis

- Determine, using well-designed prospective studies, the role of mode of birth delivery (vaginal, emergency versus elective cesarean section) and early life microbiome composition on the development of food allergy.
- Assess, through well-designed prospective studies, potential links between food allergy and antibiotic exposure in children (studies should include information on the type, dose, and frequency of antibiotic exposure).
- Determine whether pet ownership is related to food allergy by using well-designed prospective studies.
- Assess, with RCTs, the potential benefits of prebiotics and probiotics to prevent the onset of food allergy.

Allergen Avoidance and Exposure

- Elucidate the relationship, if any, between breastfeeding and the onset of food allergy (may also influence through microbiome modulation) with well-designed prospective studies and take into account the potential effect of differences in breast milk composition.
- Determine, with RCTs, whether consuming or eliminating or avoiding specific allergenic foods during pregnancy and lactation has any benefits.
- Conduct RCTs, similar to the Learning Early About Peanut study, to determine whether early introduction of peanut products has

benefit in individuals other than high-risk infants, who were studied in the original trial.
- Examine early introduction of allergenic foods in addition to peanut to determine whether this approach is beneficial in preventing the development of food allergy.

Nutrition Immunomodulation Hypothesis

- Assess, with RCTs, the potential role of specific nutrients, such as vitamin D, folate, or fatty acids, in preventing food allergy.

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6

Management in the Health Care Setting

Proper management in the health care setting begins with an appropriate diagnosis of food allergy so that the patient can be instructed on specifically which foods can trigger allergic symptoms. Once a diagnosis is established, management relies on educating the patient and family on avoiding the allergen and preparing to treat allergic symptoms, including severe allergic reactions (i.e., anaphylaxis) promptly and appropriately. Additionally, daily management of food allergy carries potential nutritional, social, and emotional ramifications that should be addressed. Achieving these goals requires significant patient and family education and counseling. Emerging approaches for treatment show promise for altering the threshold of reactivity, making exposure to small amounts of the food less problematic, and future treatments will ideally result in elimination of the allergy.

This chapter covers management of diagnosed food allergy from the perspective of a health care setting and includes topics such as the impact of food allergy on affected individuals and families and the current understanding of food allergy treatment. Dietary issues with regard to prevention are discussed in Chapter 5. This chapter also highlights the importance of educating health care providers about food allergy and management advice for the home, public environments, and high-risk scenarios. From a developmental and ecological perspective, the instructions provided at the health care setting represents only one aspect of successful management because successful adherence depends on management and sensitivity toward food allergy from all societal sectors, including families, schools, food service, and the community. Chapter 7 focuses on management of food allergies in

other settings such as schools, restaurants, and travel, and on the safety of manufactured products.

APPROACH TO LITERATURE REVIEW

The topics addressed in this chapter did not undergo individual systematic review or meta-analysis. The primary resources for discussion, findings, conclusions, and recommendations were derived from various guidelines (see Chapter 1, Table 1-1, for a description of the guidelines): the National Institute of Allergy and Infectious Diseases/National Institutes of Health (NIAID/NIH)-supported Guidelines (Boyce et al., 2010) and its associated literature reviews, the European Academy of Allergy & Clinical Immunology (EEACI) Guidelines (Muraro et al., 2014a,b) and associated systematic reviews (de Silva et al., 2014; Dhami et al., 2014), the American Academy of Allergy, Asthma & Immunology (AAAAI) Guidelines (Sampson et al., 2014); the AAAAI Practice parameter (Lieberman et al., 2015), and American Academy of Pediatrics (AAP) Clinical Reports (Sicherer et al., 2007, 2010). Additional PubMed searches were performed to identify items in the literature to supplement the discussion on specific topics, especially for papers published after the aforementioned reports. Meta-analyses and systematic reviews were selected when available.

ALLERGEN AVOIDANCE AND RECOGNITION OF AND PREPAREDNESS TO TREAT ALLERGIC REACTIONS AND ANAPHYLAXIS

General Principles of Management, Avoidance, Cross-Contact, Hidden Ingredients, Routes of Exposure

The primary advice for managing a diagnosed food allergy, whether immunoglobulin E (IgE)-mediated or non-IgE-mediated, is to avoid ingesting the culprit food allergen(s) (Boyce et al., 2010; Muraro et al., 2014b; Sampson et al., 2014). Of course, no randomized clinical trials (RCTs) have been conducted to evaluate this approach, but not ingesting the allergen is a rational management strategy for a diagnosed food allergy. No evidence exists that avoidance affects the natural course of atopic dermatitis, asthma, or eosinophilic esophagitis (Allen et al., 2009; Boyce et al., 2010). Maternal avoidance of a food allergen may be needed in some cases if the infant, diagnosed with a food allergy, experiences reactions from the maternally-ingested allergen while breastfeeding (Jarvinen et al., 1999; Lifschitz et al., 1988; Monti et al., 2006).

Achieving avoidance of a food allergen entails numerous considerations involved in obtaining or preparing allergen-safe foods. For example, *cross-*

contact is a term describing a situation where an unintended allergen may be present in an otherwise allergen-free food because of contact between the unsafe and safe food. Examples of cross-contact include having a knife used in peanut butter placed into a jar of jelly, using a fryer with oil exposed to fish and egg ingredients used for potatoes, and placing a spoon used to stir a milk-containing soup into a milk-free one.

The possibility of *hidden ingredients* is also a concern (see also Chapter 7). For example, an individual with food allergy may not have expected that chili or spaghetti sauce may contain peanut flour, that peanut butter may be used to seal the ends of an egg roll, or that "non-dairy" creamers contain casein, the major allergenic protein in cow milk.

Avoiding ingestion of a food allergen requires patient education about obtaining safe foods in numerous settings, for example reading labels on packaged foods,[1] asking before ordering in restaurants and food service, and preparing safe meals at home. Standard cleaning procedures, such as using wet wipes and washing hands with running water and soap, typically suffice to remove allergen from surfaces. However, topical antibacterial hand cleaning agents do not neutralize allergens (Perry et al., 2004). Ingestion contact with an allergen occurs from sharing utensils or straws or from intimate kissing where saliva containing the allergen may transfer to the allergic individual (Eriksson et al., 2003; Hallett et al., 2002; Maloney et al., 2006). Young children may need supervision when around food allergens to avoid taking or being fed the allergen, or having hand-to-mouth transfer of food allergens.

The primary route of exposure that triggers serious reactions—for example, severe anaphylaxis or fatal reactions—is through ingestion (Fleischer et al., 2012; Sampson et al., 2014). Modest allergen contact with intact skin is unlikely to trigger serious reactions (Simonte et al., 2003; Wainstein et al., 2007), but transfer from hand to the mouth can be a concern, and the eyelid may swell significantly with direct contact. Aerosolizing[2] food proteins (e.g., from boiling milk, frying egg or fish, cooking with wheat flours) may trigger reactions, often respiratory symptoms, depending on proximity, amount aerosolized, and patient-specific factors, such as asthma and degree of sensitivity (Roberts et al., 2002). Aerosol exposure can be a concern in occupational settings (e.g., "baker's asthma"). Peanut butter, an oily substance, does not aerosolize enough to trigger reactions (Simonte et al., 2003).

[1] The section on packaged foods below describes the current regulatory frameworks for food labeling of packaged foods that attempt to inform consumers of the presence of an allergen in a food.

[2] Aerosolizing is the process or act of converting some physical substance into the form of particles small and light enough to be carried on the air.

The complexities of avoidance management requires a proper diagnosis followed by a comprehensive approach to educating patients, families, caregivers, and others on appropriate measures. Mistakes and subsequent allergic reactions are common. A prospective study of 512 infants with food allergy followed for a median of 36 months noted 1,171 reactions among 367 children (Fleischer et al., 2012). Common reasons for reactions included accidental exposure, label reading errors, and cross-contact, but the study also noted some exposures were purposeful, suggesting they were done presumably to test whether the allergy was active. Additionally, the source of ingested foods during accidental exposure included siblings, relatives, and other caregivers. This study reflects the many potential sources of error in avoidance management and the need for comprehensive education. A 2015 systematic review regarding unexpected allergic reactions in those older than age 12 years (Versluis et al., 2015) identified 18 observational and 6 qualitative studies. The authors noted that current knowledge about the frequency of unexpected reactions is limited, that reactions can be severe and fatal, and that most reactions were noted to have taken place at home though other locations, such as restaurants and others' homes, were common. They also identified various labeling issues and risky behaviors as problems and concluded that patient education and dietary instruction are needed.

EDUCATING PATIENTS ABOUT ALLERGEN AVOIDANCE

This section presents several topics where health care providers should provide advice to their patients with food allergy. Many of the topics relate to allergen avoidance, the main advice given to patients. They include strictness of allergen avoidance, avoidance and comorbidities, and concerns about cross-reactive foods. These topics are covered to various degrees in Boyce et al. (2010); Muraro et al. (2014b); and Sampson et al. (2014). The topic of nonstrict avoidance is discussed in more detail in the review by Kim and Sicherer (2010).

Strictness of Allergen Avoidance

Typically persons with a food allergy are advised to strictly avoid the trigger food (Boyce et al., 2010; Kim and Sicherer, 2010; Muraro et al., 2014b; Sampson et al., 2014). However, individuals with a mild allergy, particularly allergies related to pollen-food allergy syndrome, may not need to strictly avoid the trigger fruit or vegetable. Similarly, those with food-associated, exercise-induced anaphylaxis may only need to avoid the identified trigger only in the hours before exercise. A majority of children with cow milk or egg allergy are able to ingest extensively heated forms of these

foods, for example when baked into a muffin. Additionally, circumstantial evidence from observational studies suggests that ingesting these forms does not impede recovery from these allergies and may speed tolerance induction (Kim et al., 2011; Leonard et al., 2012; Nowak-Wegrzyn et al., 2008; Tey et al., 2012). For individuals with a high threshold of reactivity, allowing ingestion of sub-threshold amounts of the allergen has not been studied. Limited evidence from a study of young children suggests that an isolated exposure to egg, milk, or peanut resulting in an allergic reaction does not increase allergen-specific IgE responses (Sicherer et al., 2016). More studies are needed to understand circumstances where nonstrict avoidance would suffice. In some situations, nonstrict avoidance is an option that can be considered under medical guidance. For example, as presented in Chapter 7, this committee recommends the implementation of a risk-based approach for labeling foods with unintended allergens which, under medical consultation, should improve the ability of individuals with food allergy to decide whether they can safely consume a specific packaged food.

Allergen Avoidance and Relationship to Comorbid Asthma, Atopic Dermatitis, and Allergic Rhinitis

Food allergen avoidance is generally not recommended as a primary means to address treatment of asthma, atopic dermatitis, or allergic rhinitis. However, avoidance is warranted when a specific food allergy is diagnosed in a patient with those diagnoses (Boyce et al., 2010; Sampson et al., 2014). If a food allergy is diagnosed, limited evidence suggests that avoiding the allergen may improve atopic dermatitis (Agata et al., 1993; Bath-Hextall et al., 2009; Boyce et al., 2010; Lever et al., 1998). Studies have suggested that following extended elimination of a food that had not previously caused serious reactions, for example only flare of atopic dermatitis, re-exposure to the food could result in acute systemic allergic reactions (Chang et al., 2016; David, 1984; Flinterman et al., 2006). Although this observation raises caution, no RCTs have been performed to confirm this association.

Concerns About Cross-Reactive Foods

Food with proteins that are homologous[3] to a food protein to which an individual is allergic may present a reaction risk (Boyce et al., 2010; Sampson et al., 2014). For example, an individual with a peanut allergy may be at higher risk for allergy to beans (e.g., soy) because both foods

[3] Homology between proteins is defined in terms of shared ancestry and is typically inferred from the similarity of their amino acid sequence.

are legumes. However, clinical cross-reactivity varies among families of foods and also among individuals depending upon their allergy profile. Unfortunately, testing has limited value because sensitization to foods with homologous proteins, evidenced by positive skin prick tests (SPTs) or the presence of food-specific IgE antibodies, is much more common than is clinical allergy (Boyce et al., 2010; Sampson et al., 2014; Sicherer, 2001) (see Chapter 4 for a detailed discussion of testing). Foods with high likelihood of clinically relevant cross-reactivity include milk from cows and goats; tree nuts, specifically cashew with pistachio and walnut with pecan; various fish with each other; and between crustacean shellfish, such as shrimp and lobster. In contrast, grains and legumes have less co-allergy. Decisions about avoiding related foods may rely also on factors such as concerns about accidental exposure from misidentification or cross contact. For example, an individual with food allergy who tolerates walnut but not cashew may decide to avoid all tree nuts to avoid cross-contact or misidentification. Therefore, advice about the need to avoid potentially cross-reactive foods is individualized and may require extensive testing with oral food challenges (OFCs). Adherence is, obviously, more difficult. Education of patients and families about these concerns is required for proper management.

ADVICE ON ALLERGEN AVOIDANCE IN VARIOUS SETTINGS OF CONCERN

Packaged Foods

Laws governing the labeling of allergens in packaged foods vary by country (Akiyama et al., 2011; Gendel, 2012) and are described in Chapter 7. Health care providers should discuss current labeling laws in counseling those who have a diagnosed food allergy. The current U.S. labeling law, the Food Allergen Labeling and Consumer Protection Act of 2004, requires manufacturers to use plain English terms to identify milk, egg, wheat, soy, peanut, tree nuts, fish, and crustacean shellfish ingredients. These may be included in the ingredient list and/or in a separate "contains" statement. Highly refined oils are exempt based on removal of protein by the process. The individual name of the food is required for categorical foods (e.g., walnut, cashew, shrimp, tuna, cod). Noncrustacean seafood, such as clam, oyster, scallop, is not included in the laws. Foods that are known to cause serious allergic reactions are not necessarily included on the label, for example, sesame and mustard (Caballero et al., 2002; Dalal et al., 2012) because they are not included in the U.S. list of priority allergens (see Chapter 7).

In the United States and some other countries, when manufacturers perceive the possibility of allergens being unintentionally included in the

product, they may voluntarily use precautionary or advisory terminology, such as "may contain X," "in a facility with X," and other such terms. Studies suggest varied risks with such products (Crotty and Taylor, 2010; Decastelli et al., 2012; Ford et al., 2010; Hefle et al., 2007; Robertson et al., 2013; Zurzolo et al., 2013) and consumers should be counseled that the terms do not reflect degree of risk. As Chapter 7 concludes, labeling laws help consumers to identify most, but not all, allergens, and advisory labeling has resulted in an unregulated proliferation of warnings that are not well understood by consumers or health care providers, and appears to result in risk-taking behavior. For example, findings from a recent survey administered in 16 countries suggest limited understanding among individuals with food allergy about food allergen thresholds (Marchisotto et al., 2016). In addition to managing the risks from packaged foods by replacing the current food allergen precautionary advisory labeling system, as recommended in Chapter 7, risks from consuming packaged foods should be communicated to individuals with food allergy and their caregivers by effective counseling in the health care setting.

Management at Home

Management of food allergen avoidance in the home requires constant vigilance regarding cross contact, label reading, and hidden ingredients. Typical cleaning methods should remove allergens from utensils, dishes, and surfaces. Depending on age and developmental ability, different safeguards may be needed to protect a child from ingesting the avoided allergen. For example, allergens may need to be kept out of reach of younger children who are not aware of the danger. Families may need to consider keeping the food-allergic individual away from the allergen during food preparation areas if aerosolization is likely (e.g., frying fish or eggs, boiling milk, steaming lobster, preparing food with wheat flours or powdered milk). Maintaining a continuous safe environment is challenging and time consuming. Health care providers should review these issues with patients and families.

Management in Food Service Settings and During Travel

People who are food allergic must navigate multiple issues when dining away from home, including avoiding cross-contact and hidden ingredients in foods served at food service establishments such as restaurants, ice cream parlors, bakeries, grocery stores with prepared foods, and food carts (see also Chapter 8). Informing the establishment about the allergy is the patient's or family's responsibility, but the establishment also must be able to take precautions to provide safe food to the public. Factors contributing

to risk could be the presence of allergens in the source ingredients or cross-contact with allergens at the buffets and food preparation areas.

It may be beneficial for the health care provider to understand and review with patients that a variety of errors can occur in the restaurant setting, whether from the consumer or the establishment's personnel (Ahuja and Sicherer, 2007; Furlong et al., 2001). Errors from the consumer could be due to poor communication of the allergy, assumptions made by the consumer about the safety of the foods, and selection of restaurants that may pose additional challenges depending on their allergy (e.g., seafood restaurant for an individual with shellfish allergy). Among 5,149 persons in a self-report registry for peanut and tree nut allergy, composed mostly of children, 13.7 percent reported reactions in food establishments (Furlong et al., 2001). Following a survey of a random subgroup of 129, lack of communication of the allergy was reported for 45 percent of the reactions. Reported rationales included assuming visual inspection would suffice, thinking the allergy was not too severe, and presuming the food should be safe. These findings suggest a benefit for health care personnel in advising patients with food allergy to openly and specifically discuss their allergy with staff of food establishments.

Errors on the part of the restaurant personnel can include misunderstanding of an allergy diagnosis compared with a less dangerous intolerance or preference, poor communication within the establishment, staff failure to prevent cross-contact or to know about hidden ingredients, among others (Ahuja and Sicherer, 2007). Surveys of restaurant personnel in Brighton, United Kingdom (Bailey et al., 2011) and New York City (Ahuja and Sicherer, 2007) showed that restaurant personnel, including chefs, may indicate confidence in providing a safe meal for a food-allergic consumer, but have knowledge deficits about allergy, cross-contact, and general food allergy management. These findings suggest that health care providers should discuss strategies such as encouraging patients with food allergy to review cross contact and hidden ingredients with staff when obtaining restaurant meals (i.e., educate or confirm knowledge of staff).

Travel presents additional potential obstacles for persons with food allergy (Barnett et al., 2012). A lack of global uniform guidelines requires consumers with food allergy to navigate different regulations, or regions with no regulations, internationally. Language barriers may prevent safe communication. Travel to remote regions raises concerns about obtaining safe food and managing a reaction. Several studies have reported allergic reactions on airplanes based on self-report of having unintentionally ingested or been exposed to allergens (Comstock et al., 2008; Greenhawt et al., 2013; Sicherer et al., 1999). These issues, highlighted further in Chapter 8, suggest that individuals and families with food allergy be counseled to consider their allergies when traveling and to call ahead to notify

transportation services, carry medications, ensure safe food is available, and, for younger children, inspect and wipe seating areas for residual food before the child has contact with the space.

Management in Schools and Child Care Centers

Supervision of children and procedures to provide safe foods in early care and education settings, schools, and summer camp settings is required to avoid allergen exposure and to recognize and promptly treat allergic or anaphylactic reactions. A number of recommendations and guidelines have been developed that focus on advice to school personnel, health care providers, patients, and families (CDC, 2013; Eldredge and Schellhase, 2012; Ford et al., 2014; Leo and Clark, 2012; Muraro et al., 2014d; Robinson and Ficca, 2012; Sheetz et al., 2004; Sicherer et al., 2010; Vale et al., 2015; Young et al., 2009). A discussion about approaches to providing a safe experience for children with food allergies when away from home, including the responsibilities of the school staff, is provided in Chapter 8. This chapter focuses on the responsibilities and challenges of the health care provider, parents, and students. These issues also can extend to additional settings away from home, such as religious events, sports, afterschool clubs and camps, among other supervised settings for children (Sampson et al., 2014).

For the child with possible food allergy who attends a school setting, the responsibilities of the child's physician or health care provider may include confirming the diagnosis, providing a written emergency care plan, providing advice about general management to the family and school personnel, and giving necessary medication prescriptions. As reviewed in Chapter 4, ascertaining a diagnosis and whether a child has a potentially life-threatening food allergy can be difficult. Briefly, these elements for diagnosis include deciphering a true allergy, judging its potential severity, and considering comorbid conditions such as asthma.

The physician or health care provider may work with the patient and family to notify the school about a potentially life-threatening food allergy, including providing a written plan, often referred to as an Emergency Action or Emergency Care Plan for Anaphylaxis or Allergy and Anaphylaxis. Unfortunately, no standard, evidence-based plans have been developed and so numerous forms with many different approaches are used. This may represent a significant gap in providing standard care. Survey studies suggest that an insufficient number of students with food allergy have a management plan, or that the plan may not be followed (Ewan and Clark, 2001; Gupta et al., 2014). No comprehensive studies have been conducted that provide evidence for a validated, brief written emergency plan for individual or general use. Various organizations or schools have

developed plans. Studies have identified key factors that might be included on standardized written plans, or compared plans for determination of preferences, or identified variations in using these plans, but systematic studies are lacking (Banerjee et al., 2007; Ewan and Clark, 2001; Powers et al., 2007; Weiss et al., 2004; Worth et al., 2010). Key features typically include the date, the child's name, recent weight, identifying information (child's picture, if provided), specifics about the food allergy or allergies, emergency medications and doses, descriptions of possible symptoms and related treatment instructions, advice to activate emergency services, and family contact information. Development of evidence-based, universal plans could potentially improve understanding and emergency care.

A number of factors must be considered when developing emergency plans for medical management of anaphylaxis and, more specifically, for treatment in a school setting. For example, regarding management in general, no diagnostic test exists to predict or confirm anaphylaxis, and specific symptoms may vary, resulting in treatment quandaries. Although diagnostic features of anaphylaxis have been published, (Sampson et al., 2006b), it is prudent to inject epinephrine (adrenaline) before observing symptoms diagnostic of anaphylaxis. Therefore, the decision to inject epinephrine may vary based on the patient's history, foods involved, and likelihood of an ingestion of the avoided food at the onset of mild symptoms that could be attributed to other causes and are not (yet) anaphylaxis (i.e., throat discomfort may be an early symptom of a viral infection or an initial symptoms of food allergy). For example, if an allergen was ingested that previously caused anaphylaxis, it may be advisable to inject epinephrine at the time of first symptoms, or if an allergen was definitely ingested and previously known to have caused severe anaphylaxis, it may be advisable to inject epinephrine before symptoms occur (AAAAI BOD, 1998; Sicherer et al., 2010). The supervising adult may need to differentiate a mild allergic symptom from anaphylaxis, deciding when to administer epinephrine. This can be difficult, even for experienced professionals. Current advice emphasizes educating parents and school personnel that (1) antihistamines cannot be depended on to treat anaphylaxis but are adjunctive therapies to treat an allergic reaction, (2) inhaled bronchodilators must not be depended on to treat anaphylaxis but may be given for respiratory reactions, and (3) intramuscular epinephrine is safe and, if a possibility of a severe allergic reaction exists, should be administered (side effects are mild and may include temporary fast heart rate, jitteriness, flushing, or paleness) (Sicherer et al., 2007, 2010). Administration of medications in U.S. schools has been addressed in general guidance documents (Council on School Health, 2009). However, no studies provide sufficient evidence for validation of the options discussed above.

Given the complexity of food allergy diagnosis and emergency treat-

ment, the physician may need to consider whether a licensed health care professional is available to assist the child. When one is not available, a plan that is different from one when a professional is involved must be developed. For example, a licensed health professional may administer an antihistamine for mild allergic symptoms and observe for progression of symptoms before administering epinephrine, whereas a nonlicensed, not medically trained individual may not be expected to make this kind of medical or nursing assessment. In this case, the advice may be to promptly give the epinephrine by auto-injector and call for activation of emergency medical services immediately. No studies have addressed the various approaches upon which to develop best practices in this regard.

In addition to the above issues of medical management, the physician or health care professional should address age-specific concerns (for example, the inability of preschool age children to self-monitor taking unsafe foods or the potential risk-taking activities of adolescents), potential risks, bullying, and general management. Medical identification jewelry is encouraged. Avoidance measures should be discussed and are reviewed in the *CDC Voluntary Guidelines for Managing Food Allergies in Schools and Early Care and Education Programs* (CDC, 2013). Avoidance advice may vary by age, allergy, developmental abilities, nutritional status, socioeconomic status, and other factors, and counseling may be adjusted according to the needs of the child and the circumstances of the school. However, little information is available to inform best practices on avoidance (Banejee et al., 2007; Cicutto et al., 2012; Vale et al., 2015; Worth et al., 2010). Families and patients should be educated about how and when to administer self-injectable epinephrine, the importance of avoidance strategies (e.g., no food sharing), when to have children notify an adult of any symptoms or if they may have eaten an unsafe food. The diagnosis, treatment plan, and prescriptions should be reviewed periodically and updated at least yearly. Families and schools also need to be alert to the expiration dates on epinephrine auto-injectors.

Finally, the physician and family will need to provide the school with a list of foods to be avoided and possible substitutions. Some school food programs may require physician-recommended substitutions. Additional issues from the community perspective are discussed in Chapter 8 of this report.

Educational Needs

Although it is incumbent upon health care providers to educate patients and families, these providers have noted deficits in understanding food allergy and anaphylaxis management, as described in Chapter 2. Managing food allergy requires educating all those who are involved in measures

associated with avoiding and treating allergic reactions. However, numerous studies suggest that many different stakeholders, including physicians, have deficits in their understanding of these basic concepts (Desjardins et al., 2013; Morawetz et al., 2014). For example, in an Internet survey of medical professionals, only 23 percent recognized risk factors for anaphylaxis and only 55 percent identified a case of anaphylaxis that had no hives (Wang et al., 2014). Another Web-based study of 407 primary care physicians noted a fair allergy and anaphylaxis knowledge base but specific deficits were noted, such as only 23 percent recognizing that cheese is unsafe for those with milk allergy and fewer than 30 percent indicating comfort with laboratory tests or caring for children with food allergies (Gupta et al., 2010b). Surveys of emergency department management of anaphylaxis suggest serious undertreatment of anaphylaxis and lack of referral (Clark et al., 2004). When allergy referral is achieved, previously unknown triggers are often identified (Campbell et al., 2015b).

Surveys of the general public (Gupta et al., 2009) and parents of children with food allergy (Gupta et al., 2010a) also show a variety of knowledge deficits. Studies have identified errors in using epinephrine autoinjectors among patients and health care providers (Arga et al., 2011; Brown et al., 2013; Guerlain et al., 2010; Sicherer et al., 2000). A Canadian survey of 184 respondents of caregivers of children who had experienced a first allergic reaction within the past year identified gaps in the caregivers having received food allergy and anaphylaxis education and coping strategies for fear and anxiety (Abdurrahman et al., 2013). In a qualitative manner, they found three primary areas of deficit: lack of receiving information on recognizing and managing food allergy–related reactions, long wait times to see an allergist, and significant family anxiety. Surveys of school nurses revealed the need for better understanding of emergency plan development, staff education, and delegation and avoidance measures (Carlisle et al., 2010). Surveys of pediatric dietitians (Groetch et al., 2010; Maslin et al., 2014) revealed that they considered they had moderate knowledge for educating families and evaluating safe foods and low knowledge for creating diagnostic food challenges. Knowledge deficits about food allergy also have been noted among child care providers (Greiwe et al., 2015), emergency response providers (Jacobsen et al., 2012), restaurant personnel (Ahuja and Sicherer, 2007; Bailey et al., 2011), and teachers (Ercan et al., 2012; Polloni et al., 2013). Overall, stakeholders are currently insufficiently educated and seek more information on food allergy.

Studies suggest that educating health care providers is valuable and that patients and their families may benefit from being directed to various educational resources. A number of studies report successful educational materials or programs for various stakeholders, including in-person and online programs, many of which have not been validated (Bailey et al.,

2014; Bansal et al., 2005; Camargo et al., 2007; Cavanaugh and Strickland, 2011; Chokshi et al., 2015; Desai et al., 2015; Hernandez-Trujillo and Simons, 2013; Reeves et al., 2015; Rosen et al., 2014; Sasaki et al., 2015; Shah et al., 2013; van Os-Medendorp et al., 2015; Wahl et al., 2015; White et al., 2015; Yu et al., 2008). One study found that providing simple guidelines improved anaphylaxis management in the emergency department (Desai et al., 2015). In one program that health care professionals can use with parents of children with food allergy (Sicherer et al., 2012), significant improvements were seen in the correct number of auto-injector activation steps, comfort with using the auto-injector, knowledge test scores, and the annualized rate of allergic reactions fell on average from 1.77 (historical) the year prior, to 0.42 ($P<0.001$) after the program. A number of smartphone and tablet applications are also emerging for managing food allergy (Cuervo-Pardo et al., 2015).

Food anaphylaxis can occur in any setting but proper emergency management can resolve a life-threatening occurrence. Therefore, the public, particularly first responders and aiders, need to be prepared to assist in such food-related severe reactions. There is not, however, a national standardized curriculum that includes required elements for emergency care training. Overall, food allergy anaphylaxis is not included in training curricula of organizations that offer various certifications on emergency training or specialized training for professionals such as pediatric specialization for child care providers or training for Emergency Medical Service personnel.

In summary, education of stakeholders is key for food allergy management because knowledge deficits are significant. There is a clear unmet need for education. Evidence indicates that adopting a multidisciplinary clinical approach and providing educational materials may improve knowledge, correct use of epinephrine, and reduce reactions. Although various educational programs are available or in development, most have not been extensively studied. Studies on widespread implementation also are lacking.

High-Risk Groups

Several guidelines (e.g., Muraro et al., 2014b; Sampson et al., 2014) emphasize that certain factors may increase the risk for anaphylaxis. Examples of factors that may increase risks include coexisting asthma, allergies to specific foods (e.g., peanut, tree nuts), degree of sensitivity and extent of eliciting factors (e.g., illness, exercise, medications, alcohol). The relative contributions of all of these are not established. Risk factors identified in case series of fatal food allergic reactions include adolescence or young adult age group, comorbid asthma, ingestion of peanut or tree nuts (although fatal reactions can occur from other allergens, such as

milk), delayed treatment with epinephrine, lack of skin symptoms (perhaps resulting in delayed recognition and treatment), and previously diagnosed food allergy (Bock et al., 2001, 2007; Pumphrey, 2000; Pumphrey and Gowland, 2007; Sampson et al., 1992). The AAAAI Guidelines (Sampson et al., 2014) suggests discussing self-care management techniques especially with high-risk patients, described as adolescents, young adults, and patients with asthma.

Adolescents and young adults, including those in college, may be at higher risk of fatal food-induced anaphylaxis for a variety of reasons (Akeson et al., 2007; Greenhawt et al., 2009; Macadam et al., 2012; Marrs and Lack, 2013; Monks et al., 2010; Mullins, 2003; Noimark et al., 2012; Sampson et al., 2006a). They may not understand or recognize, or may deny symptoms indicating anaphylaxis. For example, in a survey of 174 adolescents with food allergy, 61 percent did not report having anaphylaxis but described symptoms such as throat swelling, trouble breathing, and loss of consciousness (Sampson et al., 2006a). In this same study, risk-taking behaviors included not always carrying epinephrine (39 percent), purposefully ingesting unsafe food (54 percent), and ingesting foods with advisory labeling for their allergen (42 percent). The motivation behind risk-taking behaviors may include poor understanding of risk, convenience, not wanting to feel different from peers, bullying, lack of recollection of allergic reactions, success having survived self-resolving reactions without the need for treatment, fear of injections, overreliance on emergency medications on hand to justify unsafe eating behaviors, and other behavioral and psychosocial factors (Akeson et al., 2007; Greenhawt et al., 2009; Macadam et al., 2012; MacKenzie et al., 2010; Marrs and Lack, 2013; Monks et al., 2010; Noimark et al., 2012; Sampson et al., 2006a). Potential for interventions also are noted in several studies. In one study, 68 percent of adolescents with food allergy indicated a belief that educating their friends would make living with food allergy easier (Sampson et al., 2006a). In another study of adolescents with food allergy, adherence to self-care was reported by 16 percent of participants, and was more likely if the adolescents belonged to an allergy support group (odds ratio [OR]: 2.54; 95% confidence interval [CI]: 1.04-6.20), had a written management plan (OR: 3.22; 95% CI: 1.18-8.81), perceived having a more severe allergy (OR: 1.24; 95% CI: 1.01-1.52), and perceived fewer management barriers (OR: 0.87; 95% CI: 0.79-0.96) (Jones et al., 2015). Approaches for providing care and better education have not been systematically studied, but suggestions have included targeting knowledge, preparedness, empowerment, and beliefs (Marrs and Lack, 2013).

Advice on Allergens in Nonfood Items and Alcoholic Beverages

Allergens in Pet Foods, Cosmetics, and Topical Products

A variety of noningested products include allergens, which requires caution on the part of consumers when allergen disclosures may not be included. Examples include pet foods containing milk, soy, fish, or nut ingredients, and lotions with nut ingredients. Most of these products are not ingested, so the risk of anaphylaxis would be relatively low but studies have not delineated the risks. These products have no labeling requirements relating to food allergens. Physicians may discuss these potential risks with patients who have food allergy, especially with toddlers who may otherwise have access to these products and could ingest them accidentally.

Allergens in Vaccines, Medications, and Dietary Supplements

Physicians and patients with food allergy must consider potential food allergen exposures in vaccines, medications, and dietary supplement products (e.g., vitamins, probiotics), which are not regulated by labeling laws. Also, excipients (i.e., substances added to medications to improve various characteristics) may be food or derived from foods (Kelso, 2014). These include milk proteins; soy derivatives; oils from sesame, peanut, fish or soy; and beef or fish gelatin. The medications involved include vaccines; anesthetics; and oral, topical, and injected medications. With perhaps the exception of gelatin, reactions appear to be rare overall, likely because little residual protein is included in the final preparation of these items. The specific risk for each medication is not known.

Vaccines also may contain food allergens, such as egg protein or gelatin. Expert opinion based on many studies suggests that the yearly influenza vaccination and the measles, mumps, and rubella vaccines should not be deferred based on egg allergy (e.g., Turner et al., 2015). In contrast, the yellow fever and rabies vaccines should not be given to persons with severe egg allergy unless testing with the vaccine is undertaken first (Kelso et al., 2012, 2013).

Allergens in Alcoholic Beverages

Allergic or allergic-like reactions can occur from alcoholic beverages. These products are not included in allergen labeling laws and counseling of patients may be warranted. However, the literature on the allergenicity of alcoholic beverages is sparse. Persons with alcohol dehydrogenase deficiency may experience dose-related symptoms that mimic allergy, including flushing, nausea, vomiting, and sometimes wheezing. Sulfites, often found

in wine, may induce asthma symptoms. Wines may be clarified by processes that use allergens such as egg, but the final product may not likely contain residual protein (Rolland et al., 2008). Beer may have residual proteins from barley or other grains that can trigger reactions (Quercia et al., 2012). Distilled alcohol should be free from protein. Many alcoholic beverages are made from potential allergens, for example amaretto from almonds, frangelico from hazelnuts, and Irish cream from milk, but the residual allergenicity of these products has not been studied.

EMERGENCY MANAGEMENT OF ALLERGIC REACTIONS

The physician must counsel patients with food allergy, and their families, on recognizing and treating food-induced anaphylaxis. The following discusses some of the challenges involved in diagnosis and treatment of anaphylaxis at the level of first aid and physician care. The previous section "Management in Schools and Child Care Centers" includes additional information regarding written emergency plans and emergency medical identification jewelry.

Definition of Anaphylaxis, Diagnosis, and Differential Diagnosis

Anaphylaxis has been described as a severe, life-threatening, generalized or systemic hypersensitivity reaction (Muraro et al., 2014a). Life-threatening breathing, airway, or circulatory problems may occur and skin and mucosal changes usually, although not always, occur. A consensus definition was proposed in 2006, describing anaphylaxis as "a serious allergic reaction that is rapid in onset and may cause death" (Sampson et al., 2006b, p. 392). Diagnostic criteria based on consensus were published in 2006 (Sampson et al., 2006b) and some validation has been performed (Campbell et al., 2012; Harduar-Morano et al., 2010). Diagnosis may need to differentiate anaphylaxis from fainting, cardiac events, mild allergic reactions, asthma, choking, panic attacks, and many other ailments. However, no simple tests exist to confirm anaphylaxis or to predict those at risk. Serum tryptase, a mediator released from mast cells, may not be increased with food-induced anaphylaxis, although severity of the episode and differences from baseline may be relevant (De Schryver et al., 2016; Lin et al., 2000a; Sahiner et al., 2014; Sala-Cunill et al., 2013; Wongkaewpothong et al., 2014). Histamine measurements are difficult to obtain. As reviewed previously, allergy tests are not good predictors of severity of reactions. Overall, anaphylaxis is a clinical diagnosis and no rapid diagnostic test is available.

Nature of Anaphylaxis

Anaphylaxis involves more than one organ system (e.g., skin, respiratory tract, and/or gastrointestinal [GI] tract) (Boyce et al., 2010). The skin is involved in 80 to 90 percent of episodes, respiratory symptoms in up to 70 percent, GI in up to 40 percent, and cardiovascular symptoms in up to 35 percent (Boyce et al., 2010; Dhami et al., 2014; Lieberman et al., 2015; Muraro et al., 2014a; Sampson et al., 2014). Symptoms include flushing, pruritus, hives (urticaria), nasal congestion and rhinorrhea, throat itching and swelling (edema), choking, wheezing, coughing, trouble breathing, altered breathing sounds or trouble speaking, cramping abdominal pain, nausea, vomiting, diarrhea, dizziness, high or slow heart rate, sleepiness, confusion, loss of consciousness, anxiety, feeling of doom, seizure, and uterine cramps.

Food-induced anaphylaxis typically occurs within minutes to several hours of ingestion of the food (but may be longer for mammalian meat, alpha-gal-related reactions (Boyce et al., 2010; Sampson et al., 2014; Tripathi et al., 2015). The reaction usually develops and resolves completely within hours, but a biphasic course has been described where symptoms resolve but recur hours later, a phenomenon that is described for 1 to 20 percent of cases (Alqurashi et al., 2015; Ellis and Day, 2007; Lee and Greenes, 2000; Lee et al., 2015b; Lieberman, 2005; Mehr et al., 2009; Sampson et al., 1992). Biphasic reactions may be more likely with severe or undertreated reactions, but are unpredictable, and observation in an emergency department for at least 4 to 6 hours is recommended (Boyce et al., 2010). Rarely, symptoms can last for many hours or days (Sampson et al., 1992). Deaths have been reported from 30 minutes to 2 hours after exposure (Bock et al., 2001, 2007; Sampson et al., 1992). No biomarkers are available that adequately predict severity or whether a biphasic reaction will develop. Reactions could be worse, milder, or similar from time to time, presumably because of many variables including overall sensitivity, amount of allergen ingested, and other factors.

Risk Factors (Asthma, Certain Foods, Cofactors) and Risk Assessment

A number of comorbid diseases may affect the severity and treatment response of anaphylaxis (Boyce et al., 2010; Dhami et al., 2014; Lieberman et al., 2015; Muraro et al., 2014a; Sampson et al., 2014). Asthma is a significant risk factor for death, especially in adolescents and young adults (Bock et al., 2001, 2007; Pumphrey, 2000; Pumphrey and Gowland, 2007; Sampson et al., 1992). Cardiac disease is a risk factor for middle-aged or older adults (Pumphrey, 2000; Pumphrey and Gowland, 2007). Allergies to some foods are associated with more severe reactions (e.g., peanut, tree

nuts, milk, fish, shellfish, seeds, and egg) than others (fruits and vegetables). Additional risks for more severe reactions include underlying mastocytosis and lung disease diagnosis. Various medications may affect response to treatment, including beta-adrenergic antagonists, angiotensin-converting enzyme inhibitors, and alpha adrenergic blockers. No simple means exist to predict the severity of reactions or to clearly identify an individual at risk.

Medical Treatment of Anaphylaxis

Epinephrine, typically prescribed as auto-injectors for self-injection for first aid management, is first-line therapy for food-induced anaphylaxis and is recommended to be injected intramuscularly (anterolateral thigh into the vastus lateralis muscle) (Boyce et al., 2010; Lieberman et al., 2015; Muraro et al., 2014a; Sampson et al., 2014). Epinephrine should be administered promptly for anaphylaxis and when clinical features are likely to evolve into anaphylaxis (AAAAI BOD, 1994; Muraro et al., 2014a). Delay in providing therapy with epinephrine is associated with increased risk of death and morbidity. Epinephrine has a variety of actions that improve breathing and circulation and may reduce the release of additional inflammatory mediators. Treating anaphylaxis with epinephrine has no absolute contraindications.

A Cochrane Systematic Review (Sheikh et al., 2012a) of the effectiveness of epinephrine auto-injectors in relieving respiratory, cardiovascular, and other symptoms during anaphylaxis in the community setting sought randomized or quasi-randomized trials comparing auto-injectors to no intervention or other interventions and found no qualifying studies out of 1,328 references that were reviewed. Nonetheless, the conclusion was to recommend epinephrine auto-injectors as the most effective first-line treatment for anaphylaxis in the community, with a recommendation for trials comparing different doses and devices as well as syringe and ampule.

According to the NIAID/NIH-supported Guidelines, a prescription for an epinephrine auto-injector, typically two doses, should be given to those who have experienced anaphylaxis as well as patients with diagnosed food allergy who have asthma and those with allergy to foods that typically cause severe reactions (e.g., peanut, tree nuts, fish, shellfish). A prescription for anyone with a diagnosed food allergy may be considered because subsequent reaction severity is hard to predict (Boyce et al., 2010). The EAACI Anaphylaxis Guidelines (Muraro et al., 2014b) additionally comment upon a prescription being indicated when a person has had previous mild to moderate symptoms from trace food exposure, mild to moderate symptoms to a food and travel to areas remote from medical care is planned, and for teenagers or young adults with food allergy (excluding oral allergy syndrome). The AAAAI Practice Parameter on anaphylaxis discusses additional con-

siderations, such as allergy to mustard, peach, or apple, for those patients in Mediterranean regions (who tend to have more severe reactions to these fruits), and people having past reactions with throat tightness, those having food allergy and airway anatomy that predisposes to obstruction, or those having contact allergic reactions to specific foods. This document also concluded that physician discretion is needed (Lieberman et al., 2015).

Consensus has emerged on the use of premeasured auto-injector doses of 0.15 mg for those weighing 16.5 (7.5 kg) up to 55 pounds (25 kg), and a dose of 0.3 mg for those 55 pounds and greater (Boyce et al., 2010; Muraro et al., 2014a; Sampson et al., 2014). Controversy exists regarding the auto-injectors use for infants weighing less than 7.5 kg (or less than 10 kg in some guidelines [Boyce et al., 2010, Sampson et al., 2014]) and for individuals with obesity (Sicherer et al., 2007; Simons et al., 2014, 2015). Although dosing at 0.01 mg/kg epinephrine intramuscularly has been recommended, the ideal dose has not been determined through studies (Lieberman et al., 2015). Additional studies and potentially a wider range of fixed-dose auto-injectors may be beneficial.

First aid management also includes activating emergency services (calling for help, dialing 911 or equivalent), evaluating airway breathing and circulation, and providing cardiorespiratory resuscitation, if needed. It may be beneficial to place the patient in a recumbent position with the legs elevated if tolerated (although bringing a patient to a standing position may result in death, and caution is needed during transport (Pumphrey, 2003). The patient may require more than one dose of intramuscular epinephrine, as studies suggest this may occur in 10 to 20 percent of cases (Jarvinen et al., 2008; Oren et al., 2007). The intramuscular epinephrine dose can be repeated (e.g., in approximately 5 minutes from the last dose), as warranted by symptoms (Muraro et al., 2014a). Side effects of epinephrine may include restlessness, headache, dizziness, palpitations, pallor, flushing, and tremor. Rarely, epinephrine can lead to severe side effects, such as myocardial infarction or intracranial hemorrhage, but these severe side effects almost exclusively occur from overdose, which is more likely if errors in intravenous administration occur, rather than intramuscular injection from auto-injectors (Campbell et al., 2015a).

Additional treatment of anaphylaxis is considered adjunctive to epinephrine and may include bronchodilator medications, H1 and H2 antihistamines, corticosteroids, vasopressors, glucagon, atropine, supplemental oxygen, intravenous fluids, and patient positioning (Boyce et al., 2010; Lieberman et al., 2015; Muraro et al., 2014a; Sampson et al., 2014). Most of these adjunctive therapies would be available following first aid management and would be administered by emergency personnel or by emergency department staff.

Systemic antihistamines are often used during anaphylaxis. Systematic

reviews to assess the benefit or harm of H1 antihistamines for the treatment of anaphylaxis have been conducted. Randomized and quasi-randomized controlled trials to compare this therapy with placebo or no intervention have been sought. However, no studies have satisfied inclusion criteria (Nurmatov et al., 2014b; Sheikh et al., 2007). The medications presumably help to relieve cutaneous symptoms but no studies regarding effect on other symptoms of anaphylaxes or progression of reactions have been conducted. Combination treatment with H1 and H2 antihistamines may have additional efficacy compared to H1 antihistamines alone for cutaneous symptoms (Lin et al., 2000b; Runge et al., 1992). Oral (in preference to intravenous) administration is recommended for relief of cutaneous symptoms (Ellis and Brown, 2013; Muraro et al., 2014a) to avoid hypotension related to rapid intravenous administration. The onset of action of antihistamines (e.g., liquids, rapid disintegrating tablets) is approximately 30 minutes. Studies to determine the benefit or harm of antihistamines in anaphylaxis would be useful.

Oral or intravenous glucocorticoids are often used in anaphylaxis to theoretically prevent protracted symptoms or late onset of symptoms and also to address concomitant asthma. A systematic review was undertaken with the intention to perform a meta-analysis to assess benefits and harms of glucocorticoid treatment during anaphylaxis, but no randomized or quasi-randomized controlled trials comparing glucocorticoids to any control were identified and so no meta-analysis could be undertaken (Choo et al., 2012). Therefore, therapy with glucocorticoids, which have a slow onset of action, are used in anaphylaxis without clear evidence and are based on expert opinion (Boyce et al., 2010; Muraro et al., 2014a; Sampson et al., 2014). Studies on the utility of glucocorticoids in anaphylaxis could inform therapeutic approaches.

No consensus in the literature exists on the optimal time for observation of the patient who has experienced anaphylaxis, although 4 to 6 hours has been suggested, or longer if the patient experienced hypotension (Boyce et al., 2010; Muraro et al., 2014a; Sampson et al., 2014).

Post-Anaphylaxis Long-Term Management

Based on current guidelines, discharge planning or long-term management should include a written anaphylaxis emergency action plan, encouraging medical identification jewelry, and having epinephrine auto-injectors (typically two) always available, a plan for monitoring auto-injector expiration, a plan for arranging further evaluation as needed, printed information about anaphylaxis and its treatment, and consideration for referral to specialist for further evaluation. It also is recommended to have instructions on the proper use of epinephrine auto-injectors and indications for use, advice

about allergen avoidance, and additional information regarding a dietitian consult and support groups (Boyce et al., 2010; Lieberman et al., 2015; Muraro et al., 2014a; Sampson et al., 2014). As reviewed above, discharge and long-term management of patients with food allergy who are at risk for anaphylaxis has some potential pitfalls. Nutritional and psychological concerns are described below.

NUTRITIONAL CONSIDERATIONS

Adequate nutrition is important for normal child development and growth. When allergen avoidance is the one recommendation to minimize the risk of an allergic reaction, children could end up deficient on specific nutrients or calories if attention to their nutrition is not considered.

The NIAID/NIH-supported Guidelines suggest nutritional counseling and regular growth monitoring for all children with food allergies (Boyce et al., 2010) and the EAACI Guideline suggested that, ideally, the patient would receive proper counseling by a dietitian with specific competence in food allergy, recognizing this is particularly important for infants and children and may vary by age and foods avoided (Muraro et al., 2014b).

The most common allergenic foods contain nutrients whose removal may reduce diet quality (i.e., lead to nutrient deficiencies) and, therefore, may be detrimental to health, particularly for an infant or child. For example, cow milk has protein, fat, calcium, vitamin D, and riboflavin; wheat in fortified cereals contains carbohydrates, iron, thymine, niacin, riboflavin, and folate; egg includes protein, fat, iron, and riboflavin; and fish and shellfish are sources of protein, fat, and omega-3 fatty acids. When cow milk is avoided, substitutions are typically needed to account for lost nutrients (Fiocchi et al., 2010). For example, an infant or toddler who does not use cow milk may require breast milk or a human milk substitute, and older toddlers may require a calcium supplement and/or fortified alternative beverages, such as soy milk or rice, almond, oat, or coconut beverages, depending on other components of the diet and as tolerated. However, these beverages are not equivalent to cow milk in terms of fat, protein, calories, and other essential nutrients (Groetch et al., 2013). Specifically, an infant with a diagnosed cow milk allergy will typically tolerate formulas approved for use in these circumstances, such as extensively hydrolyzed casein–based or amino acid–based formula, or soy formula, as medically necessary following a diagnostic evaluation. However, partially hydrolyzed milk–based formula is not typically appropriate for an infant with a diagnosed cow milk allergy (Lee et al., 2015a). Infants with food allergy may have nutritional concerns related to their elimination diets or to underlying chronic illness. For example atopic dermatitis or GI inflammation can interfere

with nutrient absorption or result in increased caloric needs (Jarvinen et al., 2013).

No RCTs have addressed whether food allergen avoidance affects growth and nutritional status of infants and children. Multiple studies, primarily observational and cross-sectional, suggest that food allergy may be associated with impaired growth (Cho et al., 2011; Christie et al., 2002; Flammarion et al., 2011; Hobbs et al., 2015; Isolauri et al., 1998; Mehta et al., 2014; Meyer et al., 2012, 2014; Mori et al., 2015; Mukaida et al., 2010; Nachshon et al., 2014; Vieira et al., 2010). It has particularly been noted that growth may be impaired in those avoiding cow milk (Hobbs et al., 2015; Isolauri et al., 1998; Mehta et al., 2014; Mukaida et al., 2010; Tiainen et al., 1995). For example, Tiainen et al. (1995) compared 18 children (mean age 2 years, range 1 to 3.5 years) with cow milk allergy and 20 healthy controls and found that although total energy intake between the two groups did not differ, the children with milk allergy had lower protein and higher fat intake compared to controls, and the allergic children also had a lower height for age percentile (–0.6 versus 0.2 SD units; $P<0.05$). Long-term outcomes for those on a childhood milk avoidance diet can include increased risk of reduced bone mineral density and increased risk of early osteoporosis (Nachshon et al., 2014). A small (N=39) prospective study from the United Kingdom found that milk avoidance in early life can have a long-term effect on food intake and preferences (Maslin et al., 2016).

Having multiple food allergies appears to put children at increased risk of decreased growth, due to the reduced food and total energy intake (Cho et al., 2011; Christie et al., 2002; Flammarion et al., 2011; Hobbs et al., 2015; Meyer et al., 2012, 2014; Mukaida et al., 2010; Vieira et al., 2010). For example, Christie et al. compared children with food allergy to healthy controls and found that children with two or more food allergies were shorter than those with one, and children with cow milk or multiple food allergies were less likely to consume sufficient dietary calcium (Christie et al., 2002). Meyer et al. noted that children with food allergies were more underweight than the general UK population, which was linked to the number of foods excluded (Meyer et al., 2014). However, they also noted cases of obesity despite dietary elimination. A systematic review of nutrient intake and growth in children with multiple IgE-mediated food allergies identified six studies and concluded that "children with multiple food allergies have a higher risk of impaired growth and may have a higher risk of inadequate nutrient intake than children without food allergies" (Sova et al., 2013, p. 669). Although data are limited (Berni Canani et al., 2014; Christie et al., 2002), dietary counseling can potentially improve macro and micro nutrient intake and growth outcomes without evidence of inducing overweight status. Evidence-based specific dietary guidance for children with food allergy is lacking (Groetch et al., 2013; Meyer et al.,

2012). However, the data suggest that by individualizing dietary counseling, dietary intakes and nutritional status can be improved and growth impairment may be prevented.

QUALITY OF LIFE AND MENTAL HEALTH CONSIDERATIONS

Daily management of food allergy is focused on avoiding trigger foods and recognizing and managing allergic reactions, some of which are life-threatening. These considerations practically affect the routine of daily living and also carry psychological burdens that can result in anxiety and stress. Measurement of health-related quality of life (HRQL) helps determine the impact of disease on an individual, which may vary among individuals even if disease severity is similar. Tools to measure HRQL may be generic or disease specific. Generic instruments allow comparison between disorders, while disease-specific instruments are more sensitive for measuring the burden of disease and identifying changes caused by interventions.

A systematic review was undertaken to identify validated instruments specific to food allergy disease (Salvilla et al., 2014). Seventeen eligible studies were retrieved and seven disease specific HRQL instruments were subjected to detail quality appraisal. These seven were found to have robust psychometric properties (Cohen et al., 2004; DunnGalvin et al., 2008; Flokstra-de Blok et al., 2008, 2009a,b; MacKenzie et al., 2012; Resnick et al., 2010) and to be suitable for use in children, adolescents, parents and caregivers, and adults. The authors also concluded that further work is required to understand clinically important differences in score appraisal of patients with food allergy. Using this systematic review, guidelines were developed for using specific instruments based on the type of food allergy, research or clinical applications, inclusion or exclusion of comorbidities, patient age, language and cultural issues, the preferred respondent, and target population (Muraro et al., 2014c). This review pointed out that the instruments have been used in research settings only to provide quantitative information on the HRQL of patients with IgE-mediated food allergy and to assess the effect of interventions and determine outcomes. Studies to recommend use of these instruments at the individual patient level are insufficient. Additionally, the review offered a number of research recommendations, including a need to: determine optimum methods of administration, frequency, and interpretation; identify which instruments, if any, are valid to guide clinical practice of individual patients; determine efficacy of the instruments for evaluating medical and technological advances, patient satisfaction and quality of care, and health and regulatory policy; include these instruments to explain different pathways in the development, expression, and impact of chronic diseases; articulate norms for age, sex, and country or culture; explain the relationship between responses to both proxy and

self-report measures; develop optimum methods for evaluating measures in patients with comorbid conditions; and, determine how quality-adjusted life years for food allergy can be developed to help inform policy.

Aside from validated HRQL instruments, the practical emotional concerns of daily management of food allergies can result in distress. Indeed, the NIAID/NIH-supported Guidelines recommends that patients with food allergy and their caregivers be given information on food allergen avoidance and emergency management that is age and culturally appropriate because management can have substantial daily consequences, including anxiety and diminished quality of life (Boyce et al., 2010). Food-specific HRQL instruments generally query on issues such as holiday plans, restaurants, social activities, time for preparing meals or other meal-related events, taking precautions, troubles in having to carry medications, worry about health issues, not being able to get help for a reaction, other's lack of understanding about the allergy, attending school or work activities safely, having a normal life, anxiety, and worry about the allergy or reactions (Cohen et al., 2004; DunnGalvin et al., 2008; Flokstra-de Blok et al., 2008, 2009a,b; MacKenzie et al., 2012; Resnick et al., 2010). The degree of impact on HRQL can vary based on knowledge of food allergies, age, having had experiences such as emergency room visit for anaphylaxis, an injection of epinephrine, or multiple food allergies, or allergies to specific foods (e.g., milk or egg compared to peanut or tree nut), and the impact can be complex due to interactions among various factors (Springston et al., 2010; Ward and Greenhawt, 2015; Wassenberg et al., 2012).

Various factors may affect the distress, anxiety, and psychological aspects of a food allergy diagnosis and management. Additionally, the impact may vary based on age, role, and time living with a diagnosis. Compared to mothers of children without chronic illness, mothers of children with food allergy have increased anxiety and stress (Lau et al., 2014). For example, a study of families with a child having peanut allergy revealed that mothers compared to fathers reported lower psychological and physical quality of life and more stress and anxiety (King et al., 2009). This study also found that children with food allergy had greater separation anxiety than their siblings. Another study noted that mothers of children with food allergy were more empowered than fathers of children with food allergy, but empowerment was not associated with higher HRQL (Warren et al., 2015). One study found that maternal anxiety and a child's attitude toward food allergy were associated with child distress for children ages 8 to 17 years (Lebovidge et al., 2009). Another study found that child anxiety and parental stress significantly predicted parental report of their child's HRQL, and that child anxiety, parenting stress, length of diagnosis, and receiving epinephrine predicted self-reported HRQL (Roy and Roberts, 2011). A study using various scales to determine anxiety and depression found that

among parents being evaluated for a first-time allergy clinic appointment for suspected food allergy in their child, 33 percent reported mild to severe anxiety and 18 percent reported depression, with no significant change 1 month after the visit (Knibb and Semper, 2013).

Studies have focused on teens and young adults as well. A small qualitative study of adolescents and their parents found that having a child with anaphylaxis can have a significant long-term psychological impact on the parents, and in some cases, this anxiety may be transferred to the adolescents (Akeson et al., 2007). In a large study of adolescents (N=1,420) followed longitudinally, having food allergy was associated with more symptoms of separation and generalized anxiety, attention deficit and hyperactivity disorder, and anorexia nervosa. Over time, adolescents with food allergy experienced increases in generalized anxiety disorder and depression, but having food allergy was not associated with a higher likelihood of having a diagnosed psychiatric disorder (Shanahan et al., 2014). An online study of 86 food-allergic and 344 healthy adults ages 18 to 22 years evaluated autonomy, anxiety, depression, and perception of parental behavior. The study indicated that, although food allergic young adults did not differ from healthy ones, those who experienced anaphylaxis described their disease as more severe, were more worried, and indicated their parents as more protective then those who had not experienced anaphylaxis (Herbert and Dahlquist, 2008). Additionally, for adolescents and young adults, having a food allergy may be associated with dating anxiety, interference with physical intimacy, and fear of a negative evaluation by peers (Hullmann et al., 2012).

Bullying has been another focus of study among psychosocial aspects of food allergy. Episodes of bullying appear to be more common among children with food allergy compared to peers and can take the form of verbal and physical events (Lieberman et al., 2010). Bullying is significantly associated with decreased quality of life and increased distress in parents and children. Parents often may not know about their child being bullied (Shemesh et al., 2013). When parents were aware of bullying, the child's quality of life was better and distress was reduced. Food-related bullying often persists over time, although it is less likely to continue if parents intervene (Annunziato et al., 2014). The AAAAI Guidelines specifically suggests that physicians inquire about behavioral changes because of food allergy–related bullying (Sampson et al., 2014).

Overall, the relationship of a chronic disease such as food allergy and psychosocial problems is complex. A systematic review and meta-analysis of 43 studies suggested a positive association between psychosocial factors and future atopic disorders and current atopic disorders and future poor mental health, but studies of food allergy were insufficient to comment on this disease separately (Chida et al., 2008). Determinants of food allergy–

related cognition, emotion, and behavior are complex and understudied (DunnGalvin et al., 2009).

Interventions pertaining to reducing the psychosocial impact of food allergy are few. It appears that food allergy interventions themselves can result in improvement. For example, measures of food-specific HRQOL showed improvement for those on desensitization therapy in small or uncontrolled studies (Arasi et al., 2014; Carraro et al., 2012; Factor et al., 2012; Otani et al., 2014). Also, anxiety may decrease and HRQL may improve following a diagnostic OFC, whether the outcome confirms an allergy or not (Franxman et al., 2015; Knibb et al., 2012; Soller et al., 2014; van der Velde et al., 2012; Zijlstra et al., 2010). However, no comprehensive, evidence-based protocols exist for the clinical management of psychosocial concerns related to food allergy, and studies are few. Availability of a 24-hour helpline for expert management improved quality of life for participants randomized to this intervention (Kelleher et al., 2013). A pilot study of a telephone-based intervention teaching parents self-regulation for chronic disease management resulted in improvement in some components of HRQL (Baptist et al., 2012). Data to understand the value of support groups for food allergy are limited (Sharma et al., 2012).

Referral to a mental health professional would presumably be of value, if indicated, to improve psychosocial health concerns. Unfortunately, one study of mental health screening of families with food allergy failed to result in a greater consultation rate with a mental health professional compared to a referral by the patient's allergist (Shemesh et al., 2015). An expert review on the topic of addressing the psychosocial aspect of food allergy on a patient-level basis suggested that medical providers can validate feelings, normalize the challenge of balancing management with participation in daily activities, and provide education about food allergy and its psychosocial impact, with referral to a mental health expert when indicated (Herbert et al., 2016).

In conclusion, food allergy may affect different aspects of mental health and HRQL. Health professionals should address these issues. However, more information is needed to refine understanding about identification, prevention, and management of these issues.

TREATMENT MODALITIES UNDER INVESTIGATION

The following summarizes approaches under investigation to treat food allergy. This is not meant to be a comprehensive review of risks and benefits of these approaches, nor a compendium of all approaches under study, but rather an overview with summaries of expert reports and suggested additional references. The committee did not make an assessment in regard to

which treatment modalities have more promise in the future nor where the research gaps exist.

A number of food allergy treatment strategies are under investigation. Examples that are furthest along in study and are allergen-specific include oral, sublingual, and epicutaneous immunotherapy.

Oral immunotherapy (OIT) involves ingesting the food allergen in gradually increasing amounts. Protocols typically begin with ingestion of trace amounts, building up to a small dose on a first day and then increasing the dose, which is taken daily, on a biweekly basis toward a daily "maintenance" dose. Sublingual immunotherapy (SLIT) takes a similar approach but the allergen is retained for a period under the tongue and much lower doses are used compared to OIT. Epicutaneous immunotherapy (EPIT) involves placement of a membrane impregnated with allergen on the skin. These therapies are often evaluated in context of promoting "desensitization" to the targeted food allergen. That is, these treatment approaches may raise the threshold of reactivity while the therapy is in progress, while cessation of therapy may result in loss of protection. A curative therapy would not depend upon daily treatments to maintain a threshold where the food can be ingested without concerns for dose ingested or other factors that may alter the safe ingestion of the food (e.g., concomitant exercise, illness). Approaches that are not allergen-specific also have been suggested. For example, omalizumab is a humanized monoclonal antibody against IgE that is approved for use in recalcitrant allergic asthma and for chronic hives. It may increase the threshold of reactivity to allergens and may, in co-administration with OIT, allow more rapid dosing with fewer symptoms (Begin et al., 2014; Schneider et al., 2013; Wood et al., 2015). Studies with a similar agent suggested an increased threshold to peanut during oral food challenges (Leung et al., 2003).

The 2010 NIAID/NIH-supported Guidelines concluded that allergen-specific immunotherapy is not recommended, and also did not recommend immunotherapy with cross-reactive allergens (i.e., pollen allergens to treat oral allergy syndrome) (Boyce et al., 2010). The 2014 EAACI Guidelines concluded that allergen-specific immunotherapy is promising, but is associated with risks, including anaphylaxis and is not recommended for routine clinical use (Muraro et al., 2014b). These Guidelines (p. 1019) also stated that "the use of anti-IgE alone or in combination with specific immunotherapy is currently not recommended . . . although it represents a promising treatment modality." In addition, the 2010 NIAID/NIH-supported Guidelines and the EACCI Guidelines both recommend not using pollen immunotherapy to primarily treat food allergy. The AAAAI Guidelines similarly concluded that immunotherapeutic approaches such as OIT show promise, but are not ready for implementation in clinical practice because

of inadequate evidence of therapeutic benefit over risks (Sampson et al., 2014).

The field of allergen-specific immunotherapy is rapidly progressing. A number of systematic reviews and meta-analyses have addressed the utility of immunotherapy (primarily OIT and SLIT) for food allergy. A 2012 meta-analysis of milk OIT identified five trials. The authors noted the poor quality of the trials and concluded that treatment could lead to desensitization in a majority of individuals. Although most were mild, a major drawback was the frequency of side effects (Yeung et al., 2012). A 2014 systematic review and meta-analysis of milk oral OIT identified six qualifying articles and concluded that it was effective for treating IgE-mediated cow milk allergy because significantly more patients were desensitized on treatment compared to those on an avoidance diet. The treatment was considered reasonably safe because side effects were mild to moderate and intramuscular epinephrine was rarely required (Martorell Calatayud et al., 2014). A 2012 review and meta-analysis of peanut OIT (Sheikh et al., 2012b) identified six qualifying studies with 85 participants, but given the case series design of all the studies, they were considered to have high risk of bias.[4] The authors noted suggestive evidence that treatment could increase the threshold for many participants but that adverse reactions were common. Although most were minor, some were potentially life-threatening. They concluded that the treatment was promising for short- or medium-term management of carefully selected patients, but that more robust studies were needed and that OIT should not be administered outside of carefully designed clinical trials. A 2014 meta-analysis (Sun et al., 2014) of RCTs of peanut OIT and SLIT identified three studies with a total of 86 participants. These immunotherapies were determined to have a positive effect on peanut allergy (OR: 38.44; 95% CI: 6-246). The authors cautioned that the findings were based on a small number of trials and larger, well-designed and double-blind RCTs are needed. A 2013 review of pediatric SLIT (Larenas-Linnemann et al., 2013) concluded that food OIT was more promising than SLIT, but few studies were included. A 2014 meta-analysis (Nurmatov et al., 2014a) identified 21 eligible trials of OIT or SLIT to foods. The meta-analysis revealed a lower risk of reactions on treatment (risk ratio [RR]: 0.21; 95% CI: 0.12-0.38). Additionally, SPT responses significantly decreased (mean difference: –2.96 millimeters [mm]; 95% CI: –4.48 to –1.45), and allergen-specific IgG4 concentrations increased by an average of 19.9 (95% CI: 17.1-22.6) µg/ml. Safety data showed an increased risk of local oral-pharyngeal and gastrointestinal adverse reactions with treatment (RR: 1.47; 95% CI: 1.11-1.95).

[4] Case series design studies are considered to be vulnerable to selection bias because they, for example, might draw their patients from a particular population and might not represent the wider population.

Also, a non-significant increased average risk of systemic adverse reactions occurred with treatment (RR: 1.08; 95% CI: 0.97-1.19). The authors concluded that OIT can induce immunomodulatory changes and thereby promote desensitization. However, based on limited evidence on long-term efficacy and safety, as well as cost-effectiveness, they concluded that the treatment should not currently be used outside of experimental conditions.

Overall, these reviews and meta-analyses are in agreement with the guidelines noted above. However, OIT is being used clinically by a number of practice settings with various motivations (Greenhawt and Vickery, 2015; Pajno et al., 2014). Phase 3 studies are currently under way for OIT and EPIT. Numerous other approaches have been tried or are in development, such as a panoply of biologics, immune adjuvants, modified protein vaccines, traditional Chinese medicine practices, probiotics, and many others (Bauer et al., 2015; Keet and Wood, 2014; Kumar et al., 2013; Le and Burks, 2014; Nermes et al., 2013; Nowak-Wegrzyn and Sampson, 2011; Oyoshi et al., 2014; Sato et al., 2014; Senti and Kundig, 2016). Clearly, many strategies can be pursued to address treatment of food allergy.

OVERALL CONCLUSIONS

Management in the health care setting involves education about the daily strategies that patients need to follow to avoid allergen ingestion and to recognize and treat reactions promptly. Although these management approaches begin in the health care setting, success often requires involvement at the community level (see Chapter 8). Allergen avoidance, usually strict avoidance even of trace amounts of allergen, is the primary means of management. This requires significant education and caution throughout the day. In addition, it relies upon others in the community to provide safety, seriously affects quality of life, and increases anxiety. Counseling about avoidance involves emphasizing key concerns, such as cross-contact and hidden ingredients and discussing foods related to the diagnosed allergens, which may need to be avoided upon a full food allergy evaluation. Counseling is directed to managing food allergies at home, reading labels (and knowing about products that are not included in mandatory labeling laws), asking questions when eating in restaurants and during travel, and, for children, avoiding food allergens when away from home (e.g., at schools, camp, or when with friends and relatives). Such counseling should address common pitfalls that have been identified in a variety of studies. However, data to be able to provide individualized risk assessments upon which to base instructions regarding avoidance and emergency management are limited. Also, limited programs exist for educating patients, caregivers, and other stakeholders, with few evidence-based programs to ensure effectiveness, and limited information exists on implementation. Adolescents

and young adults appear to be at increased risk for fatal anaphylaxis, and their risk-taking behavior has been identified as a possible cause.

Emergency management depends upon recognizing a reaction and promptly instituting therapy. Epinephrine is the primary treatment for anaphylaxis, with auto-injectors having fixed doses used for first-aid care. However, dosing of epinephrine has not been extensively studied and current auto-injectors may not provide appropriate doses for infants or individuals with obesity. Anaphylaxis is often underrecognized and undertreated. A number of risk factors have been identified for anaphylaxis, but there are no means to reliably predict severity of anaphylaxis. Medications used as primary and adjunctive therapy for anaphylaxis have not been studied. Post-anaphylaxis care includes observation in the medical setting to ensure resolution of symptoms, prescription of medications, education on avoidance and management, and possibly referral for additional testing and management. However, numerous pitfalls to these strategies have been identified.

Avoidance diets, particularly ones involving milk or multiple foods, can affect nutrition and growth and dietitian intervention is warranted. However, data on best practices are limited. Considering the significant impact of food allergy on quality of life and emotional status, information on how best to approach these issues is severely lacking. In addition, data on aspects of management for adults are sparse.

Emerging studies show promising results for desensitizing specific allergens but more information is needed about the safest and most effective approaches and how they may be individualized based on patients allergies and needs.

The committee did not wish to repeat all reasonable management recommendations that are already noted in professional guidelines, committee reports, and practice parameters. However, the committee emphasizes some key research recommendations in alignment with such reports where the study findings suggest areas of high need and frequent deficits in management.

RECOMMENDATIONS

Numerous clinical guidelines and parameters provide advice for health care providers and patients and their caregivers on diagnosing, preventing, and managing food allergy. The committee generally supports current guidelines and U.S. practice parameters for food allergy management and the committee emphasizes those areas where improvements would lead to significant changes in the quality of life of patients and their caregivers, such as training and education of the general public and all stakeholders.

Public Health Authorities, Health Care Providers, and Their Patients and Caregivers

The committee recommends that the Centers for Disease Control and Prevention work with other public health authorities to plan and initiate a public health campaign for the general public, individuals with food allergy, and all relevant stakeholders to increase awareness and empathy as well as to dispel misconceptions about food allergy and its management.

For example, as part of that campaign and taking advantage of the popularity of digital media among the public, particularly children and adolescents, public health authorities could develop effective media engagement programs. To plan for this campaign and develop media programs, public health authorities could conduct formative research with all potential audiences.

The committee recommends that public health authorities, such as the National Institutes of Health and the World Health Organization, and professional organizations, such as the American Academy of Pediatrics; the American Academy of Allergy, Asthma & Immunology; American Academy of Family Physicians; and the Academy of Nutrition and Dietetics, regularly update guidelines on diagnosis, prevention, and management of food allergy based on strong scientific evidence, as emerging scientific data become available.

For example, current evidence is insufficient to associate any of the following behaviors with prevention of food allergy: food allergen avoidance diets for pregnant or lactating women, prolonged allergen avoidance in infancy, vaginal delivery, breastfeeding, infant formulas containing extensively or partially hydrolyzed protein, and supplementation with specific nutrients (e.g., vitamin D, folate, fatty acids) in children or adults.

The committee recommends that medical schools as well as residency and fellowship programs and other relevant schools include training for health care providers in the management of food allergy and anaphylaxis. Health care providers, including dietitians and mental health professionals, also should receive training on approaches to counseling patients and their caregivers. Counseling training is envisioned to be provided, in part, by professional organizations through various means, including the Internet.

The following elements of food allergy training are appropriate for all health care providers, including emergency medical technicians, emergency room staff, nurses, dietitians, and others:

- *Emergency management*. This includes training to recognize and manage an anaphylaxis emergency, such as the use of intramuscular epinephrine as a first line of emergency management for episodes of anaphylaxis.
- *Counseling on food allergy management and anaphylaxis*. This includes identifying food allergies as well as managing and treating them in various settings (e.g., home, school, restaurants), as well as emergency management of anaphylaxis.

As appropriate, physicians and other health care providers also may receive training to provide the following:

- *Nutrition counseling*. This includes discussion of safe and nutritionally adequate avoidance diets to individuals with food allergies, particularly children and their caregivers. The training also could include offering referral to a dietitian when needed and as part of reimbursable care. In addition, dietitians may receive training in providing individualized dietary advice to people with food allergies and their caregivers.
- *Psychosocial counseling*. This includes identifying and discussing with patients and caregivers psychosocial concerns (e.g., bullying), validation of feelings, and balancing management with participation in daily activities. Training also could include offering referral to a mental health professional when needed and as part of reimbursable care. In addition, mental health professionals may receive training in counseling individuals with food allergy and their caregivers.

The committee recommends that health care providers counsel patients and their caregivers on food allergies following the most recent food allergy guidelines and emphasizing the need to take age-appropriate responsibility for managing their food allergy. Counseling is particularly important for those at high risk of food allergy and severe food allergy reactions, such as adolescents, young adults, and those with both food allergy and asthma.

The committee recommends that health care providers and others use intramuscular epinephrine (adrenaline) in all infants, children, and adults as a first line of emergency management for episodes of food allergy anaphylaxis. The Food and Drug Administration should evaluate the need for, and, if indicated, industry should develop an auto-injector with 0.075 mg epinephrine specifically designed for use in infants.

Current auto-injectors have 0.15 mg or 0.30 mg epinephrine, which is not suitable for infants. Consensus is currently lacking on first aid management using available auto-injectors when managing infants. A dose of 0.075 mg from an auto-injector could fill this gap. Labeling the auto-injectors in a standard manner to differentiate doses also could be beneficial.

Training First Responders and First Aiders

The committee recommends that organizations, such as the American Red Cross or the National Safety Council, who provide emergency training (e.g., first aid training, basic life support) to the general public and to first responders and first aid personnel in various professions and workplaces, include food allergy and anaphylaxis management in their curricula.

RESEARCH NEEDS

Health Care Settings

Food allergy management primarily requires avoiding the trigger allergen(s), but this approach requires extreme care; knowledge of cross-contact, hidden ingredients, and the effect of processing; and knowledge of ingredients through label reading and other methods. It is prone to accidents resulting in allergic reactions. Numerous obstacles arise for food-allergic consumers attempting to obtain safe meals outside the home. Surveys among individuals with food allergy, caregivers, and health care providers reveal deficiencies in food allergy knowledge and concerns about accidents, especially among adolescents and young adults. Only limited programs are available for educating individuals, caregivers, and health care providers on strategies to obtain and provide safe meals outside the home, with few validated programs and limited information on implementation. In addition, validated, evidence-based dietary guidance is lacking for those avoiding allergens, such as milk or multiple foods. Knowledge about potential interventions that health professionals could use to improve individual

psychosocial status, such as to improve quality of life or alleviate anxiety, also is lacking.

In regard to management, some areas of research need further study. For example, no means are currently available to reliably predict severity of anaphylaxis, which would be valuable for health care providers, individuals with food allergy, and their caregivers. In terms of managing anaphylaxis, underuse of epinephrine, the primary treatment for anaphylaxis, is common but the reasons are unknown. In addition, the fixed doses of epinephrine in auto-injectors may not be appropriate for infants or for individuals with obesity. Also, medications used as primary and adjunctive therapy for anaphylaxis (e.g., epinephrine dosing, bronchodilators, antihistamines, corticosteroids) have not been studied. Standardized emergency plans for individuals that can be used by caregivers at home or school also do not exist.

To address those gaps in knowledge, the following research areas should be pursued on all affected populations (ages, sexes, ethnicities, comorbidities, socioeconomic strata), especially on underrepresented populations:

- Determine the effectiveness of evidence-based guidelines and evidence-based educational programs on food allergy management, including avoidance of allergens and emergency management of allergic reactions and anaphylaxis, for health care providers and for patients, particularly for high-risk groups.
- Assess the following management issues:
  - the effectiveness of approaches other than strict allergen avoidance
  - the role of food allergy in other chronic allergic conditions
  - the identification of means to recognize clinically relevant versus nonrelevant allergen cross-reactivity
- Identify risk factors and biomarkers of food-induced anaphylaxis, particularly to identify individuals at high risk of severe reactions.
- Assess the safety and efficacy of adjunctive therapies for anaphylaxis, especially bronchodilators, antihistamines, and corticosteroids.
- Devise safe and effective therapies for food allergy, including those that can induce long-term desensitization and tolerance (i.e., sustained remission), and ideally a true cure.
- Improve understanding of the nutritional needs of persons on food allergen avoidance diets, how best to determine their need for dietitian evaluation/management, and how to develop evidence-based medical nutrition therapy.

- Evaluate whether consulting with a dietitian or a mental health professional improves quality of life and understand barriers to referring patients to dietitians or mental health professionals.
- Explore the best means to identify and intervene about psychosocial concerns associated with managing food allergy.
- Identify best practices for providing a uniform written emergency action plan for anaphylaxis. Consider using the recent American Academy of Pediatrics guidelines as the reference for a best practice study.
- Determine the proper dose of epinephrine in infants less than 10 kg and in individuals with obesity.
- Characterize risks associated with non-oral allergen exposures (e.g., skin-exposure and inhalation).

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7

Management of Packaged Foods

Consumers with a food allergy, like the general population, rely on packaged foods as a key component of their diet. Therefore, the packaged foods industry is an essential stakeholder if consumers with food allergies are to succeed in their prevention approaches and be safe. For this reason, the labeling of allergenic foods is an important public health intervention that assists consumers in avoiding potentially allergenic foods.

The food supply chain from production to consumption is complex (see Figure 7-1). Packaged foods are made and assembled primarily in commercial food processing facilities but also in restaurants, retail grocery stores, and other retail outlets. Commercial food processing facilities range from very large companies that may make dozens of different products within a single facility to very small companies that tend to make a narrower range of products but also often use shared facilities. In addition, food processing equipment is frequently shared to make different products. Furthermore, a packaged food may contain several dozen ingredients that may be obtained from a range of suppliers who likewise may have upstream suppliers. Finally, the farms and other suppliers that are sources of these ingredients (e.g., oceans, mines) are also often diversified and often share harvesting equipment, transportation vehicles, and storage facilities.

Allergens, then, can enter foods from many sources along the food chain, intentionally or unintentionally, through cross-contact[1] in farms,

[1] Cross-contact is the inadvertent introduction of allergenic food residues into a product. It is generally the result of environmental exposure during processing or handling, which may occur when multiple foods are produced in the same facility, when the same processing line

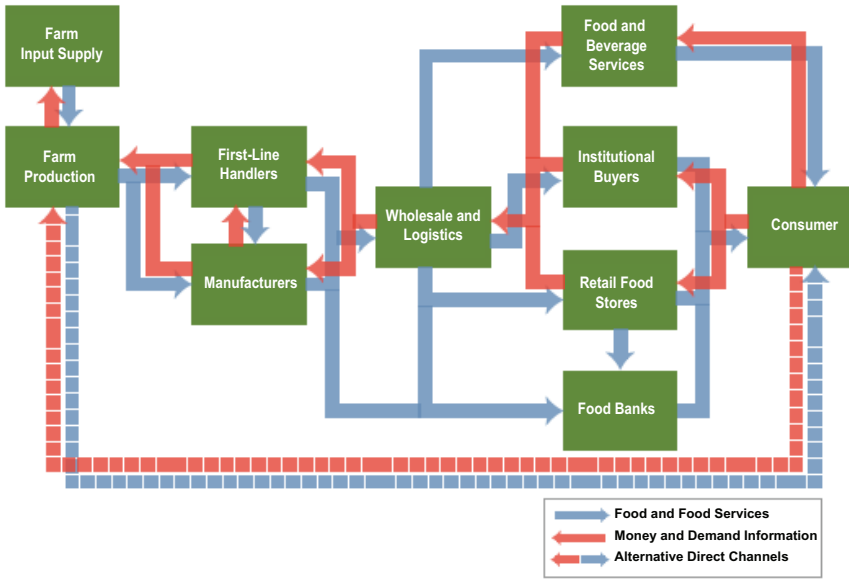

FIGURE 7-1 Conceptual model of a food supply chain. Elements or actors in this supply chain in one area (e.g., region or country) also have interactions (e.g., international trade) with actors in other areas.
SOURCE: IOM and NRC, 2015.

storage, distribution and manufacturing facilities, food service establishments, or the home. The food industry, of course, wishes to prevent the possibility that a consumer with a food allergy will experience an adverse reaction after consuming a packaged food product. In reality, achieving this goal at all times is challenging. From the food industry perspective, three general approaches can be used to minimize the risk of a reaction from an allergenic food: (1) eliminate potential allergens or specific allergens from products; (2) list the allergen on the product label as an ingredient, when it is intentionally added as such; and (3) implement strict allergen control plans (ACPs) to minimize allergen contamination and use advisory labels (precautionary allergen labeling, or PAL) to inform the consumer about the risk when necessary. The Food and Drug Administration (FDA) Food Safety

is used to produce allergenic and nonallergenic food as the result of ineffective cleaning, the generation of dust or aerosols containing an allergen, or other causes (http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/Allergens/ucm106890.htm#q19 [accessed January 5, 2017]).

Modernization Act[2] (FSMA) identifies allergens as a hazard that is reasonably likely to occur in food manufacturing operations and requires that food manufacturing develop ACPs, In so doing, the FSMA acknowledges the importance of food allergy as a public health priority for the packaged food industry. This chapter includes a brief description of ACPs in Box 7-1 but does not attempt to review them in depth even though the development of effective ACPs has an impact on both labeling and PAL.

Likewise, although the committee recognizes that processing can affect the allergenicity of foods either by reducing the amount of the allergenic protein or by altering the protein in some manner, the chapter does not examine the effects of processing in depth. The main focus of this chapter is on labeling and PAL because of the obvious importance of these approaches to the consumer.

Although this chapter focuses on the food manufacturing industry, it is important to note that in addition to packaged foods, foods are consumed in many other forms and venues (e.g., homes, restaurants, other retail food establishments, places of worship, camps, recreational facilities). A few of these situations are addressed in Chapter 8. Following a review of the current labeling practices in packaged foods, the chapter describes a labeling approach based on risk and makes recommendations to that effect. Research needs are also included. The Annex to this chapter delves into data inputs needed for a risk-based approach and their limitations.

ELIMINATING ALLERGENS FROM PACKAGED FOODS

As noted above, one approach to managing food allergen hazards within food manufacturing operations is to eliminate one or more allergens from the group of products being manufactured in shared facilities. Within the product development groups in some major food companies, a so-called allergen-gating process has been implemented as a best practice. This process is intended to question and, if desirable or possible, eliminate specific allergenic foods (or ingredients derived from those foods) from a new food product under development. Allergen-gating can take several forms. For example, a food company might question the development of a new product containing a peanut butter component because the manufacturing of that new product might introduce peanut into a manufacturing facility that presently does not include peanuts. In another example, a milk ingredient might be considered as a relatively minor part of a new product formulation. The decision to include the milk ingredient could be questioned and the product might be formulated without the milk ingredient if that change has no impact on product quality. Finally, in a third varia-

[2] Public Law 353, 111th Cong., 2d sess. (January 4, 2011).

BOX 7-1
Allergen Control Plans in the Packaged Foods Industry

To protect consumers with food allergy, food manufacturing companies need to implement comprehensive allergen control plans (ACPs). For products regulated by the U.S. Department of Agriculture (USDA), in addition to good manufacturing practices, food companies have been required since 2005 to have hazard analysis and critical control points (HACCP[a]) written plans. Presumably, companies have considered food allergens as a hazard in their HACCP plans or prerequisite programs.[b] In addition, over the past two decades and together with the increasing recognition of the public health importance of food allergy, many, but not all, companies that manufacture Food and Drug Administration (FDA)-regulated foods have developed and implemented comprehensive ACPs. ACPs began to be adopted from the mid-1990s (Deibel et al., 1997) and were rather widely adopted in the United States by the mid-2000s (Taylor et al., 2006). This industry-led initiative will become a requirement when the FDA Preventive Controls for Human Foods Rule, part of the 2010 Food Safety Modernization Act (FSMA), is implemented late in 2016. The Preventive Control for Human Foods Rule established food allergens as a hazard that is reasonably likely to occur within food processing facilities. Thus, as the rule becomes fully implemented by the FDA, food companies will be expected to hone their ACPs.

The following are the ideal steps in a comprehensive ACP. The development of an ACP starts with a facility hazard and risk assessment done by the food manufacturer. The first step is the identification of the hazard, which would be all sources of allergenic foods. This assessment starts with an assessment of all raw materials to identify those that are allergenic foods or ingredients derived from allergenic foods. Any allergenic raw materials must then be segregated in receiving, storage, and handling that occurs ahead of processing. Ingredient suppliers are expected to have adequate ACPs and are periodically audited for compliance. Segregation must then be maintained through processing, packaging, and labeling of the finished food product. During processing and packaging, segregation

tion of this approach, a food company might decide to harmonize certain ingredients across all products made on shared equipment. For example, if a food company made 30 different cake mixes on shared equipment and 27 of those cake mixes contained milk ingredients, they could decide to add milk to the other three formulations. Consumers have been known to protest harmonization efforts because this decision can eliminate popular food products from the diets of consumers with specific food allergies. Each of these "allergen-gating" decisions would be advantageous to the company because it would avoid additional costs and reduce the complexity of the company's ACP.

With the enhanced awareness of food allergies among consumers,

can be accomplished by separation in either space or time. With separation in space, allergen-containing formulations can be processed on separate lines or even in separate facilities from other formulations that do not contain the specific allergen. Dedicated facilities or dedicated equipment are used in feasible situations. With separation in time, the scheduling of different formulations with varying allergen content is managed. For example, a wheat-containing product might be run first, followed by wheat plus milk, and finished with wheat plus milk plus peanut. After the most complex formulation, the shared equipment is cleaned to remove allergen residues. The critical control points[c] within the manufacturing operation are identified and monitored to prevent unintentional cross-contact. The cleaning of shared equipment and facilities is a critical component of the ACP because allergen residues must be removed after the manufacturing of an allergenic food product. With the scale of food processing equipment, allergen cleaning can be daunting in some situations. Understandably, the control of allergens in processing facilities and along the food chain is extremely complex and beyond the scope of this document. However, the essence of ACPs can be reviewed in several documents including an on-line brochure (www.http://farrp.unl.edu/allergen-control-food-industry [accessed January 5, 2017]).

[a] Hazard analysis and critical control points (HACCP) is a systematic management approach to food safety from biological, chemical, and physical hazards in production processes. It includes tools to reduce these risks to a safe level and it focuses on prevention at all stages of the food chain and processes rather than on inspection of the finish product. The Food and Drug Administration (FDA) and the U.S. Department of Agriculture (USDA) require mandatory HACCP programs for juice, seafood, and meat as an effective approach to food safety and protecting public health.

[b] Prerequisite programs are practices and conditions needed before and during the implementation of HACCP, such as Good Manufacturing Practices or Pest Control Programs, and which are essential for food safety

[c] Critical control point (CCP) is a point in the food manufacturing operation where the failure of a standard operating procedure (SOP) could cause harm to consumers and to the business, or even loss of the business.

marketing interest has grown in the development of "free-from" foods. Dairy-free[3] and gluten-free products have been marketed for years, but their availability and popularity with consumers has increased greatly recently. Now, some foods are marketed as peanut-free, peanut- and tree nut–free (nut-free), and allergen-free, which typically means the absence of all of the eight most allergenic foods and food groups (milk, egg, peanut, tree nuts, wheat, soybean, fish, and crustacean shellfish).

Of course, producing allergen-free food precludes the need to develop and implement ACPs if done in a facility dedicated to allergen-free food

[3] It should be noted that dairy-free and nondairy foods may contain caseins, the major allergenic proteins in cow milk.

manufacturing. However, the chief reason for the expanding commercial interest in "free-from" foods is the opportunity to exploit a profitable niche market. In such cases, the involved food companies must exercise extreme vigilance to assure that their suppliers do not have the allergens of interest in any of the ingredients and perhaps even in their facilities. Although some companies do make "free-from" products in facilities where the allergens of interest are also present in other formulations, great care must be taken to assure that no cross-contact occurs under those circumstances.

LABELING OF FOOD ALLERGENS

As described above, the label on a food package is a tool that ideally should alert consumers of the presence of specific allergens so they can make informed decisions about the level of risk they are willing to take. Two types of labeling exist and they serve two distinct purposes: (1) mandatory labeling, used when the allergen is intentionally added as an ingredient; and (2) voluntary labeling, used when the allergen may inadvertently be in the food as a result of cross-contact. Even when ACPs (see Box 7-1) are strictly followed, errors occur that might result in the presence of low levels of the allergen in the formulated food (i.e., residue). This is shown in part by the number of food recalls that are due to undeclared allergens in food products (see Box 7-2). Such unintentional allergens, when the possible cross-contact is predictable, can be identified on the labels of packaged foods using PAL statements, such as "May Contain X." Although PAL statements on packaged food are voluntary, the FDA has indicated that they should be truthful and not misleading.

The food industry, however, lacks the ability to conduct allergen risk assessments to determine threshold doses and safe levels. As a result of the uncertainties regarding limits necessary to avoid cross-contact as well as unacceptable risks that could result in litigation, PAL statements have proliferated. They are now applied to a wide range of products, including products that likely pose little risk to consumers with a food allergy. Another result of this uncertainty is that the majority of food recalls in the United States are now due to undeclared food allergens (see Box 7-2). Recalls, however, can happen for numerous reasons and are not limited to cross-contact. Important lessons can be learned from product recalls if information is shared about root causes, preventive and corrective actions that are implemented to prevent recurrences, and consumer complaints.

The mandatory ingredient labeling of packaged foods is a government regulatory issue. Despite the fact that PAL is voluntary, its widespread use invites regulatory limitations. If government chooses to move forward, it would have to answer several questions, such as: What allergens should be labeled? What criteria to identify allergens should appear on a label?

BOX 7-2
Packaged Food Recalls

Beginning in the early 1990s, the Food and Drug Administration (FDA) began to recognize that food allergies were a public health priority for the United States. The FDA recognized that the ingredient label on packaged food products provided essential information to consumers following avoidance diets. Food industry awareness of the importance of accuracy in the labeling of food allergens in food ingredient labeling emerged simultaneously. As a result, recalls of packaged food products with undeclared allergens began to occur at an increasing rate. By 1999, 36 percent of all FDA recalls in the United States were associated with undeclared allergens (Vierk et al., 2002). More recently, undeclared allergens became the leading cause for Reportable Food Registry (RFR) reports to the FDA (Gendel, 2014). Many of these RFR reports led to product recalls. Undeclared allergens also have become one of the leading causes of meat and poultry product recalls occurring under the auspices of the USDA's Food Safety and Inspection Service (FSIS). Undeclared allergens also have become a leading cause of food product recalls in Canada (Zarkadas et al., 1999).

These recalls reveal that, despite the allergen control efforts of the food industry, errors do continue to occur that potentially can affect the health of consumers with a food allergy. Several root causes are involved in these product recalls, including placement of a product in the wrong package, inappropriate labeling terminology (e.g., casein not identified as from milk), failure to carry forward information from an ingredient to the final product, cross-contact occurring within the manufacturing facility, and mislabeling of an ingredient by a supplier (Gendel, 2014). In some cases, food manufacturers recognize their error and initiate recalls before consumer complaints have been received; in some of these situations, the level of undeclared allergen in the product may be insufficient to pose a hazard. In other cases, regulatory inspections can reveal labeling issues that result in recalls, especially in the case of FSIS, where continuous federal inspection occurs. The percentage of product recalls that are initiated as a result of consumer complaints of allergic reactions is unclear. Product recalls clearly indicate that there is room for improvement in allergen control within the food processing industry.

Although the discussion below is centered on the United States, policies in other countries are also described to illustrate the global diversity in the criteria used and lists of major allergens. For the packaged food industry, labeling is a matter of compliance with regulatory requirements, including the variable requirements of different countries. As more allergens are added to the priority lists, the complexity of ACPs increases for the food industry.

Which Allergens Need to Be Labeled?

A Historical Perspective

Many countries have implemented laws, regulations, or standards specifically governing food allergen labeling for a list of priority allergenic foods. The foods on such lists vary around the world due to several factors, including differing eating habits and differing criteria to select the priority allergenic foods (see Table 7-1). Likewise, the regulatory framework for the labeling of allergenic foods differs from country to country (Gendel, 2012), which can affect individuals as they travel between countries.

Increased attention to the labeling of allergenic foods emerged within the Codex Alimentarius Commission (CAC)[4] in 1993, when a working paper on food allergens was developed by the Nordic countries. This working paper led to the creation of a Food and Agricultural Organization of the United Nations (FAO) Technical Consultation in 1995 that was charged with developing a list of priority foods that cause food allergies and sensitivities. Ultimately, the priority foods list promulgated by the FAO Technical Consultation was adopted by CAC in 1999 and continues to serve as guidance to all countries (individual countries have the option to adopt this list or to modify the list as they might choose).

Part of the background discussion that occurred within the 1995 FAO Technical Consultation has been reported by Taylor and Baumert (2015). They reported that, in 1995, the amount of published information available to the FAO Technical Consultation concerning the comparative prevalence of allergies to specific foods was limited largely to pediatric populations, with virtually no information on the prevalence of food allergy among adults. Comparative prevalence was the main criterion of the FAO Technical Consultation, although the differential severity of certain allergenic foods also was recognized as a criterion. In 1999, a revised CAC priority was released. As a consequence of data gaps, expert judgment was used, in part, to develop this list. The 1999 CAC priority list included milk, egg, fish, crustacean shellfish, peanut, soybean, tree nuts, cereal grain sources of gluten, and sulfites. Several of these items were added because the FAO Technical Consultation also considered celiac disease, intolerances, and sensitivity reactions in addition to immunoglobulin E (IgE)-mediated food allergies in its deliberations. For example, gluten was included because of its association with celiac disease. Sulfites were added because of the documented severity of sulfite-induced asthma.

Following this, a Task Force of the International Life Sciences Institute-

[4] Codex Alimentarius Commission is an organization formed jointly by the Food and Agricultural Organization (FAO) and the World Health Organization (WHO) to develop food standards and guidelines that would be recognized worldwide.

TABLE 7-1 Priority Allergenic Food Lists

Food	Codex Alimentarius Commission	USA	European Union	Australia/ New Zealand	Canada	Japan
Milk	X	X	X	X	X	X
Egg	X	X	X	X	X	X
Fish	X	X	X	X	X	
Crustacea	X	X	X	X	X	X[a]
Tree nuts[b]	X	X	X	X	X	
Peanut	X	X	X	X	X	X
Wheat	X	X	X	X	X	X[a]
Soybean	X	X	X	X	X	
Gluten	X		X	X	X	
Sesame seed			X	X	X	
Molluscs			X		X	
Mustard			X		X	
Celery			X			
Lupine			X			
Buckwheat						X
Other						X[a]

[a] Japan: Shrimp and crab are the only crustacea on the list. Grains include wheat and buckwheat but not other cereal sources of gluten. Other includes foods that are not required, but are on a recommended labeling list include salmon, salmon roe, mackerel, abalone, squid, beef, pork, chicken, soybean, walnut, orange, kiwi, banana, peach, apple, yam, matsutake mushroom, and gelatin.

[b] See Box 7-3.

SOURCE: Taylor and Baumert, 2015.

Europe (ILSI-EU) conducted a more thorough assessment of foods that warranted placement on a list of priority allergenic foods (Bousquet et al., 1998). The criteria used by the ILSI-EU group included published evidence of severe or fatal anaphylactic reactions. The ILSI-EU Task Force recommended a priority food allergens list that included milk, egg, fish, crustacean shellfish, peanut, soy, tree nuts, wheat, and sesame seed. Other groups within ILSI-EU have continued to develop criteria for the selection of allergenic foods of public health importance and have recently recommended that the criteria should encompass consideration of prevalence, severity and potency[5] (Bjorksten et al., 2008; Houben et al., 2016; van Bilsen et al., 2011).

In the United States, the priority list of allergenic foods was established by the Congress with the passage of the Food Allergen Labeling and Consumer Protection Act[6,7] (FALCPA) of 2004. The FALCPA list mirrored the 1999 CAC list except that the FALCPA list did not address celiac disease and therefore did not recognize cereal sources of gluten as major allergenic foods.

In the European Union (EU), the first priority list of allergenic foods was established by EC Directive 2003/89[8] as a result of deliberations within the EU Parliament. The initial EU list included the eight foods or food groups from the CAC list, but also included sesame seed, mustard, and celery.[9] In addition to allergenic foods, the EU list also includes cereal sources of gluten and sulfites. Subsequently, the EU priority list of allergenic foods was updated by EC Directive 2007/68[10] and included the addition of molluscan shellfish and lupine to the EU list based on the opinion of the European Food Safety Authority (EFSA) Panel Scientific Panel on Dietetic Products, Nutrition, and Allergies (EFSA, 2005, 2006). The decision to include lupine appeared to be based on the recognition that some peanut-allergic individuals will experience allergic reactions on ingestion of lupine due to the presence of cross-reacting allergens in these two legumes.

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[5] Prevalence is defined as the percentage of the general population who have a clinically confirmed allergic reaction to a specific food. Severity is defined as the frequency of occurrence of fatal or life-threatening allergic reactions to a specific food. Potency is defined as the minimal eliciting dose or threshold dose needed to provoke objective symptoms among individuals allergic to a specific food.

[6] For an analysis on Food Allergen Labeling and Consumer Protection Act see Derr, 2006.

[7] Public Law 282, 108th Cong., 2d sess. (August 2, 2004).

[8] See http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32003L0089 (accessed July 3, 2016).

[9] "Celery" in the EU priority list of food allergens refers to "celery root." Celery root and celery stalk are marketed as foods derived from different varieties of *Apium graveolens*. Allergy to celery root is frequent in some European countries but not in the United States.

[10] See http://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1467581123948&uri=CELEX:32007L0068 (accessed July 3, 2016).

In Canada, the priority allergen list includes the eight foods and food groups on the 1999 CAC list plus molluscan shellfish, sesame seeds, and mustard. Australia and New Zealand were the first countries to develop a priority list of allergenic foods that includes sesame seeds in addition to the 1999 CAC list.

Japan uses a unique approach, with a short mandatory labeling list and a longer recommended labeling list. The mandatory priority list includes wheat, milk, egg, peanut, buckwheat, and crustacean shellfish. Among the crustacean shellfish, only crab and shrimp are identified on the Japanese list. Japan and Korea are the only countries to include buckwheat on their priority allergen lists. Buckwheat can cause frequent and occasionally severe allergies in countries where buckwheat (soba) noodles are frequently consumed (Akiyama et al., 2011). The recommended priority list in Japan is lengthy, including several molluscan shellfish (abalone, squid), several fish (mackerel, salmon, and salmon roe), several fruits (orange, kiwi, peach, apple, banana), one tree nut (walnut), several meats (pork, chicken, beef), soybean, matsutake mushroom, yam, and gelatin. A survey of Japanese allergy clinics on the causative foods in more than 1,500 cases of food allergy was used as the basis for the priority list in Japan (Ebisawa, 2003).

As previously noted, many countries simply refer to the 1999 CAC list in their food labeling regulations. A few countries (Argentina, Switzerland, Ukraine) have adopted the EU regulatory framework instead (Gendel, 2012).

How Should Foods Be Selected for Priority Allergen Lists?

Initially, the CAC sought expert opinion and attempted to use the available scientific information in establishing the 1999 list of priority allergenic foods. Although the list of eight priority allergenic foods or food groups established by the CAC remains valid in general, the list has not been reviewed since 1999 and it should be reconsidered now and periodically thereafter. As mentioned, scientific and clinical data regarding the prevalence of allergies to specific foods were insufficient. In particular, data were missing on the prevalence of specific food allergies in adults and the variability in the prevalence of specific food allergies between countries. Allergies to some foods that are common in young children are much less prevalent among adults (e.g., milk, egg, wheat, soy) (Boyce et al., 2010) (see Chapter 3). Based on self-report, soybean allergy appears to be relatively frequent among young infants in the United States (Gupta et al., 2011), but they tend to outgrow this allergy within a few years (Savage et al., 2010). A systematic review (Nwaru et al., 2014) showed soy allergy to be generally lower than previously thought in the general population when oral food

challenge was used as the method of assesment, but none of the data was collected in the United States (see Chapter 3).

In general, data are lacking on the comparative prevalence of allergies to specific foods among adults. This knowledge gap should be addressed and prevalence data on the overall population also should be considered so that priority allergenic foods for regulatory purposes can be identified.

A logical next question is whether any foods should be added to this global priority list. Certain foods and food groups are considered major allergens in some countries but not others (e.g., sesame seed, molluscan shellfish, mustard, buckwheat, lupine). The decisions about the placement (or removal) of additional allergenic foods on global priority lists should be based on scientific evidence regarding the prevalence, severity, and potency of allergies to those specific foods. Individual countries may have justifiable reasons for expanding this list due to cultural dietary habits but such decisions also should be made on the basis of scientific and clinical evidence. For example, in the United States, the priority list of allergenic foods established by Congress is currently undergoing a legislative review, and the addition of sesame seeds is being considered. This decision should be based on scientific and clinical evidence of the prevalence, severity, and potency of sesame seed allergy compared to allergies to the existing eight foods or food groups. The prevalence of sesame seed allergy in the United States appears to be equivalent to the existing eight priority foods or food groups recognized in the United States among children (Gupta et al., 2013).

Insufficient evidence exists on the prevalence and severity of allergies to other foods on the lists of priority allergenic foods in other countries, including molluscan shellfish, mustard, celery root, and buckwheat, to warrant their addition to the priority list in the United States. However, alterations in consumer eating habits could increase the prevalence of allergies to these or perhaps other foods. So, the list of priority allergenic foods should remain dynamic and subject to change as new data on prevalence and severity might dictate (see Box 7-3).

Ingredient Labeling of Allergens

Ingredient labels on packaged food products are particularly critical to consumers with food allergies who are attempting to follow an allergen avoidance diet. In most countries, the ingredient statement on packaged food products must include the names of all foods (e.g., milk) and ingredients (e.g., caseinate) that are added deliberately and that have a technical or functional effect in the finished food product. However, the allergenic source of the ingredient (e.g., milk) cannot always be readily discerned from its common or usual name appearing on ingredient lists (e.g., caseinate). To help U.S. consumers with this information, FALCPA requires that the

BOX 7-3
What Specific Fish, Crustacean Shellfish, and Tree Nuts Are Considered Major Allergenic Foods?

Fish and Crustacean Shellfish. In most countries, fish is used to include all species of finfish with the exception of Japan, where only mackerel and salmon are included on the recommended priority list for allergenic foods. Similarly, most countries include all species of shrimp, crab, and lobster among the crustacean shellfish, with the exception of Japan. In several countries, including Canada, the labeling regulations refer only to shellfish and do not specifically distinguish between crustacean shellfish and molluscan shellfish.

Tree nuts. The identification of which tree nuts merit recognition as part of the group covered by the priority allergen labeling regulations differs widely among various countries. As noted, only walnut appears on the priority allergenic foods list in Japan. In Europe for regulatory purposes, tree nuts include walnuts, pecans, cashews, pistachios, almonds, hazelnuts, Brazil nuts, and macadamia nuts. In Canada, those same eight nuts plus pine nuts are listed. In the United States, the Congress did not identify the specific tree nuts that required mandatory labeling under the provisions of Food Allergen Labeling and Consumer Protection Act of 2004 (FALCPA), leaving the decision to the discretion of the Food and Drug Administration (FDA). An FDA guidance document released in 2006 included a very long list of 19 tree nuts that would need to be specifically included on U.S. food labels. The nine tree nuts on the Canadian list were included and clinical evidence exists of allergic reactions occurring to all of those nuts. However, scientific and clinical evidence supporting the inclusion of the other 10 tree nuts on the U.S. list is lacking. Unfortunately, this list includes coconut and litchi, which are not tree nuts. Coconuts grow on palms that are distantly related to the dicotyledonous trees that produce the 8 or 9 nuts that are on the lists in Canada and the European Union. Litchi is a fruit. Although clinical evidence exists of allergies to coconut and litchi, scant evidence exists of any cross-reactivity between coconut or litchi with any of the other eight or nine tree nuts.

source should be clearly indicated if the ingredient was derived from a food on the priority allergenic foods list. Examples include labeling caseinate as "caseinate (milk)," whey as "whey (milk)," gluten as "gluten (usually wheat)," glucose syrup as "glucose syrup (occasionally wheat)," semolina as "semolina (wheat)," and lecithin as "lecithin (often soy)." Similar legislation does not exist in many countries.

Exemptions

Flavors, spices, or processing aid Artificial or natural flavors, spices, colors, or processing aids (i.e., minor ingredients that have no technical or

functional effect in the finished product) are often exempt from labeling requirements, which could affect consumers with food allergies. Flavors can occasionally contain allergenic proteins, although at a rather low level, so they have caused only a few documented episodes (Taylor and Dormedy, 1998). Spices are not commonly allergenic, with possible exception of mustard and sesame seed. In addition, some colors, such as carmine and annatto, contain proteins that have caused allergic reactions (Lucas et al., 2001). In the United States, certain ingredients can be grouped as "spices," "flavors," "natural flavors," "artificial flavors," and "artificial colors." In the United States, to circumvent the possibility of a hidden allergen in such ingredients, the priority allergenic foods must be declared if they are contained in flavors, spices, colors, or processing aids.

Ingredients with low levels of allergenic protein Ingredients derived from allergenic sources contain widely different levels of allergenic protein (Taylor and Hefle, 2000). Some ingredients, such as casein, whey, and gluten, contain substantial amounts of specific allergenic proteins from the allergenic source. In contrast, a few examples of ingredients, such as fish gelatin, contain substantial protein from the allergenic source but the protein fraction in the ingredient does not include much of the major allergen from the source (Koppelman et al., 2012). Other ingredients from priority allergenic sources contain low to moderate levels of protein. Food-grade lactose may contain as much as 1 percent milk protein, although the amount of protein in lactose will depend upon the method of manufacture of this ingredient. Lactose with 1 percent milk protein likely has sufficient milk allergens to provoke allergic reactions, so its clear identification as a milk-derived ingredient on food labels is prudent. However, some ingredients from priority allergenic sources contain no detectable protein or very low levels of detectable proteins. Examples include highly refined oils from soybeans and peanuts, soy lecithin, wheat starch, and several milk-derived flavors (butter oil, butter ester, butter acid, starter distillate).

Due to this variation in levels of allergen content, in a few countries, selected ingredients are exempted from source labeling. In the United States, highly refined oils were exempted by Congress when it passed FALCPA. Congress also established a regulatory process under FALCPA where food ingredient manufacturers could petition for source labeling exemptions. Under that process, only one successful petition to the FDA has occurred for a source labeling exemption and that was for the use of specific soy lecithin ingredients when used as a processing aid as a stick-release agent in bakeries.

In the EU, the initial directive provided a means for companies to petition for source labeling exemptions for specific ingredients derived from the priority allergens. In this process, petitions were evaluated by the EFSA

Panel of Dietetic Products, Nutrition and Allergies and several ingredients were exempted from source labeling requirements but often only for specific purposes (see Box 7-4). Although the EU appears to have the highest number of source labeling exemptions, it does not appear to have established a permanent process to seek further exemptions in a manner similar to the United States.

Australia and New Zealand have considered the necessity of labeling the fish origin of isinglass, an ingredient used in the clarification of alcoholic beverages, including wines. Isinglass, which is comprised of collagen derived from fish swim bladders, contains little detectable parvalbumin, the major fish allergen and is exempt from source labeling in the EU (Weber et al., 2009). Currently, Australia and New Zealand are also not requiring the declaration of isinglass or its fish origin on labels of alcoholic beverages. Very recently, Food Standards Australia and New Zealand exempted the source labeling of fully refined soybean oil, glucose syrup from wheat, tocopherols (including vitamin E), and phytosterols from soybeans, and distilled alcohol[11] from wheat or whey (Food Standards Australia New Zealand, 2015).

Voluntary Precautionary Allergen Labeling

The existing regulations in most countries focus on intentionally added ingredients as described above. However, greater public health concerns exist regarding the potential that residues of allergenic foods may occur inadvertenly as the result of cross-contact due to common food industry practices such as the use of shared equipment. Such practices can result in the presence of detectable levels of allergen residues in various foods. As mentioned above, to avoid risks due to cross-contact contamination of food allergens, the food industry has made a concerted effort by implementing voluntary ACPs (see Box 7-1) in their manufacturing processes. For the most part, these plans rely on segregation and cleaning procedures to remove allergens, but errors do occur occasionally. In addition, for products regulated by the FDA, preventive control plans were not required until FSMA rules were final in 2015 and therefore ACPs were not developed across all food manufacturing companies.

Therefore, even with strict allergen control plans, it is not possible to ensure that a product will be free of allergens (unless the product is designed to be allergen-free). One approach to inform consumers about the risk of food allergens in a food product is through the use of an advisory label on

[11] Alcoholic beverages in the United States are mostly regulated by TTB (Tax & Trade Bureau), and allergen labeling is not clearly mandated. TTB does generally follow the FDA approaches but is not required to do so. Isinglass is not typically labeled in the United States.

BOX 7-4
Ingredients with Source Labeling Exemption in the European Union

Cereals
- Wheat-based glucose syrups including dextrose[a]
- Wheat-based maltodextrins[a]
- Glucose syrups based on barley
- Cereals used for making distillated or ethyl alcohol of agricultural origin for spirit drinks and other alcoholic beverages

Fish Products
- Fish gelatin used as a carrier for vitamin or carotenoid preparations
- Fish gelatin or isinglass used as a refining agent in beer and wine

Soybean Products
- Fully refined soybean oil and fat[a]
- Natural mixed tocopherols (E306), natural D-alpha tocopherol, natural D-alpha tocopherol acetate, natural D-alpha tocopherol succinate from soybean sources
- Vegetable oils derived from phytosterols and phytosterol esters from soybean sources
- Plant stanol ester produced from vegetable oil sterols from soybean sources

Milk and Milk Products
- Whey used for making distillates or ethyl alcohol of agricultural origin for spirit drinks and other alcoholic beverages
- Lactitol

Nuts
- Nuts used for making distillates or ethyl alcohol of agricultural origin for spirit drinks and other alcoholic beverages

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[a] And the products thereof, in so far as the process that they have undergone is not likely to increase the level of allergenicity assessed by the Authority for the relevant product from which they originated.

SOURCE: Adapted from *European Commission. Directive 2007/68/EC, Official Journal of 28 November 2007, L 310, pp. 11-14.* http://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1467581123948&uri=CELEX:32007L0068 (accessed July 3, 2016).

the packages. Increasingly, food companies in many countries are providing consumers with voluntary PAL statements to alert them to products that are at risk of inadvertent allergen contamination. PAL is not required in any country; instead, many countries (United States, EU-member nations,

Canada, Australia, and New Zealand) have allowed its voluntary use on packaged foods and, if a company decides to display PAL, some countries do mandate certain forms of PAL. Partly because it is not regulated, different forms of PAL are employed by various food companies worldwide (Taylor and Baumert, 2010). For example, Canada uses "may contain X," while the United Kingdom uses "not suitable for X allergy sufferers." In the United States, which has no standard form for PAL, three formats predominate: (a) "may contain X," (b) "manufactured on shared equipment with X" and (c) "manufactured in shared facility with X," (Hefle et al., 2007; Pieretti et al., 2009).

Many problems are acknowledged with the current voluntary PAL approach (Allen et al., 2014b; DunnGalvin et al., 2015). First, food companies do not have the capability to determine which allergen levels in foods might be hazardous and, therefore, PAL, as currently implemented, does not correlate with risk. This is shown by analytical surveys of products both with and without PAL indicating that many products having PAL do not contain detectable allergen levels while some products without PAL do contain detectable allergen levels (Crotty and Taylor, 2010; Ford et al., 2010; Hefle et al., 2007; Pele et al., 2007; Remington et al., 2013a, 2015; Robertson et al., 2013; Zurzolo et al., 2013). Thus, evidence suggests that food companies are both overusing and underusing PAL (DunnGalvin et al., 2015). Second, various stakeholders, including consumers, food industry management professionals, health care professionals, psychologists, food industry auditors, analysts, and regulatory professionals, agree that PAL has lost its credibility due to its inconsistent application and lack of association with actual risk (DunnGalvin et al., 2015). Stakeholders agree that PAL should bear a relationship to actual risk and that the decision-making criteria for application of such labeling should be transparent to all stakeholders (DunnGalvin et al., 2015). Additionally, if PAL is applied in some risk-based coordinated manner, then some mechanism should be provided on the food label to indicate that the food has been evaluated for PAL but that no PAL statement is needed. Otherwise, consumers with a food allergy will never know whether the packaged food lacks a PAL statement because it does not need one or because the food manufacturing company did not apply the risk assessment process.

A NEW PARADIGM: AVOIDING FOOD ALLERGENS AT LEVELS THAT PRESENT RISKS

Avoiding Allergens Is Important

There is no question that avoidance diets remain essential to prevent adverse reactions among individuals with a food allergy (de Silva et al.,

2014; Sampson et al., 2014). However, as Chapter 6 reflects, there are special situations where, under medical consultation, non-strict allergen avoidance is also an option. Whether an individual needs to avoid the food strictly or not, foods that pose a meaningful risk to those with food allergies should be adequately labeled. As already explained in Chapters 1 and 6, consumers are not adequately informed about food allergies in general and about the risks of packaged foods in particular. Partly because of the absence of a labeling approach that informs about food allergy risks, all individuals with food allergy are given the same advice, namely that they should completely avoid the offending food(s). This situation has consequences for the food industry (e.g., foods that are made in shared facilities that pose almost no risk to consumers with a food allergy still carry a PAL) and for individuals with food allergy (e.g., some individuals who are currently following a strict avoidance diet could in reality safely ingest low levels of the allergen). However, a more meaningful, evidence-based approach is possible. In reality, individuals with one or more food allergies should avoid only the specific food(s) that have allergen levels sufficient to trigger their conditions. A risk assessment approach would lead to a decrease in the occurrence of allergic reactions while maximizing the quality of life of individuals with a food allergy.

However, Low Doses of Allergenic Foods May Not Always Pose a Problem

The first evidence that individuals with food allergy could safely be exposed to low doses of allergens perhaps occurred with the development of hypoallergenic infant formulas for infants with milk allergy. With some exceptions, oral food challenges (OFCs) with hypoallergenic infant formulas derived from cow milk in infants with cow milk allergy do not generally lead to adverse reactions to the formula under study (AAP, 2000). Similar findings were published for highly refined peanut oil (Hourihane et al., 1997b) and codfish oil (Hansen et al., 2004). Evidence now clearly demonstrates that individuals with a food allergy have threshold doses below which they will not experience adverse reactions (Buchanan et al., 2007; Hourihane et al., 1997a; Jones et al., 2009; Taylor et al., 2010). It also is known that considerable individual variability occurs in the minimal amounts of the offending food that are needed to provoke allergic reactions, ranging from 0.1 mg up to as much as 10 g for peanut (Taylor et al., 2010).

Furthermore, the dose of the food allergen directly affects the likelihood and the severity of an allergic reaction. Different individuals with the same food allergy (e.g., peanut) have different minimal reactive doses (known as threshold doses) for the allergenic food (Bindslev-Jensen et al., 2002; Taylor et al., 2009). However, no evidence indicates that sensitiv-

ity and severity are related, that is, the most sensitive individuals are not always the ones who experience more frequent severe reactions. In fact, small (sometimes very small) doses have a lesser impact. For cow milk and egg, low milligram (mg) doses can provoke severe reactions in some children with allergy but the percentage of children experiencing severe reactions increases as the challenge dose increases (Rolinck-Werninghaus et al., 2012). The dose-severity relationship may vary among allergenic foods, as wheat and soy challenges are unlikely to provoke severe reactions at initial low challenge doses (Rolinck-Werninghaus et al., 2012).

A NEW APPROACH TO CREATING A SAFE ENVIRONMENT: THE RISK ASSESSMENT CONCEPT

Risk analysis is the overall process for controlling situations in which an organism, system, or given population could be exposed to a hazard. The risk analysis process has three components: risk assessment, risk management, and risk communication (IPCS, 2004). Risk assessment, developed by the National Research Council (NRC, 1980), is the process that serves to estimate the risk to a given target organism, system, or population, including the identification of attendant uncertainties following exposure to a particular agent. Risk assessment also takes into account the inherent characteristics of the agent of concern as well as the characteristics of the specific target (e.g., a given population) (IPCS, 2004). For allergenic foods, risk assessment would estimate the level of risk to a population of individuals with a specific food allergy based on exposure to that food and would allow risk managers throughout the food chain, including public health authorities, to define an acceptable levels of risk (e.g., that 1 percent of individuals with food allergy will have mild reactions). If the risk needs to be mitigated (i.e., when the risk is higher than an established acceptable level of risk), appropriate interventions will follow (i.e., risk management), together with communication of that risk to affected individuals (i.e., risk communication).

Public health authorities have generally applied the risk assessment concept to determine the public health risk from chemical or microbiological contaminants on a population basis (e.g., aflatoxin levels in oilseeds and grains; arsenic levels in infant rice cereals; mercury levels in seafoods). The FDA has used risk assessment principles of increasing sophistication for many years. Although the appropriateness of using these concepts in the setting of allergenic foods was questionable in the past, improved understanding of the mechanism for allergic reactions to food, together with emerging data from individuals with food allergy has led to the realization that the classical principles, terminology, and methodologies of chemical toxicology risk assessment can be applied to food allergens. A common,

in-depth understanding of the risk assessment terminology and concept is essential to achieve consensus about conducting the assessment itself and to define and implement risk management approaches (e.g., labeling) and risk communication approaches.

Risk assessment incorporates a number of features, which are defined in Box 7-5, and encompasses four steps: hazard identification, hazard characterization, exposure assessment, and risk characterization, which are defined in Box 7-6.

Application of Risk Assessment to Allergenic Foods

As noted, the risk assessment process can be applied to allergenic foods. Although its general features are similar to those used for chemical hazards, a few unique differences exist and are highlighted in this section. Further details about the data inputs, their characteristics and limitations can be found in the Annex to this chapter.

Hazard Identification

The allergen (hazard) is identified through case reports of adverse reactions in humans and can be confirmed with clinical diagnosis (e.g., with clinical OFCs or food-specific IgE antibodies in the serum or tissues of affected individuals). Unlike the risk assessment process for chemicals, typical experimental animals do not serve as good predictive models for identifying food allergens to humans (Kimber et al., 2003). Hazard identification also may include data on the prevalence and severity of the reactions. However, numerous foods, such as peanut, cow milk, and egg, are already widely recognized as allergenic foods based on prevalence (Gendel, 2012). Several foods, notably peanut and tree nuts, are recognized as frequent causative factors of severe allergic reactions in children and adults (Bock et al., 2007). Hazard identification can include a demonstration that residues of that allergenic food are present in some food product, especially for allergenic foods known to be more prevalent and/or severe than other foods. If the allergenic food residues are not declared on the label of a packaged food, then the potential hazard is particularly acute. Thus, for packaged foods, an undeclared allergenic food is considered the identified hazard.

Hazard Characterization

In the hazard characterization step of food allergy, safe levels of exposure (Reference Doses estimated as protein from the allergenic food) can be derived from OFC data. Oral food challenges have been used in the clinical practice of food allergy for several decades as a diagnosis method

BOX 7-5
Definitions

Acceptable Level of Risk: A risk management decision regarding the degree of risk that would be acceptable within the affected population.

Hazard: An inherent property of an agent or situation having the potential to cause adverse effects when an organism, system, or given population is exposed to that agent (e.g., allergen).

Lowest-Observed-Adverse-Effect Level (LOAEL): The lowest dose of a hazard (e.g., allergen, expressed as mg of total protein from the allergenic food) that can provoke an observable reaction in an individual or population. Also known as the Minimal Eliciting Dose (MED).

No-Observed-Adverse-Effect Level (NOAEL) or Threshold: The highest dose of a hazard (e.g., allergen, expressed as mg of total protein from the allergenic food) that will not provoke an observable reaction in an individual or population.

Objective Response: A reaction that can be independently verified by a clinically trained observer (e.g., urticaria [hives], vomiting, flushing, angioedema).

Reference Dose: The lowest dose of a hazard (e.g., allergen, expressed in milligrams [mg] of total protein from the allergenic source) that is predicted to elicit symptoms of a reaction when ingested by a defined, small percentage of the population of individuals who are known to experience adverse reactions to that hazard.

Risk: The probability of an adverse effect in an organism, system, or (sub)population caused under specified circumstances by exposure to an agent.

Safety: The control of recognized hazards to achieve an acceptable level of risk.

Subjective Response: A mild transitory reaction that cannot be independently confirmed by a clinically trained observer (e.g., palatal itching or stomach cramping).

(see also Chapter 4). In addition to their use in diagnosis, low-dose OFCs are becoming more widely used to identify the most sensitive individuals and to identify the starting dose for oral immunotherapy trials. The more widespread use of low-dose OFCs in clinical practice has confirmed the fact that individuals with food allergy have a threshold dose below which they ordinarily will not experience an adverse reaction upon ingesting the allergenic food (Hourihane et al., 1997a; Taylor et al., 2002). Thus, food

BOX 7-6
Risk Assessment Steps

Hazard Identification and Hazard Characterization (Hazard Assessment)

Hazard identification includes the determination that the substance with the hazardous properties is present, but also more generally refers to the identification of the type and nature of the adverse effects that an agent can cause in an organism, system, or given population. In the hazard identification of an allergenic food, the prevalence and severity of the specific food allergy would be considered.

Hazard characterization includes a description, preferably quantitative, of the relationship between a dose of the hazard and the effect.

A hazard assessment (involving both hazard identification and hazard characterization) can be used to derive safe levels of exposure, for instance through the elaboration of a Reference Dose (Crevel et al., 2014; Taylor et al., 2014). Usually, the Reference Dose describes the daily dose that is likely to have no deleterious effect even if continued exposure occurs over a lifetime. For allergenic foods (with effects that are not cumulative), the Reference Dose would be an amount of the allergenic food that would pose some defined level of risk (perhaps risk of mild, transitory allergic symptoms that resolve without pharmacological intervention) that could accrue to a defined percentage of the allergic population (e.g., the 1 percent or 5 percent most-sensitive individuals with peanut allergy) (Crevel et al., 2014; Taylor et al., 2014). Clearly, establishing the appropriate Reference Dose requires a definition by public health authorities of the acceptable level of risk that should be allowed.

Exposure Assessment

Dose is a critical parameter to the risk posed by a substance. Thus, exposure assessment plays an essential role in determining whether the hazardous properties of a substance will translate to adverse health effects. For foods, the exposure assessment estimates the amounts (or range of amounts) of the hazard that are likely to be consumed. If these amounts exceed the Reference Dose or the established maximum level in foods (established using the hazard assessment), then a risk of adverse health consequences to the exposed (sub)population is predicted. In contrast, an exposure at or below the Reference Dose or maximum level in foods is assumed to be safe for the majority of individuals (e.g., for the 99 percent of the population with a food allergy to the specific food). In the case of food allergens, the Reference Dose could also be used as a benchmark to derive an action level to determine when PAL should be applied to a product package.

Risk Characterization

Risk characterization can be used to assess the likelihood of risk even in cases where a Reference Dose or maximum level has not been established. The risk characterization is the determination of quantitative probability, including attendant uncertainties, that adverse health effects will occur in a given individual or (sub)population, under defined conditions of exposure.

challenge trials in clinical settings provide human data that can be used for risk assessment purposes, specifically to establish adverse effects associated with specific levels of allergenic foods and to derive Reference Doses (Taylor et al., 2014). Although for each individual, the response is likely related to the dose of exposure, the full spectrum of adverse responses over a range of doses cannot be determined due to the ethical concerns about administering high doses. However, unlike for other hazards, the individual minimal eliciting dose (MED) for sensitive individuals or lowest-observed-adverse-effect level (LOAEL) can be determined. In addition, the individual threshold, or no-observed-adverse-effect level (NOAEL) can be determined with OFCs. Determining the true threshold dose for an individual has some caveats. First, as noted in Chapter 6 and in the Annex to this chapter, multiple factors can influence the threshold dose for individuals with food allergy. Although evidence indicates that concurrent viral infections, exercise, and consumption of alcohol affect an individual's threshold dose (Crevel et al., 2014), additional factors could contribute to the variation. Researchers and clinicians should take these factors into account by performning OFCs to determine thresholds in controlled settings and counseling patients on exacerbating factors. Second, because OFCs are conducted using interval (versus continuous) dosing of the food, the true threshold dose cannot be exactly determined but lies somewhere between the NOAEL and the LOAEL for that individual. For example, if the first objective response occurs at 100 mg but no response occurs at the prior dose of 10 mg, then for that individual the NOAEL is 10 mg and the LOAEL is 100 mg. However, the patient's true threshold dose is somewhere between 10 and 100 mg. Taylor et al. pioneered the use of interval censoring survival analysis (ICSA) in the dose-distribution modeling of OFC data (Taylor et al., 2009). ICSA assigns individual thresholds to an interval range rather than a fixed value by assigning equal probability to the likelihood that the true threshold dose could lie anywhere along that continuum. ICSA allows the use of first-dose reactors (i.e., their true threshold dose is between zero and the first dose administered in the challenge trial) and those individuals who fail to react to any of the challenge doses (i.e., they have a true threshold dose between the highest dose administered in the trial and infinity) in the dose-distribution analysis. Questions still remain among stakeholders about the extent of individual variability despite the lack of evidence supporting it. Still, in performing the risk assessment, regulators need to take into account that an individual's threshold may be lower depending on various factors, such as use of alcohol, use of nonsteroidal anti-inflammatory drugs, or exercising.

The NOAELs also can be estimated on a population basis, as the largest amount of the allergenic food that will not result in an allergic reaction when tested experimentally in a defined population individuals with a food

allergy. With probabilistic modeling, the degree of risk posed by a specific dose of the allergenic food can be predicted based on the distribution of individual threshold doses. In this manner, although zero risk cannot be predicted, acceptable risk levels can be defined by choosing a Reference Dose (see the following discussion).

Although the data demonstrate the usability of clinical OFCs to estimate Reference Doses for food allergens, methodological considerations, potential biases, and uncertainty factors should be recognized and are described in the Annex.

Determining population thresholds for a risk assessment: Dose distribution and probabilistic modeling The use of probabilistic modeling[12] in risk assessment of food allergens requires the use of individual NOAELs and LOAELs.

Increasing amounts of quality NOAEL and LOAEL data from clinical low-dose OFCs from a number of different allergenic foods continue to become available (Ballmer-Weber et al., 2015; Blom et al., 2013; Dano et al., 2015). Taylor et al. provide a summary of the data available in 2014 (Taylor et al., 2014).

When estimating the population-based NOAEL, defining the population of study is a key aspect because the dose distribution will vary according to the population definition and characteristics. For example, the dose distribution (and the NOAEL) could be affected if patients with a history of severe reactions are excluded from OFC studies, as happens in some clinics. However, findings from one study suggest that the predicted eliciting dose (ED) is similar for individuals with severe reactions and for those with less severe reactions (Taylor et al., 2010) (see the Annex to this chapter).

From the published clinical literature, individual LOAEL data can be found from three different types of studies: diagnostic series, threshold studies, and immunotherapy trials (Allen et al., 2014a; Clark et al., 2009; Skripak et al., 2008; Taylor et al., 2009). Published studies often report only the LOAEL but they also report the dosage progression scheme so that the NOAEL can be discerned as well (Taylor et al., 2009). With fewer individuals, more uncertainty exists in population threshold estimates. The greatest improvement in the accuracy of the estimates is achieved by increasing the number of individuals from 20 up to 60 (Klein Entink et al., 2014). A large quantity of data (>200 patients) are available for peanut, milk, egg, and hazelnut (Klein Entink et al., 2014). Data are less available but still sufficient to support probabilistic modeling approaches for shrimp (crustacean shellfish), fish, soybean, wheat, cashew, walnut, sesame seed,

[12] Probabalistic modeling is a statistical analysis tool that estimates, on the basis of past (historical) data, the probability of an event occurring again.

lupine, celery root, and mustard (Ballmer-Weber et al., 2015; Blom et al., 2013; Dano et al., 2015; Taylor et al., 2014). The range of individual NOAELs and LOAELs for individuals with a food allergy can be quite broad. For example, in the examination of individual thresholds among 450 individuals with a peanut allergy, the range of individual LOAELs spanned five orders of magnitude from 0.1 mg up to 2.5 g of peanut protein or 0.4 mg to 10 g of whole peanut (Taylor et al., 2010).

Probabilistic risk assessment (see Figure 7-2) has been performed with the log-normal, log-logistic and Weibull modeling approaches, as are commonly used in other risk assessments. No biological reason exists to favor one of these models over another. Figure 7-3 presents the three probabilistic approaches to the dose–response for peanut. The probabilistic models allow the derivation of an ED, where ED_p refers to the dose of total protein from the allergenic food that is predicted to produce an objective response in

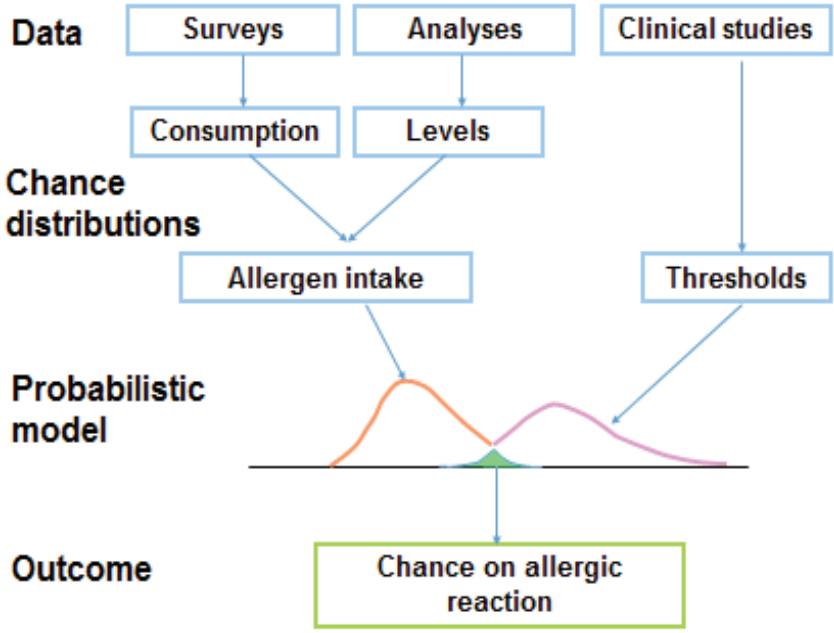

FIGURE 7-2 Figure prepresenting the concept of probabilistic risk assessment. The area in green represents those individuals who would react because their intake is above the Reference Dose.
SOURCE: Spanjersberg et al., 2007. Reprinted with permission from Elsevier.

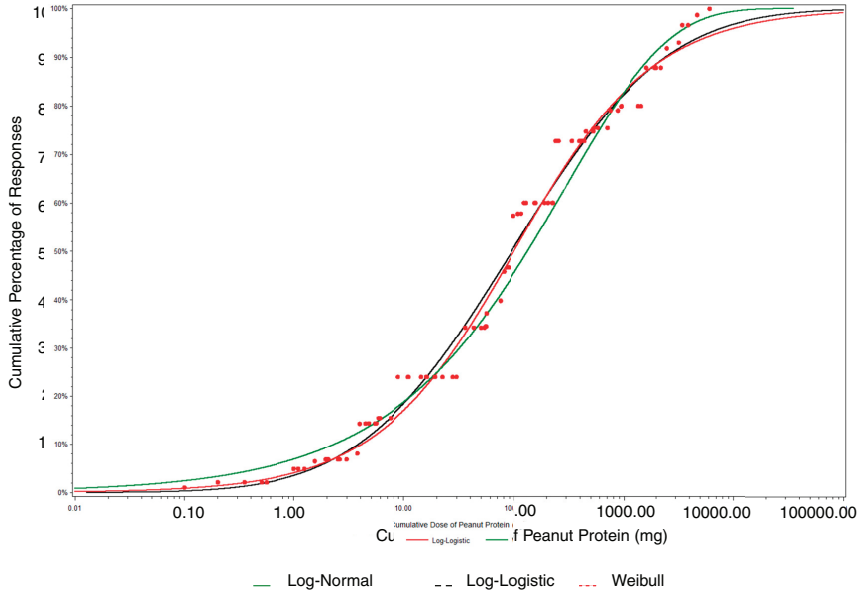

FIGURE 7-3 Dose distribution modeling of peanut protein minimum eliciting doses using log-normal, log-logistic, and Weibull probabilistic models.
SOURCE: Taylor et al., 2014. Reprinted with permission from Elsevier.

p percent of the allergic population (Crevel et al., 2007). However, these approaches do not identify a dose below which no allergic individual would react (zero risk). The ED estimate can be used to describe the population threshold or establish Reference Doses; the value of p, however, defines the acceptable risk, which is a risk management decision. These statistical models also allow estimation of the 95 percent confidence intervals (CIs) around any ED_p value. The lower 95 percent CI also could be selected as a population threshold or Reference Dose as another risk management choice.

Exposure Assessment

Risk is a function of hazard and exposure to the hazard. Thus, exposure assessment is another component of the overall risk assessment. Because allergenic foods are required to carry labels whenever they are used as intentional ingredients, the risk to the consumer is only actually imposed from exposure to any unintended presence of allergens (e.g., contamination due to cross-contact). Exposure assessment has two components: the level of contamination in the food (concentration and frequency) and the intake (amount and frequency) of the particular food. These two components of

contamination and intake can be used as inputs in quantitative risk assessment to generate an allergen intake distribution. Because the threshold dose distribution is given in terms of doses of protein from the allergenic food, the intake distribution also should be calculated in terms of protein from the allergenic food. The challenges and considerations in collecting data to develop an accurate exposure assessment, including validated methods of detection in food and lack of intake data for consumers with food allergies are described in the Annex.

Risk Characterization

Risk characterization involves combining the hazard assessment and exposure assessment approaches to determine the level of risk posed to consumers with food allergy using selected scenarios. Risk characterization involves three key input distributions: the dose-distribution of individual threshold doses, the intake distribution, and the contamination distribution. Highlighted below are two approaches to conduct a risk characterization: examining the individual threshold dose-distribution to arrive at acceptable Reference Doses or using probabilistic modeling.

Using the individual threshold dose-distribution A comparatively simple strategy can be used by examining the individual threshold dose distribution to arrive at acceptable Reference Doses. For example, the dose calculated to elicit an allergic reaction in p percent of allergic individuals (ED_p) can be selected as the Reference Dose. If more caution is desirable, the dose can be selected to be at the 95 percent lower CI of the ED_p. The selection of the appropriate ED_p value is a risk management decision. Establishing acceptable Reference Doses (or action levels) is a simple approach to risk characterization. Action levels can easily be calculated by the following formula:

$$[ED_p \text{ (in mg)} / \text{intake (in kg)}] = \text{action level (in mg/kg or ppm)}]$$

If a contamination level is found to be above the action level, then an appropriate action would be taken. For example, a precautionary label would be placed on the product or a product recall would be initiated if the product is already in the market with an undeclared allergen.

When elaborating action levels using this combination of a chosen food intake level and an ED_p value, the choice of the intake level is critical. Crevel et al. provide an example of bread consumption (Crevel et al., 2014). For this example, Crevel et al. assume that the ED_p has been selected as the ED_1, that peanut is the allergenic food of concern, and that the Reference Dose is 0.2 mg peanut protein, based on the individual threshold dose

distribution (Taylor et al., 2014). The portion size for the single serving of sliced brown wheat bread is given as 35 g but the mean consumption per meal is 140 g (4 slices) and the 95 percent intake level is 210 g (6 slices). In calculating the action level using the single serving size, then the action level would be 5.7 ppm (parts per million) peanut protein. However, if the mean meal intake level was used, the action level would be 1.4 ppm peanut protein. If the 95 percent intake level of 210 g was used, the action level would be 1.0 ppm peanut protein. The selection of the appropriate consumption level complicates the use of this simplistic risk assessment approach. An underestimate of consumption amount results in selection of a higher action level and carries an associated higher level of risk. Action levels allow risk characterization to be conducted in a very straightforward manner that allows a definitive risk management decision.

Probabilistic modeling Risk characterization also can be conducted in a more complex manner using probabilistic modeling as depicted in Figure 7-2 (Crevel et al., 2014; Spanjersberg et al., 2007). In this approach, in addition to data inputs for allergen thresholds, the consumption patterns and allergen contamination test results can be fitted to statistical distributions for use in a Monte Carlo simulation.[13] The allergen intake distribution of a particular product can be determined based on the allergen distribution in the product (based on analytical testing) and the consumption distribution (based on surveys). The results can predict objective allergic reactions in an estimated fraction of the population with food allergy. The frequency of consumption of a particular type of food can be further incorporated into the model to obtain an estimate of the allergic population's risk. The prevalence of the specific food allergy within the general population can additionally be incorporated into the model to obtain an estimate of the overall population risk. This probabilistic modeling approach is generally considered to be the most thorough way to characterize allergic risks (Kruizinga et al., 2008; Madsen et al., 2009; Spanjersberg et al., 2007, 2010). Quantitative probabilistic risk assessment has been applied to characterize the allergic risks in several practical examples (Remington et al., 2013a,b, 2015; Robertson et al., 2013; Spanjersberg et al., 2007, 2010).

Probabilistic modeling inherently accounts for some of the uncertainties associated with the input variables and reflects those in the probability distribution for the output (Crevel et al., 2014). However, probabilistic modeling does not account for factors, such as systematic bias in the selection of the challenge population, unless these systematic factors can be quantified.

[13] In a Monte Carlo simulation, the program repeatedly samples the three input distributions, picking a value from each at random and building a distribution representing the probability of an allergic reaction given the values and distributions of the specified variables.

DEVELOPING POPULATION THRESHOLDS: MOVING FORWARD

Bindslev-Jensen et al. were the first to attempt the use of dose-distribution modeling for allergenic foods (Bindslev-Jensen et al., 2002). The authors used data on four commonly allergenic foods using individual threshold doses from the peer-reviewed clinical literature to merely illustrate their model. Crevel et al. expanded upon the value of statistical dose-distribution modeling to estimate population thresholds for allergenic foods and also pointed out the data limitations to use of that approach (Crevel et al., 2007). In 2006, the FDA, through an ad hoc internal Threshold Working Group (TWG), evaluated various approaches to establishing population thresholds for allergenic foods and produced a report with recommendations (Gendel et al., 2008). The TWG recommended the use of statistical dose-distribution modeling as the preferred ideal approach for establishing this threshold. As mentioned, the use of statistical dose-distribution modeling relies upon the availability of sufficient quantities of food challenge data from low-dose clinical OFC studies. The TWG concluded that insufficient data existed to use this preferred approach. Gendel et al. cited several concerns with the data that existed before 2005: (1) the general paucity of data on low-dose challenges for many allergenic foods; (2) the representativeness of the populations of individuals with food allergy in those studies; (3) potential exclusion of individuals with histories of severe reactions; and (4) lack of comparative data to establish the optimal parametric dose-distribution relationship to use for modeling purposes (Gendel et al., 2008). The following section describes the progress made over the ensuing 10 years to address those concerns.

Do Sufficient Data Exist?

Since 2005, numerous low-dose challenge studies have been performed by multiple clinical investigators so that extensive data now exist for modeling purposes (Taylor et al., 2014; Zhu et al., 2015). Table 1 in Taylor et al. provides a list of the number of data points for each of the priority allergenic foods used to establish Reference Doses as of 2014 (Taylor et al., 2014). More individual threshold data points exist for peanut, milk, egg, and hazelnut than for other allergenic foods. Using statistical analysis, Klein Entink et al. determined that the largest gain in reliability of population threshold estimates occurs as the number of data points increases from N=20 to N=60 (Klein Entink et al., 2014). However, population threshold estimates can be made from small numbers of subjects provided that the statistical confidence intervals are included (Taylor et al., 2014). Appropriately, the FDA TWG recommended that population threshold estimates should be adjusted as more individual threshold data are acquired (Gendel et al., 2008).

Do Subjects with Histories of Severe Reactions Have Lower Thresholds?

Several studies have demonstrated that no relationship exists between reaction severity by challenge or history and threshold dose (Blumchen et al., 2014; Eller et al., 2012; Taylor et al., 2010; Turner et al., 2016; Zhu et al., 2015). Symptom severity increases, however, with increasing challenge doses for milk and egg (Rolinck-Werninghaus et al., 2012). Several studies have documented that severe reactions occur on the initial challenge dose (Perry et al., 2004; Sicherer et al., 2000) but these observations stem from challenges that were initiated at doses above 100 mg of the allergenic foods (much higher than the low doses now used in low-dose OFCs). A recent single-dose study administering the predicted log-normal ED05 dose of peanut to 375 unselected peanut-allergic individuals documented that 8 of 375 subjects (2.1%) experienced objective responses to this dose and that none experienced severe reactions (Hourihane et al., In press). Although peanut is recognized among the allergenic foods as most likely to provoke severe reactions (Blumchen et al., 2014; Zhu et al., 2015), the ED05 dose of peanut (6 mg whole peanut or 1.5 mg peanut protein) is unlikely to provoke severe reactions (Hourihane et al., In press).

Do Sufficient Data Exist from a Wide and Varied Enough Population?

Although most low-dose challenge studies have been conducted in Europe, the United States, or Australia, evidence suggests that thresholds do not differ on the basis of age or geography (Allen et al., 2014a). Patient selection bias can affect threshold distributions (Allen et al., 2014a), but the comparisons show that patients involved in immunotherapy trials tend to be more highly sensitive, which favors the establishment of conservative population thresholds. Differences in dosing ranges can affect threshold distributions (Allen et al., 2014a) but these effects can be lessened by normalizing the data on the basis of protein content (Taylor et al., 2009) and focusing on data from low-dose studies with initial doses in the low mg range.

How Much Inter-Individual Variability in Thresholds Exists?

The persistence of individual threshold doses has not been thoroughly investigated. However, it is well known that infants and children with milk, egg, soy, and wheat allergies will frequently outgrow their condition (Keet et al., 2009; Savage et al., 2007, 2010; Skripak et al., 2007). Presumably their individual threshold doses increase over time until tolerance is achieved although this has not been specifically investigated. Peanut allergy is more persistent, although about 20 percent of peanut-allergic individu-

als also outgrow their condition (Skolnick et al., 2001). Individual peanut thresholds were found to be relatively stable over a period of years and multiple OFCs with the exception of 6 percent of patients whose peanut allergy resolved (Crevel et al., 2010). Little scientific evidence exists to suggest that individuals become more sensitive over time, although this is a point of frequent conjecture.

Which Statistical Models Are Optimal for Estimating Population Thresholds?

As mentioned above, several parametric models (log-normal, log-logistic, and Weibull) have been compared (Taylor et al., 2009, 2014). For peanut, the Weibull model offers the most conservative predicted population threshold (Taylor et al., 2014), but recent data suggest that the log-normal and log-logistic models are optimal (Hourihane et al., In press). In this study, the predicted log-normal ED05 dose for peanut was administered as a single dose to 375 unselected peanut-allergic individuals. Only 2.1 percent of these individuals experienced objective reactions (none severe) indicating that even the log-normal prediction was overly conservative and indicating that the extra conservatism predicted by the Weibull model is unnecessary (Hourihane et al., In press).

With the generation of additional clinical data on individual threshold doses from low-dose clinical challenges, the feasibility of statistical dose-distribution modeling has improved. Following on from this, other groups in Europe (Crevel et al., 2014; Madsen et al., 2009) and Australia (Taylor et al., 2014) also have recommended the use of statistical dose-distribution modeling as the ideal approach to estimating population thresholds for various allergenic foods.

The VITAL Program

The Allergen Bureau of Australia and New Zealand (an industry consortium) has recommended establishing Reference Doses based on statistical dose-distribution modeling and the use of the Reference Doses to support their VITAL® (Voluntary Incidental Trace Allergen Labeling) program. VITAL is a voluntary program aimed at the food industry that aims to provide a scientific basis for precautionary labeling decisions. The Allergen Bureau has established an entire risk management program using these Reference Doses as the basis.[14]

The Allergen Bureau of Australia and New Zealand established an

[14] The VITAL program can be found at http://allergenbureau.net/vital (accessed July 8, 2016).

expert panel to examine existing individual threshold dose distributions and apply statistical modeling approaches (log-normal, log-logistic, and Weibull) to those distributions. The expert panel recommended using ED_1 estimates for peanut, milk, egg, and hazelnut because sufficient data (from >200 individuals) were available. The panel selected the 95 percent lower CI of the ED_5 for other foods when data from fewer individuals were available (Taylor et al., 2014). Subsequently, the Task Force on Thresholds to Action Levels of the ILSI-EU endorsed the same ED_p levels and the same Reference Doses (Crevel et al., 2014). The Reference Doses for 11 allergenic foods taken from priority lists in Australia and New Zealand and the EU are provided in Table 7-2. Attempts were made to examine individual threshold dose distributions for celery and fish as well, but the existing data did not fit any of the probabilistic models. The Allergen Bureau did establish a Reference Dose for fish but it was not established on the basis of the existing clinical evidence. The ED_p value used by the Allergen Bureau is rather conservative by comparison to the approaches used to define hypoallergenic infant formula (the ED_{10}) and similar to ED_p values used for chemical toxicants. As subsequent data become available from low-dose clinical food challenges and single-dose validation studies, the selection of the optimal ED_p value should be re-examined.

Although this risk assessment approach has achieved acknowledgement from expert groups in the United States, European Union, and Australia and New Zealand (Crevel et al., 2014; Taylor et al., 2014), its adoption by governmental public health agencies remains unfulfilled as it has not been incorporated into public health policy regulation.

Now that statistical dose-distribution modeling for the hazard characterization step of the risk assessment process is available, it can be integrated with exposure assessment inputs to make risk characterization feasible. The first demonstrations of the use of this approach came from the Netherlands Organization for Applied Scientific Research (Kruizinga et al., 2008; Spanjersberg et al., 2007, 2010). This approach was later adopted and used by groups in France (Rimbaud et al., 2010), the United States (Remington et al., 2013a,b), and Ireland (Robertson et al., 2013). Improvements on the risk assessment approach for allergenic foods continue to be developed, together with the recognition that this approach provides the best way to quantitatively assess the magnitude of the risk of any given scenario to appropriate segments of the populationwith food allergies.

OVERALL CONCLUSIONS

The labeling of allergenic packaged foods is an important public health measure assisting consumers with a food allergy to avoid potentially aller-

TABLE 7-2 Reference Doses Established by Allergen Bureau of Australia and New Zealand[a]

Allergen	N with Objective Symptoms	Right Censored[b]	Left Censored[c]	Population	Basis of RD	RD (mg total protein)
Peanut	750	132	30	Children and Adults	ED_{01}	0.2 mg
Milk	351	19	59	Children and Adults	ED_{01}	0.1 mg
Egg	206	33	24	Children and Adults	ED_{01}	0.03 mg
Hazelnut	202	67	4	Children and Adults	ED_{01}	0.1 mg
Soybean	80	28	6	Children and Adults	LCI ED_{05}	1.0 mg
Wheat	40	1	5	Children and Adults	LCI ED_{05}	1.0 mg
Cashew	31	16	1	Children	Hazelnut	0.1 mg
Mustard	33	10	2	Children and Adults	LCI ED_{05}	0.05 mg
Lupin	24	7	2	Children and Adults	LCI ED_{05}	4.0 mg
Sesame	21	1	2	Children and Adults	LCI ED_{05}	0.2 mg
Shrimp	48	26	0	Adults	LCI ED_{05}	10 mg
Celery	39	4	15	Children and Adults		NR
Fish	19	2	6	Children and Adults	LCI ED_{05}	0.1 mg (provisional)

NOTE: ED = eliciting dose, LCI = lower confidence interval, LOAEL = lowest-observed-adverse-effect level, mg =milligram, NOAEL = no-observed-adverse-effect level, NR = no recommendation, RD = Reference Dose.

[a] The Allergen Bureau of Australia and New Zealand adopted the RD recommendations of the VITAL Scientific Expert Panel (Taylor et al., 2014) except for cashew, fish, and celery. For cashew, due to lack of clinical data on adults, the RD dose was based on that of hazelnut. Fish had insufficient clinical data and, therefore, an arbitrary RD was selected. Likewise, celery had insufficient clinical data; however, celery is not included in the food allergen priority list of Australia and New Zealand, and therefore, a recommendation for celery was not needed.

[b] Number of right-censored subjects (NOAEL = highest challenge dose; LOAEL set to infinity).

[c] Number of left-censored subjects (NOAEL set at zero; LOAEL = lowest challenge dose).

genic foods. The current precautionary labeling system for allergenic foods is not effective in informing consumers about the risks from food allergens in the food for various reasons.

First, although all proteins can be allergenic, it is critical for public health authorities to select the list of major allergens to be included in food packaging labels. Although a panel of experts recommended prevalence, potency, and severity as criteria to select the major allergens (Houben et al., 2016; van Bilsen et al., 2011), the 1999 CAC list, which forms the basis for priority lists of allergens in different countries, was developed when data on the prevalence, potency, and severity for most allergenic foods were just beginning to emerge. Since then, various countries have added other allergenic foods based on a variety of reasons, including their regional diets and other criteria. Consequently, although the eight basic major allergenic foods are common in the priority lists of all countries, the lists also have substantial differences. The committee concludes that prevalence, severity, and potency should be used as scientific criteria for addition of foods to the U.S. priority list in the future. Methods for collecting data on prevalence and severity are outlined in Chapter 3. The probabilistic modeling of individual threshold dose-distributions is advocated as an approach to measure allergenic potency. At the same time, the committee recognizes that such an approach will be difficult in the case of novel foods due to the absence of data to support the criteria, potency in particular.

Second, the PAL system for warning consumers about the presence of low levels of allergens in food is not effective. Initially, preventive approaches related to packaged foods centered on mandatory labeling of intentionally added allergenic foods or ingredients. However, potential risks associated with unintentional residues of allergenic foods also exist. Manufacturing companies develop ACPs to minimize the possibility of allergen residues in foods due to shared processing equipment or manufacturing facilities (i.e., cross-contact). However, low-level residues might still be present. Few analytical surveys have been conducted to determine the frequency of packaged foods containing undeclared allergens in the marketplace, but the frequency of product recalls in the United States and Canada suggests that foods with undeclared allergens are on the market in both countries. Concerns about potential risks to consumers with a food allergy due to shared processing equipment or facilities prompted the packaged foods industry to use PAL statements. PAL statements are voluntary, but regulatory authorities indicate that statements must be truthful and not misleading. Because the food industry has no capability to conduct allergen risk assessments to determine threshold doses and safe levels, the food industry has clearly struggled to make prudent and effective use of PAL. Therefore, PAL statements are applied to a wide range of products, including products that likely pose little risk to consumers with a food

allergy. The use of PAL also is driven by the potential legal consequences associated with manufacturing a packaged food that can provoke allergic reactions, and the desire to avoid litigation is thus an additional motivator. The result is a labeling system for unintentional allergen residues that bears almost no relationship to actual risk. For the consumer, the degree of risk posed by a particular food bearing a PAL is unknown. The implementation of a complete avoidance diet poses burdensome restrictions on individuals and adversely affects their quality of life (Soller et al., 2014). In addition, evidence suggests that consumers with a food allergy attempt to apply a risk matrix to the various forms of PAL statements and that they ignore PAL in some situations (Hefle et al., 2007; Sheth et al., 2010). Meanwhile, the limited analytical surveys indicate that packaged food products with PAL statements often do not contain detectable food allergen residues (Crotty and Taylor, 2010; Ford et al., 2010; Hefle et al., 2007; Remington et al., 2013a, 2015; Robertson et al., 2013; Zurzolo et al., 2013). Many different stakeholders are critical of the current usage of PAL on packaged foods and agree that the lack of Reference Doses has contributed to the inconsistent application of PAL by the food industry (DunnGalvin et al., 2015).

The ineffectiveness of PAL statements and the lack of consistency and transparency in the implementation of voluntary PAL statements to protect the consumer with food allergies call for public health authorities to use a risk-based approach predicated upon risk assessment principles. Quantitative risk assessments can be conducted to assess the level of risk to consumers from exposure to residue levels of allergenic foods in specific food products (Crevel et al., 2007; Remington et al., 2013a, 2015; Spanjersberg et al., 2007). In this manner, the estimated level of risk to consumers with a food allergy can be communicated to consumers through more consistent application of PAL strategies. Public health authorities in various countries could use the information on individual thresholds to reach consensus about population thresholds for specific allergenic foods and, ideally, these population thresholds would be used to guide regulatory and food industry labeling practices with the goal to match labeling to risk in a more meaningful way. Ultimately, knowledge of population and individual thresholds for specific allergenic foods could be helpful to allergic individuals, their physicians, the food industry, and governmental regulatory agencies in protecting the health of these consumers.

The approach described in this chapter is not currently used except in Australia and New Zealand. The Allergen Bureau of Australia and New Zealand, formed voluntarily by the food industry in an attempt to curtail the widespread use of PAL, has developed the VITAL program. VITAL has established Reference Doses for allergenic foods based on clinical data on the distribution of individual threshold doses for individuals with spe-

cific food allergies (Allen et al., 2014a; Taylor et al., 2014). In the VITAL approach, the use of PAL in food packaging is based on risk.

Although the voluntary establishment of Reference Doses by organizations such as the Allergen Bureau is laudable and a sign of progress, the endorsement of Reference Doses by public health authorities would enhance the impact of such approaches. Moreover, while the VITAL program has emerged as a noteworthy, benchmark approach, it will be important to critically assess its overall effectiveness.

In closing, it is important to emphasize that the largest share of the responsibility for the implementation of safe and effective avoidance diets falls onto consumers with a food allergy or their caregivers. However, individuals often lack much of the critical information that is needed (see Chapters 6 and 8). As mentioned in those chapters, all relevant stakeholders, including health care professionals, public health authorities, and food allergy advocacy groups, should be trained to offer consistent, evidence-based advice on allergen risks and allergen avoidance diets. which should also be consistent with regulations and food industry labeling practices. Risk assessment based on the best available scientific and clinical evidence offers the best approach to achieve the desired consensus.

RECOMMENDATIONS

The committee recommends that the Codex Alimentarius Commission and public health authorities in individual countries decide on a periodic basis about which allergenic foods should be included in their priority lists based on scientific and clinical evidence of regional prevalence and severity of food allergies as well as allergen potency.

For example, in the United States, some foods listed by the FDA as tree nuts (i.e., beech nut, butternut, chestnut, chinquapin, coconut, gingko nut, hickory nut, lichee nut, pili nut, shea nut) could be removed from the current priority list based on the paucity of data or low frequency of allergic reactions. In addition, evidence of the allergy prevalence and reaction severity to sesame seeds may warrant their inclusion on the priority allergen list in the United States.

The committee recommends that the Food and Drug Administration makes its decisions about labeling exemptions for ingredients derived from priority allergenic sources based on a quantitative risk assessment framework.

A quantitative risk assessment is based on knowledge of the detectable level of protein, its presence in the ingredient, exposure levels to the ingredient, and threshold dose-distributions for individuals allergic to the food.

The committee recommends that the food manufacturing industry, the Food and Drug Administration (FDA), and the U.S. Department of Agriculture (USDA) work cooperatively to replace the Precautionary Allergen Labeling system for low-level allergen contaminants with a new risk-based labeling approach, such as the VITAL program used in Australia and New Zealand.

To meet this risk-based approach, the following three steps are recommended:

1. The FDA and the USDA should establish Reference Doses (thresholds) for allergenic foods, where possible. The committee concludes that at this time, sufficient data exist on milk, egg, peanut, certain tree nuts (i.e., cashew, walnut, hazelnut), wheat, soybean, fish, and crustacean shellfish (shrimp) to establish Reference Doses. The FDA and the USDA should review the Reference Doses periodically, with particular attention to the remaining tree nuts for which data to establish Reference Doses are not currently available (i.e., almond, Brazil nut, macadamia nut, and pine nut).
2. Once Reference Doses are established, a food product would carry an advisory label (e.g., "peanut may be present") only in situations when ingesting the product would expose the individual to a level above the Reference Dose for that allergen. The FDA should restrict the number of allowable advisory labels to one phrase. Because this labeling is voluntary, the product should clearly inform the consumer, through labeling as appropriate, as to whether a risk-based approach (such as VITAL) has been followed for each specific product. The FDA and the USDA should educate health care providers and consumers about the meaning of such a food allergy advisory statement.
3. The FDA and the USDA, together with the food industry and the analytical testing industry, should develop and validate detection methods and sampling plans for the various food allergens for which Reference Doses are established. A common unit of reporting also should be established, such

as parts per million of protein from the allergenic source, so that comparisons can be made between methods and between levels in the food and clinical threshold values.

RESEARCH NEEDS

Some allergenic foods have higher potency and cause more severe reactions than do others. Likewise, evidence indicates that changes in proteins during food processing can contribute to their allergenicity, but these changes and their effects are not the same for all allergenic proteins. The relationship between specific protein characteristics (e.g., structure, sensitivity to heat, and digestibility) and specific processing conditions and potency needs to be elucidated so it can be considered when designing research studies and when prescribing prevention approaches for individuals.

In addition to age and geographical differences, circumstantial factors might modify the severity of a food allergy reaction and the level of allergen needed for a reaction in an individual. The effect of exercise on experiencing a food allergy reaction has been reported and it is well recognized. However, for other factors, such as alcohol or medication use, biological cycles, psychological factors, stress, and concomitant allergen exposures, anecdotes are the main source of information. Identifying the factors that can modify the severity of allergic reactions and defining their influence on whether an allergic reaction is experienced upon exposure to a food allergen or in changing in the specific eliciting dose are key pieces of information needed to provide advice to individual patients (see Chapters 6 and 7).

To fill gaps in knowledge in this area, studies should be conducted to accomplish the following objectives:

- Strengthen current knowledge about food allergen risk assessment and management, including continued assessment of threshold doses for individual allergens; single dose oral challenges for confirmation of threshold doses; the development, application, and improvement of parametric dose-distribution modeling approaches for allergen risk assessment; food consumption patterns of populations with food allergy; and methods to detect allergen residues in food matrices.
- Study the mechanisms that make some food proteins more allergenic than others and the effects of food processing methods and other ingredients on their allergenicity and thresholds.
- Study the possible effects of augmentation factors on threshold doses (e.g., exercise, alcohol) or on modifying the severity of reactions, and the mechanisms underlying such effects.

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ANNEX 7: DATA INPUTS FOR RISK ASSESSMENT

Oral Food Challenges as Inputs to Determine Thresholds in Risk Assessment

General Protocol Considerations

For the purposes of hazard characterization, individuals with a food allergy should be challenged orally with the food over a range of incremental doses to determine the minimal dose needed to elicit an allergic reaction. These oral food challenges (OFCs) are most often conducted in controlled clinical settings. Consensus clinical protocols exist for such testing (Bindslev-Jensen et al., 2004; Taylor et al., 2004), including avoidance of certain medications before and during challenges, time intervals between doses, use of placebo-controlled crossover designs, use of objective symptoms (or abdominal pain in infants and young children) as the criteria for stopping challenges, and a fasting period before challenges. There are various types of OFC depending on the protocol.[15] Ideally, the design would be a double-blind, placebo-control test with doses ranging wide enough to ensure reactions at some dose. Thus, the initial doses should be sufficiently low (low milligram [mg] or even sub-milligram levels) to ensure that very few individuals react at the initial dose (Cochrane et al., 2012). Many variations on that general protocol, such as dosage schemes, have been used by different investigators.

Dosing schemes The dosing schemes used in clinical OFC protocols vary, and the Interval-Censoring Survival Analysis approach has been used to adjust for the different dosing schemes. However, it is important to note that the outcomes of the probabilistic modeling can be influenced if a large proportion of the data are not interval-censored (e.g., first dose or left-censored reactors) (Taylor et al., 2009). Recently, concerns have been raised about the time interval between doses, generally 20 or 30 minutes, being too short (Blumchen et al., 2014). Clearly, an entire dose is unlikely to be fully assimilated (digested, absorbed, and presented to the immune system) in 20 to 30 minutes. However, by recording both the discrete and cumulative doses that provoke the first objective signs and comparing these two doses in the probabilistic modeling, this concern is abated due to the small

[15] There are three types of oral food challenges (OFCs) depending on the protocol. An open OFC is one where the food is in its natural form; a single-blind OFC is one where the food is masked from the patient's perspective so less patient bias occurs because of anxiety; a double-blind, placebo-controlled OFC involves masking the tested allergen and feeding it or indistinguishable placebo randomly without the patient or observer knowing if the allergen or placebo is being tested.

BOX 7A-1
Host-Associated Factors That Might Affect Allergic Reactivity

- Genetic predisposition (including gender, ethnicity)
- Circadian, menstrual, and other biological cycles (including age)
- Psychological factors (including stress)
- Environmental factors
- Concomitant or cumulative allergen exposures (priming)
- Activity (including exercise)
- Infections
- Alcohol usage
- Medication status
- Coexisting disease (e.g., asthma, diabetes, cardiovascular disease)
- Individual day-to-day variability

differences that occur at the lowest doses. In fact, the estimated population threshold for peanut obtained by Blumchen et al. (2014) was in agreement with earlier estimates based on shorter time intervals between doses (Taylor et al., 2010, 2014).

In addition to the dosing scheme, other variables in the clinical OFC protocol, such as the nature of the challenge materials and the matrix for blinding of challenges, also should be considered (Crevel et al., 2014). The nature of the material is important because the potency of the allergen may vary depending on the source or processing. The matrix also is a consideration because the allergen may be released more slowly from some matrices as opposed to others.

Identifying objective versus subjective reactions By definition, to determine an individual's threshold, the level of allergen that provokes a response needs to be measured. Clinicians and others need to reach consensus about what constitutes an allergic response (see Box A7-1). In some studies, subjective responses over three successive, increasing doses is considered a reaction (Ballmer-Weber et al., 2015; Flinterman et al., 2006). However, a new consensus has emerged that only objective responses should serve as the basis for identifying an individual's threshold in an OFC (Crevel et al., 2014).[16] In clinical settings, objective symptoms can be confirmed to occur and their reproducibility readily assessed (Taylor et al., 2014).

[16] One exception is for abdominal pain in infants and children younger than the age of 3 years, which is accepted as a response.

Nature of the challenge material and matrix Various forms of the allergenic food can be used in OFC trials. For example, peanut could be in the form of crushed peanuts, peanut butter, or peanut flour. These forms of peanut vary in their protein and allergen content (e.g., peanuts are approximately 25 percent protein while peanut flour is approximately 50 percent protein). Thus, the challenge material doses can be normalized on the basis of protein content (Taylor et al., 2014), an appropriate approach considering that food allergens are proteins. In general, all forms of the allergenic food are assumed to have equivalent allergenicity at any given dose of protein although this is not true when comparing different fractions of a food (e.g., egg white and whole egg). Of course, processing of the food could have an effect on allergenicity. In fact, clinical studies have documented that many milk- and egg-allergic patients become tolerant of baked milk or egg before they develop a tolerance for these foods in forms that are subjected to lesser degrees of heat processing, and this is reflected in increased individual thresholds (Lemon-Mule et al., 2008; Nowak-Wegrzyn et al., 2008). For some allergenic foods, such as milk and egg, challenges should ideally use less processed forms of food, such as pasteurized, spray-dried or even raw, where possible in order to ensure an elicitation will occur at the lowest possible dose (Crevel et al., 2014; Taylor et al., 2014). However, for foods such as peanut, where the allergens are more heat-stable, the use of typical heat-processed forms of the food, such as roasted peanuts or peanut butter, is less likely to influence estimated lowest-observed-adverse-effect levels (LOAELs) and no-observed-adverse-effect levels (NOAELs) (Crevel et al., 2014). The individual threshold data used in probabilistic modelling have been obtained from mildly processed forms for many of the foods, as the challenge materials are pasteurized and/or spray-dried at most. The outcome of challenges also may depend upon the matrix or vehicle used for the OFCs, such as the level of fat (e.g., chocolate versus other vehicles) (Cochrane et al., 2012; Grimshaw et al., 2003; Mackie et al., 2012). This factor has not been thoroughly investigated but, to date, OFCs are generally administered in readily digestible matrices that mimic the food in which they would actually be eaten.

Biases

Population biases One obvious limitation for developing a dose distribution of individual minimal eliciting doses (EDs) for any population with a food allergy is the prevalence of that specific food allergy. This is because of the need to assemble a sufficient number of individuals to have a robust dose-distribution relationship. Besides that, challenge testing of individuals with a food allergy has revealed a wide variation of individual minimal EDs, ranging from 0.4 mg up to 10 g of whole peanut (Taylor et al., 2009,

2010). Thus, to develop a dose-distribution of individual minimal EDs for any population with a food allergy, individuals must be selected who are representative of the entire population of individuals allergic to the particular food in question. In this respect, the possibility of patient selection biases is one of the chief concerns. Dose–response data for statistical modeling to estimate population thresholds can be obtained from three types of published (and unpublished) studies: diagnostic series, threshold studies, and immunotherapy trials (Taylor et al., 2009). The possibility of patient selection biases in such studies is demonstrated by the existence of different ED_5[17] estimates for peanut for patients from these three types of studies (Taylor et al., 2009). Individuals enrolled in diagnostic trials should ideally include all patients who are seeking confirmation of a particular food allergy. However, in some clinics, patients with histories of severe allergic reactions are excluded from OFCs. In addition, diagnostic series do not always start at low doses, as the recommended initial dose for diagnostic OFCs is 500 mg (Bock et al., 1988). When the first dosage interval between 0 and the first dose is large, these data are difficult to include in the model because of the effect of the interval width. Thus, data from diagnostic series should be sought from OFCs that start at rather low doses (low mg or less). An Australian study illustrated the effect of the choice of the dosing scheme on the ED estimate. In this study of milk, the first dose ranged from 66 to 300 mg (Allen et al., 2014). The ED_{05} for the Australian patients was 69.5 mg milk protein compared to 1.9 and 2.0 mg for the Netherlands and Italy, respectively. This difference was attributed to the dosing scheme (Allen et al., 2014).

In threshold studies, the intent is to determine the threshold doses for a group of patients with a specific food allergy. A clinical patient selection bias could occur due to efforts to include highly sensitive patients as documented by their patient history. The ED estimates for threshold studies tend to be lower than for diagnostic series, which may confirm the existence of patient selection bias toward the more highly sensitive (Allen et al., 2014; Taylor et al., 2009).

In immunotherapy trials, the goal is to desensitize patients with a specific food allergy by administering low, steadily increasing, doses of the allergenic food over time (see Chapter 6). The placebo arm of the immunotherapy trial is an oral, low-dose challenge that establishes the minimal ED, which then dictates the choice of the initial immunotherapy doses. This initial OFC provides the patient's individual threshold dose. A patient selection bias might occur in such studies, as the selection of highly

[17] The subscript represents the percentage of the allergic population in whom the dose of total protein from the allergenic food is predicted to produce an objective response. In this case the predicted percentage is 5 percent.

sensitive patients establishes a more rigorous test of the effectiveness of immunotherapy. In several instances, the ED estimates for immunotherapy patient populations is lower than for diagnostic series (Allen et al., 2014), indicating a possible selection bias toward more highly sensitive individuals. However, in a study of anti-immunoglobulin E (IgE) immunotherapy, a comparison revealed that patient selection in that study was biased toward less sensitive subjects (Taylor et al., 2009). By including patients from all three types of studies in the statistical modeling, the effects of patient selection bias are muted to some degree (Allen et al., 2014; Taylor et al., 2009).

The possible under-representation of patients with histories of severe reactions in datasets used for probabilistic modeling has been an expressed concern because patients with histories of severe allergic reactions are excluded from OFCs in some clinics (Luccioli and Kwegyir-Afful, 2014). However, in one large diagnostic series study of patients with peanut allergy where all patients were enrolled in OFCs regardless of a history of severe reactions, no differences were found in the estimated ED_{05} between patients with histories of severe reactions and patients who had histories of mild or moderate reactions (Taylor et al., 2010). Additionally, these patients are not always excluded from oral immunotherapy trials, which represent one of the largest sources of data for this probabilistic modeling.

Uncertainty Factors

The data supporting the establishment of population thresholds are robust because they are derived from controlled OFCs in individuals who have reacted at low doses of the allergenic food. However, several uncertainties should be recognized.

Geographic and age differences Much of the low-dose challenge data emanate from Europe, so concerns have been raised regarding the possibility of geographic differences in population thresholds. Geographic differences in ED estimates have been noted for milk and peanut (Allen et al., 2014). However, the differences for peanut ED estimates may be attributable to patient selection biases because most data are from immunotherapy studies in the United Kingdom. Additionally, the differences for milk ED estimates are mostly likely attributable to the choice of dose progression scheme in Australia, as described above (Allen et al., 2014). The possibility of age differences also has been investigated for peanut and hazelnut, without much difference in ED_p estimates (Allen et al., 2014). However, clearly for milk, egg, and several other foods, many infants and young children do outgrow their food allergy and become fully tolerant (Keet et al., 2009; Savage et al., 2010; Sicherer et al., 2014; Wood et al., 2013), which implies that their

individual thresholds increase over time, although this assumption has never been completely tested.

Validation of statistical models and ED estimates The use of a single dose oral challenge at a particular, predicted ED_p, (e.g., ED_{05}), could be used to validate the probabilistic model estimates of population thresholds (Zurzolo et al., 2013). A single dose peanut trial at the ED_{05} has recently been completed but not yet published. Such studies also will allow determination of the range of reactions experienced by patients allergic to a specific food at the ED_{05} dose.

Other factors Concerns have arisen about the possibility of differences between controlled clinical challenge trials and reactions occurring within the community due to additional factors that are not controlled in an OFC, such as dose of exposure, medication status, coexisting clinical conditions (e.g., influenza or other acute or chronic illness) (Crevel et al., 2014). Box 7A-1 includes several host-related factors that should be recognized and could be considered. Data on the impact of these host-related factors on the NOAELs and the LOAELs are extremely limited. Some of these sources of variability, such as certain biological cycles (e.g., circadian), psychological factors, stress, and concomitant allergen exposures (e.g., seasonal pollen) are likely already incorporated implicitly into the threshold datasets because attempts are not made to control these factors during clinical challenges. Others, such as genetic predisposition and host–environment interactions, have not been well studied. The assumption is that they would likely yield small differences in estimated population thresholds. The quantitative impact of other uncertainty factors (e.g., menstrual status, physical activity, health and medication status, and alcohol usage) on population threshold estimates, including individual NOAELs and LOAELs, has not been well investigated but is acknowledged to be potentially important. Certainly ample, mostly anecdotal, evidence exists that exercise can be a determinant of reaction occurrence, and food-dependent, exercise-induced allergy (FDEIA) is a well-documented condition (Wong and Krishna, 2013). However, the association between FDEIA and individual NOAEL and LOAEL has not been studied. Menstrual cycles seem to be a factor in oral immunotherapy trials (Varshney et al., 2009) suggesting that they might affect individual NOAEL and LOAEL as well. These factors can ideally be addressed in clinical guidance where patients are given personalized advice about behavior (Crevel et al., 2014) but currently this advice is probably not consistently given to patients. Further studies are needed on allergic reactions occurring within the community setting to determine whether exposure dose is the key determinant of reaction occurrence and severity and identify any role that these other factors might play. Despite these host-

related concerns, the imposition of additional uncertainty factors in the establishment of Reference Doses has not been suggested in part because the ED_p values used for Reference Doses are already quite low (ED_{01} or 95 percent lower confidence interval of ED_{05} and probabilistic modeling integrates uncertainty and variability into the approach (Crevel et al., 2014; Taylor et al., 2014).

Exposure Assessment as an Input to Risk Assessment

Exposure assessment has two components: the level of contamination (concentration and frequency) and the intake (amount and frequency) of the particular food. These two components of contamination and intake or consumption can be used in quantitative risk assessment to generate an allergen intake distribution in terms of protein from the allergenic food. Probabilistic modeling can then be used to estimate the probability of an allergic reaction occurring based on the concentration of the allergen in the product, the amount of product consumed, and the probability that an allergic person with a threshold lower than dose of the allergen would consume the allergen. Several variables must be considered in developing an accurate exposure assessment.

Concentration of the Allergenic Residues in Foods

The overall food allergen distribution also requires knowledge of the concentration of allergenic food residue (or protein from the allergenic source) in the particular food in question. The concentration of the allergenic food residue can be determined either through calculation or by quantitative analysis of the ingredient or finished food product in question. Calculation can be made in instances where the allergenic food or food ingredient was inadvertently included in a formulation at a consistent level (e.g., a supplier changed the formulation of a component of the finished food to include a milk ingredient but failed to notify the manufacturer of the finished food). However, calculation cannot be used in most circumstances because the unintended allergen residues arise from the use of shared facilities or equipment at the food manufacturing site or at the site of a supplier. In those cases, quantitative analysis of the food product or ingredient is the most common approach to determining the concentration of the allergenic residue. In IgE-mediated food allergy, specific proteins from the allergenic source are involved in binding to IgE and initiating the allergic reactions. The quantitative methods used to determine the concentration of allergenic food residues should ideally detect proteins from the allergenic source either as total source protein, a certain protein fraction (e.g., casein), or a specific allergen (e.g., Ara h 1 from peanut). However, for risk assessment, it is critical to express the analytical

result as a concentration of total protein from the allergenic source so that it matches to the human threshold data from clinical challenges expressed as doses of protein from the allergenic source as has been explained above. Box 7A-2 describes current methods to detect allergen residues. Although immunochemical methods, such as Enzyme-Linked Immunosorbent Assays (ELISAs), are widely used and various kits are commercialized, many factors can affect the reliability of estimates of the allergenic protein residues occurring in food products. The selection of the best ELISA method is of paramount importance but that choice is often not straightforward nor well comprehended.

Probabilistic risk assessment can incorporate a distribution of concentrations for the unintended allergenic food residue into the risk assessment model. Analytical assessment of a number of samples taken from a batch or multiple batches of production can be used to establish a distribution of the concentration of allergenic residue that may be expected over time during a production cycle. Selecting a sufficient number of samples to obtain a representative distribution of the expected concentration of the allergenic residue is somewhat straightforward when the allergenic residue of concern is homogeneously distributed in the product of interest. However, sampling becomes more difficult when the source of contamination is due to particulates that can be randomly distributed throughout the product in question. In this instance, the likelihood and size distribution of the particulates, along with the dose distribution (based on the expected size distribution of the particles) can be included as input variables in the risk assessment model.

Consumption of Foods by Allergic Individuals

Food allergy reactions, especially IgE-mediated reactions, occur within minutes to hours after ingestion of the offending food. Therefore, the exposure scenario is based on intake of the specific food during a single eating occasion rather than cumulative exposures. The food intake patterns of consumers are typically obtained from national food surveys such as the National Health and Nutrition Examination Survey conducted by the Centers for Disease Control and Prevention's National Center for Health Statistics. However, the use of national food surveys for food allergen risk assessments assumes that the food intake of people with allergies is the same as that of the general population. Ideally, for the quantitative risk assessment of allergenic foods, the focus should be placed on the risk for those who consume the foods as opposed to the overall mean intake levels of the food (Crevel et al., 2014). The food consumption patterns of individuals with food allergy require further evaluation.

Another important, and often incorrect, assumption is that consumers

BOX 7A-2
Detection Methods for Allergen Residues

Immunochemical methods. These methods, primarily Enzyme-Linked Immunosorbent Assays (ELISAs), have become the food industry standard for both qualitative and quantitative detection of allergen residues in food products or on equipment contact surfaces (Jackson et al., 2008; Wang et al., 2010). ELISAs detect protein(s) from the allergenic source of interest, are sufficiently sensitive with detection limits in the low parts per million (ppm) (mg/kg) range, and provide rapid assessments especially when used in a qualitative format, such as lateral flow strips (Jackson et al., 2008). ELISA methods have limitations: (1) lack of standardization (e.g., results are not always reported as concentration of total allergenic protein from the source) and validation (Abbott et al., 2010); (2) kits use of a variety of IgG antibodies, which can affect the reliability of results; (3) kits use either monoclonal antibodies or polyclonal antisera, which vary in terms of specificity against the allergen (e.g., one peanut ELISA kit detected primarily Ara h 2, a heat-stable and especially potent peanut allergen that may be a preferable target for heat-processed foods (Jayasena et al., 2015); and (4) the extraction of allergenic foods can be affected by aggregation, which reduces solubility (Downs and Taylor, 2010), and by the nature of the food matrix.

Mass spectrometry. The use of mass spectrometry methods for the qualitative and quantitative detection of allergenic food proteins has been explored in recent years (Johnson et al., 2011). Like ELISA, mass spectrometry methods can detect the allergenic proteins of interest and thus can provide a direct evaluation of the level of allergenic residue of concern for risk assessment purposes. Mass spectrometry methods may have the ability to detect multiple food allergen residues simultaneously but considerable method development will be needed to achieve that goal (Heick et al., 2011). The sensitivity of mass spectrometry methods approaches that of ELISA methods in several food matrices. Because mass spectrometry is not as widely available as ELISA, mass spectrometry will most likely be used as a reliable confirmatory method in the foreseeable future.

Polymerase chain reaction. Polymerase chain reaction (PCR) methods are available to detect deoxyribonucleic acid (DNA) from a number of allergenic sources, including several sources where ELISA methods may not be available. However, PCR tests do not detect proteins from the allergenic source so their utility in food allergy risk assessment is limited (van Hengel, 2007).

Adenosine Tri-Phosphate and total protein methods. Other analytical methods such as the Adenosine Tri-Phosphate (ATP) test and total protein tests, are used by food industry for routine monitoring of cleaning and sanitation (Jackson et al., 2008). Although these methods are useful tools for monitoring the cleaning process, they do not provide the quantitative detection of specific proteins from the allergenic source of interest that is needed to conduct a thorough risk assessment.

in countries where national consumption surveys do not exist behave similarly to U.S. or British consumers with respect to food consumption. Finally, the frequency of intake and the amount of food consumed by users of the particular product are also considered within quantitative risk assessment. Often the intake amounts of the 90th or 95th percentile user is taken to assure a worst-case assessment. Finally, a single meal could contain more than one source of a particular unanticipated allergen. The probability of such combined exposures is generally quite small and often ignored, but a discussion of its possible impact is available (Crevel et al., 2014).

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8

Managing Food Allergies in Retail, Food Service, Schools, Higher Education, and Travel Settings

In Chapter 5, this report described current knowledge about how biological and environmental systems influence the development of food allergies. The key roles of the individual, the family, and the health care system in managing food allergies were addressed in Chapter 6. The food processing industry also has an essential role in preventing food allergies, with their ability to inform individuals at risk about the presence of allergens in packaged foods, and this was discussed in Chapter 7. However, in order for an individual with food allergy to manage his or her food allergy successfully, it is vital to acknowledge the individual's interactions with many social systems beyond those directly providing health care. These interactions were outlined in the developmental and ecological model described in Chapter 1. For example, after birth, a child has direct experiences with other people and physical environments in addition to the health care system (e.g., early care education settings). As they develop, children continue to interact with numerous new systems, including peer groups, schools, and community services for children and families. Eventually, children begin to interact directly with media, workplaces, and social and recreational contexts, such as sport teams, and religious or other cultural contexts. Although an individual with food allergy must always try to avoid allergenic foods, direct interactions with foods can occur in many of those settings and avoidance is not easy. Moreover, settings that could be of concern for an individual with food allergy change as an individual becomes more independent. For adolescents and adults, who make many independent decisions about food every day, the safety of their food environment is essential. Thus, in addition to schools, the food environment includes many settings that

offer food information (media, food labels) and food itself (restaurants and friends' houses). It would not be feasible to include here a description of how all these settings can influence the safety of individuals in regard to food allergies. Rather, this chapter describes those that the committee views as essential to consider in depth. Those selected settings—food service and retail, schools and day care centers, higher education, and the travel industry—are organized in the chapter from the more general (food retail that everybody experiences) to the narrower (travel). For each setting, the chapter emphasizes the current approaches (i.e., policies, guidelines, and practices) to manage food allergies. The recommendations and research needs related to these settings are at the end of the chapter.

FOOD RETAIL AND FOOD SERVICE

Consumers with food allergies must depend on personnel in restaurants, retail outlets, and retail food service establishments (e.g., ice cream parlors, bakeries, grocery stores, food carts) to obtain allergen-safe foods. Errors could be deadly. In two publications of case series of fatal food-allergic reactions in the United States, at least 17 of 63 deaths involved restaurant meals or items from food services (Bock et al., 2001, 2007). A systematic review of unexpected allergic reactions suggested that 21 to 31 percent occur in restaurants (Versluis et al., 2015). Errors resulting in allergic reactions could occur from problems with communication from the consumer or from a variety of circumstances in the establishment such as hidden ingredients and cross-contact. Although most severe reactions from food allergens originate from consumption of the relevant food and the risk of an allergic reaction from environmental contact is rather low (see Box 8-1), less severe food allergic reactions also have been reported in food establishments (see Chapter 6; Furlong et al., 2001) and some of those might be due to environmental exposures. In a survey directed to understand allergic reactions in restaurant foods or other establishments, 7 (out of 156 episodes) were reported to be due to skin contact or inhalation (i.e., due to residual food on tables, peanut shells covering floors, or being within 2 feet of the cooking of the food).

Several studies have characterized potential problems in understanding and managing food allergy on the part of restaurant and food service staff. In 2006, Ahuja and Sicherer conducted a survey of 100 personnel (42 managers, 32 servers, 24 chefs, 2 other) in 100 establishments in the New York City area (48 restaurants [17 continental, 19 Asian, 12 Italian], 18 fast food, 34 take-out [8 bakery, 13 ice cream, 9 Asian, 4 pizza]) (Ahuja and Sicherer, 2007). The personnel turnover rate was high (on average, between 5 and 30 new staff per year), suggesting a serious challenge to training. Even so, respondents reported high levels of comfort in providing "safe" meals.

BOX 8-1
Risk of Reaction from Environmental Exposure to a Food Allergen

The primary route of exposure to a food allergen that can trigger serious reactions, for example severe anaphylaxis or fatal reactions, is through ingestion (Fleischer et al., 2012; Sampson et al., 2014). In 2003, Simonte et al. conducted a challenge in children with peanut allergy to determine the clinical relevance of exposure to peanut butter by means of inhalation and skin contact. Of the 30 children who underwent the challenge, none experienced a systemic or respiratory reaction. The authors concluded that casual exposure to peanut butter (through skin contact or air exposure) is unlikely to elicit significant allergic reactions (Simonte et al., 2003). A study of peanut-sensitive children found that prolonged skin contact with peanut butter led to localized urticarial (i.e., hives) in 41 percent of the children and no children had a systemic reaction to skin exposure (Wainstein et al., 2007). In this case, the authors also concluded that systemic reactions from skin contact with peanut butter are highly unlikely.

In terms of allergens in dust, Brough et al. hypothesized that the rates of food allergy may be directly proportional to the amount of nonoral exposure an individual has within a home (Brough et al., 2013a,b). They conducted a study in which 45 homes were asked not to vacuum or wash their sheets for 5 days. They found the highest concentration of peanut dust in a child's play area and discovered the most contaminated surface was the dishwasher handle. In general, the dust had more peanut protein than any surfaces. Peanut protein levels in the air were virtually undetectable once shelling ended (Brough et al., 2013a) and the authors concluded that residual dust levels after shelling had variable effect on activating basophils in the laboratory (Brough et al., 2013b). The authors concluded that residual levels of peanut protein may sensitize, but probably will not cause an allergic reaction.

A food allergen also can be present in its aerosolized form, for instance, when boiling, steaming, or frying a food containing the allergen. This may provoke the release of significant quantities of particulates (and allergenic protein) in the form of vapor into the air, a potential factor to initiate a reaction after exposure to the allergen by inhalation. Roberts et al. showed that children afflicted with both asthma and immunoglobulin E (IgE)-meditated allergy developed early- and late-phase asthmatic responses upon exposure to aerosolized food allergens (Roberts et al., 2002). The children were exposed for 20 minutes to fish, chickpea, milk, egg, or buckwheat as they were being cooked. Allergic reactions from such exposures have been described (Gonzalez-Mendiola et al., 2003; Martinez Alonso et al., 2005; Vitaliti et al., 2012); such exposures are likely due to water soluble protein in the cooking vapor.

A rating of "very" or "somewhat" comfortable was selected by 72 percent for providing a safe meal and 70 percent for "guaranteeing" a safe meal. Regarding food allergy training, 42 percent indicated prior training and 6 percent were unsure. Training was primarily (76 percent) through "one-on-

one" (apprentice) sessions rather than a set program. Importantly, respondents did not show high understanding of food allergy when faced with knowledge-based questions. For example, 24 percent thought that small ingestions of the food were acceptable, 35 percent thought heat destroys most allergens, 34 percent thought giving water is an appropriate response to a consumer having an allergic reaction, 54 percent thought a buffet "kept clean" was safe for an allergic patron, and 25 percent thought removing a nut from a finished meal was safe. Only 22 percent of participants selected the correct response for all five of the true-false questions. Rates of correct responses did not vary significantly among managers, servers, and chefs. Also, the number of correct responses was not associated with comfort level for providing or guaranteeing a safe meal ($P>0.9$), suggesting that staff may profess knowledge to a patron but lack understanding. In regard to training, 61 percent indicated an interest in future training programs, 22 percent were not interested and 17 percent were unsure. Respondents were asked whether they thought certification and regulation should be required for food allergy education. To this question 55 percent agreed, 24 percent disagreed, and 21 percent were unsure. Studies conducted in a similar manner using the Ahuja and Sicherer (2007) survey in Brighton, United Kingdom (Bailey et al., 2011), and in Turkey (Sogut et al., 2015) and other surveys (Lee and Xu, 2015; Leitch et al., 2005; Mandalbach et al., 2005) have come to similar conclusions. No studies of issues have been conducted for retail food outlets, such as supermarkets that sell prepared foods, but these outlets have particular food allergy–related issues that would be useful to investigate in studies. These issues include take-away samples that are not allergen labeled, nut butter grinding, self-serve areas, bulk bins, shellfish steaming, open food preparation areas, and shared equipment.

The Food Code[1] (FDA, 2013) provides advice from the Food and Drug Administration (FDA) for uniform systems and practices that address the safety of food that is sold in food service and certain retail establishments. As of October 2015, all 50 states and the District of Columbia

[1] The Food Code began with the activities of the U.S. Public Health Service (PHS) in the area of food protection, particularly studies on the role of milk in the spread of disease at the turn of the 20th century. The first model code, Grade A Pasteurized Milk Ordinance—Recommendations of the PHS/Food and Drug Administration (FDA), was initially published in 1924. Today, the FDA maintains an updated model food code, the FDA Food Code, to assist food control jurisdictions at all levels of government. The model Food Code is neither federal law nor federal regulation and is not preemptive. Instead, it is a model code and reference document for state, city, county, and tribal agencies that regulate operations such as restaurants, retail food stores, food vendors, and foodservice operations in institutions, such as schools, hospitals, assisted living, nursing homes, and child care centers. It is developed by the Conference of Food Protection, a nonprofit organization created to provide a formal process to develop food safety guidance. Members of industry, regulatory, academia, and consumer and professional organizations contribute to the development of the Food Code.

have adopted codes patterned after previous versions of the FDA Food Code, but only 7 states have adopted the 2013 Food Code, which includes food allergen provisions (see the Annex of this chapter for selected 2013 Food Code provisions) based on the 2004 Food Allergen Labeling and Consumer Protection Act.[2] The 2013 Food Code defines "major food allergens" and suggests that a "person in charge" who can respond correctly to an inspector's questions about the specific food operation should be present during all hours of operations. The areas of knowledge include the identification of major food allergens and food allergy symptoms in a sensitive individual who has an allergic reaction. The Food Code also references the need for restaurant and food service managers "to be aware of the serious nature of food allergies" and "to avoid cross-contact during food preparation and service." In addition, the Food Code indicates that the person in charge shall ensure that employees are properly trained in food allergy awareness. That statement "allows industry to develop and implement operational-specific training programs for food employees." However, "it is not intended to require that all food employees pass a test that is part of an accredited program." The Food Code also mandates the information that should appear on a label. The Food Code does not provide specific advice on methods to ensure safety for those with food allergy, but does provide specific procedures about activities such as general cleaning, managing raw foods, and other details aimed primarily at reducing infection risks.

Individual states in the United States decide upon adoption of the Food Code. As mentioned above, only seven states have adopted the 2013 Food Code, which includes the provisions relevant to food allergies. In addition, several states (i.e., Massachusetts, Michigan, Rhode Island, Virginia) have adopted food allergy laws that include requirements for informative posters with notices such as "Before placing your order, please inform your server if a person in your party has a food allergy," and requirements that food safety managers complete required training courses, among other provisions (FARE, 2016a).

Food allergy training is available for personnel in food establishments from several resources. For example, the National Restaurant Association's ServSafe is a 1.5- to 2-hour online course that addresses issues, including defining food allergens, recognizing symptoms, identifying allergens, dangers of cross-contact, proper cleaning methods, proper communication, workstations and self-serve areas, special dietary requests, dealing with emergencies, importance of food labels, handling food deliveries, proper

[2] Public Law 282, 108th Cong., 2nd sess. (August 2, 2004). The Food Allergen Labeling and Consumer Protection Act mandates that the labels of foods containing major food allergens (milk, egg, peanut, tree nuts, wheat, soy, fish, and crustacean shellfish) declare the allergen in plain language.

food preparation, and cleaning and personal hygiene. Many additional programs are available through vendors, and individual companies also have created their own programs. A study of such educational programs suggest they are effective at improving knowledge and changes in practice (Bailey et al., 2014).

EARLY CARE AND EDUCATION SETTINGS AND SCHOOLS

Early care and education settings and schools play an important role in the lives of our children. Although a parent can rather effectively alter the food environment at home to accommodate the needs of a child with food allergy, these types of accommodation become more complex and difficult to implement outside the home.

It has been reported that 16 to 18 percent of school-aged children with food allergy have experienced a reaction in school (Nowak-Wegrzyn et al., 2001; Sicherer et al., 2001). However, although the potential of a reaction from skin exposure to dust with allergen particles exists, the studies to date do not indicate that the risk of reactions, especially severe reactions, is high from environmental exposures (see Box 8-1).

Schools can be a risky setting in which to suffer a severe reaction, such as anaphylaxis. Alarmingly, one study noted that 24 percent of the severe and potentially life-threatening reactions (anaphylaxis) that were reported at schools occurred in children who had no previous diagnosis of food allergy (McIntyre et al., 2005). In a case series of food allergy–related fatalities in children, 9 of 32 happened in school and were associated primarily with significant delays in administering epinephrine (Bock et al., 2001). However, the majority of food allergic reactions that occur in preschool- and school-aged children are not anaphylaxis (Boros et al., 2000; Gold and Sainsbury, 2000) and deaths are rare overall (Macdougall et al., 2002; Umasunthar et al., 2013).

State Laws for School Settings

Fortunately, much progress has been made in the area of ensuring appropriate access to medical treatment for anaphylaxis. In 2013, the School Access to Emergency Epinephrine Act[3] authorized the U.S. Department of Health and Human Services to give funding preferences to schools if they maintain an emergency supply of epinephrine and if they develop a plan so that epinephrine can be administered at the school. Since then, almost all states have authorized schools to keep medications on hand to treat severe allergic reactions, with 10 states requiring schools to keep epi-

[3] Public Law 48, 113th Cong., 1st sess. (November 13, 2013).

nephrine auto-injectors on hand (AAFA, 2015). Furthermore, every state grants students the right to carry and use their anaphylaxis medications while at school and most states have approved laws that allow for stocking of epinephrine auto-injectors at school (FARE, 2016b). The Chicago Public Schools, for example, implemented an initiative to stock undesignated epinephrine auto-injectors in all of its schools. The importance of this initiative based on the use of undesignated epinephrine auto-injectors for food allergy has been reported (DeSantiago-Cardenas et al., 2015). However, implementation of these laws requires training personnel in recognizing symptoms, in administering medication, and in following best practices, and the laws are not monitored by any government agency. According to the nonprofit Asthma and Allergy Foundation of America (AAFA), school settings lag in prompt recognition of allergic reactions and anaphylaxis, treatment of reactions, and extension of these goals to address previously undiagnosed children. This is especially problematic in early care and education settings and schools that lack access to a medical provider, such as a school nurse. It is estimated that 25 percent of schools have no school nurse (AAFA, 2015), and the number of early care and education settings that have access to a nurse is unknown.

Since 2008, the AAFA has identified U.S. states with the best public policies for children and youth in elementary, middle, and high schools who have asthma, food allergy, related allergic diseases, or who have experienced anaphylaxis. All states and the District of Columbia are assessed for 23 standards that are grouped into three broad categories (medications and treatment, awareness, and school environment). In the 2015 report, 14 states met the standards for being a State Honor Roll of Asthma and Allergy Policies for Schools (AAFA, 2015).

The Centers for Disease Control and Prevention School Guidelines

In 2011, Congress passed the FDA Food Safety Modernization Act[4] in an effort to improve food safety in the United States by focusing on prevention. Section 112 of the act calls for the Centers for Disease Control and Prevention (CDC) to develop voluntary guidelines for schools and early care and education settings to help them manage the risk of food allergy and severe reactions in children. Accordingly, in 2013, the CDC, in consultation with the U.S. Department of Education and others, developed the *Voluntary Guidelines for Managing Food Allergies in Schools and Early Care and Education Programs* (CDC, 2013). (Box 8-2 lists the complete set of topics that are included in the CDC guidelines.)

[4] Public Law 353, 111th Cong., 2d sess. (January 4, 2011).

BOX 8-2
Topics included in the *Voluntary Guidelines for Managing Food Allergies in Schools and Early Care and Education Programs*

Section 1. Food Allergy Management in Schools and Early Care and Education Programs

Essential First Steps

1. Use a Coordinated Approach That Is Based on Effective Partnerships
2. Provide Clear Leadership to Guide Planning and Ensure Implementation of Food Allergy Management Plans and Practices
3. Develop and Implement a Comprehensive Plan for Managing Food Allergies

Priorities for Managing Food Allergies

1. Ensure the Daily Management of Food Allergies for Individual Children
2. Prepare for Food Allergy Emergencies
3. Provide Professional Development on Food Allergies for Staff
4. Educate Children and Family Members About Food Allergies
5. Create and Maintain a Healthy and Safe Educational Environment

Food Allergy Management and Prevention Plan Checklist

Section 2. Putting Guidelines into Practice: Actions for School Boards and District Staff

School Board Members
School District Superintendent
Health Services Director
Student Support Services Director
District School Food Service Director

The *Voluntary Guidelines for Managing Food Allergies* calls for Food Allergy Management and Prevention Plans (FAMPPs) to

- Meet the requirements of federal, state, and local laws and regulations;
- Reflect clear goals, purposes, and expectations for food allergy management that are consistent with the school's or early childhood education program's mission and policies;
- Be clear and easy to understand and implement;
- Be responsive to the needs of any child with food allergy by taking into account the different and unique requirements of each child; and

- Be adaptable and updated regularly on the basis of experiences, best practices, current research and changes in district policy or state or county law.

The *Guidelines* recommendations include five priority areas that should be addressed in each FAMPP. These are (1) ensure the daily management of food allergy in individual children, which includes the child's Emergency Care Plan[5] (see Chapter 6), (2) prepare for food allergy emergencies, (3)

[5] Emergency Care Plan for Anaphylaxis or Allergy and Anaphylaxis is a plan written by the physician or health care provider and the patient and family that serves to notify the school about a potentially life-threatening food allergy and about a management approach. These plans come in many forms, but, to date, none is standardized. Key features include the child's name, weight, identifying information (child's picture, if provided), specifics about the food

provide professional development on food allergies for staff members, (4) educate children and family members about food allergy, and (5) create and maintain a healthy and safe educational environment. To help with dissemination and adoption of the guidelines, the CDC has developed a tool kit for schools and early care and education programs (http://www.cdc.gov/healthyschools/foodallergies/toolkit.htm [accessed January 6, 2017]). The extent of implementation of the *Guidelines* is unknown. However, it has been documented that the use of emergency care plans is less than desirable. For example, in a study of the Chicago Public School district, the third largest public school district in the United States, only half of students with food allergy had filed a health management plan with their school (Gupta et al., 2014). In the same study the authors found that Black and Hispanic and low-income students were less likely to have a school health management plan than Caucasian and higher income students.

Unlike the United States, Australia mandated in 2014 that all schools (including private schools) must comply with Ministerial Order 706[6] if they have a student enrolled who is at risk of anaphylaxis. This law requires schools to

- Develop a school Anaphylaxis Management Policy;
- Develop and review Individual Anaphylaxis Management Plans for affected students, which include an individual Australasian Society of Clinical Immunology and Allergy (ASCIA) Action Plan for Anaphylaxis;
- Identify and train school staff in anaphylaxis management;
- Purchase backup adrenaline auto-injectors for general use;
- Complete an annual Anaphylaxis Risk Management Checklist;
- Develop a Communication Plan that ensures that all school staff (including volunteers and casual staff), students, and parents are provided with information about anaphylaxis and the school's Anaphylaxis Management Policy;
- Identify prevention strategies to be used by the school to minimize the risk of an anaphylactic reaction; and
- Develop School First Aid and Emergency Response Procedures that can be followed when responding to an anaphylactic reaction.

allergy or allergies, medications and doses, descriptions of possible symptoms and related treatment instructions, advice to activate emergency services, and family contact information (see also Chapter 6).

[6] Victorian code 706. Anaphylaxis management in Victorian schools. See http://www.education.vic.gov.au/Documents/school/teachers/health/Anaphylaxis_MinisterialOrder706.pdf (accessed June 26, 2016).

Other Federal Policies

Meanwhile, other federal laws, such as the FDA Food Code (explained in more detail above), Section 504 of the Rehabilitation Act of 1973,[7] the Americans with Disabilities Act (ADA)[8] and the Richard B. Russell National School Lunch Act[9] as well as state laws in 15 states, pertain to children with food allergy and need to be considered when schools or early care and education settings create management prevention plans, such as FAMPPs. While it is duly noted that the management prevention plans are voluntary, if an individual plan is developed for a child with food allergy, by law it is considered an education record for the purposes of Section 444 of the General Education Provisions Act (better known as the Family Educational Rights and Privacy Act).[10] In addition, if a school or early care and education setting participates in the School Nutrition Programs (i.e., National School Lunch and School Breakfast Programs, the Special Milk Program, and the Fresh Fruit and Vegetable Program), then the U.S. Department of Agriculture (USDA) nondiscrimination regulation (7 CFR 15b) and the Richard B. Russell National School Lunch Act must be followed. These policies state that accommodations to program meals must be made for children who are determined to have a food allergy disability. Furthermore, USDA Food and Nutrition Service (FNS) guidance requires that accommodations must be made at no additional cost to the student, that a food allergy or intolerance impacting a major bodily function (i.e., digestive or respiratory system) must be considered a disability, and that a medical statement from a state-licensed health care professional authorized to write medical prescriptions should be provided to school administrators in certain situations. FNS issued a memorandum in September 2016 (SP 59-2016) that clarifies these requirements. FNS is currently conducting training on the requirements and revising guidance so that current versions of the ADA, Section 504 of the Rehabilitation Act of 1973, and the Individuals with Disabilities Education Act (IDEA)[11] are incorporated.

In addition, FNS has developed food safety guidelines specifically targeted at school nutrition directors. These guidelines include a section on managing food allergies with references to many resources (USDA, 2016).

[7] Public Law 112, 93rd Cong., 1st sess. (September 26, 1973).

[8] Public Law 336, 101st Cong., 2d. sess. (July 26, 1990). The ADA defines a person with a disability as "a person who has a physical or mental impairment that substantially limits one or more major life activity." Major life activities include eating and therefore individuals with food allergies have a disability as defined by the ADA, particularly those with more severe responses, such as difficulty swallowing and breathing, asthma, or anaphylactic shock.

[9] Public Law 396, 79th Cong., 2d sess. (June 4, 1946).

[10] Public Law 380, 93rd Cong., 2d sess. (August 21, 1974).

[11] Public Law 142, 94th Cong., 1st sess. (November 29, 1975).

Also, FNS has funded other initiatives related to food allergies through the Institute of Child Nutrition,[12] which offers resources in many formats and conducts training and research. For example, it offers a 4-hour online course on "Managing Food Allergies in School Nutrition Programs" directed to district school nutrition directors and supervisors, managers, and food service assistants and technicians. Many of the resources also are available in Spanish. FNS is updating these resources so that they reflect the requirements included in SP 59-2016.

The FDA Food Code

Like other food establishments, school cafeterias must comply with the version of the FDA Food Code adopted by the local or state government. As mentioned above, as of October 2015, only seven states have adopted the 2013 versions of the FDA Food Code dated after the implementation of the Food Allergen Labeling and Consumer Protection Act (FALCPA) in January 1, 2006, which includes new provisions regarding food allergens. The Annex to this chapter includes some highlights of the 2013 FDA Food Code relevant to food allergy, including some of the new provisions. The 2013 FDA Food Code recognizes the importance of restaurant and retail food service managers by adding a provision to ensure that the food safety training of employees includes food allergy awareness. FALCPA also requires that the FDA works in cooperation with the Conference for Food Protection to pursue revision of the Food Code to provide guidelines for preparing allergen free foods in food establishments, including elementary and secondary school cafeterias.

HIGHER EDUCATION INSTITUTIONS

As Chapter 6 argues, adolescents are particularly at risk when it comes to food allergy. As adolescents continue from high school into higher education, they are increasingly less dependent on guardians or parents to remain safe, and the physical separation that often occurs by leaving home coincides with their desire for independence. Perhaps for this reason, young adults may prefer to manage their food allergy on their own as they enter institutions of higher education. It appears that fewer regulations govern the management of food allergy in higher education institutions.

[12] The Institute of Child Nutrition at the University of Mississippi was established by Congress in the Child Nutrition and the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) Reauthorization Act of 1989 and funded by a grant administered through the U.S. Department of Agriculture (USDA), Food and Nutrition Service (FNS). The Institute's mission is to provide information and services that promote the continuous improvement of child nutrition programs.

Some of the obvious policies and resources that help students with managing food allergy at a college or university are described in this section. Schools vary considerably in their food service structure but their facilities generally include various cafeteria-style facilities and fast-food restaurants. In addition to the role of food service in preventing food allergy, other staff influence aspects of college life that have a potential impact. These staff also have a responsibility to work with students and families to ensure the proper management of food allergy and adequate quality of life and well-being for the students. Campus health centers, for example, are important institutions as they offer diagnostic services, and tools and management approaches for individuals (see Chapter 6 for a discussion of the health care system, which includes campus health centers). In addition, campus housing has a role in working with students who have food allergy and determining their needs. This section briefly refers to these diverse areas in a higher education setting where policies and procedures need to consider the needs of individuals with food allergy.

Federal and State Policies

Cafeterias or restaurants, when defined by the local and state governments as a food establishment, need to follow the version of U.S. Food Code adopted by the relevant state or local government. However, as explained above, not all states have adopted the most recent version of the Food Code, the 2013 Food Code, which includes new important provisions related to food allergy, such as training of personnel and food labeling (see above and the Annex for details on these provisions).

Although no other specific federal or state policies cover higher education in regard to food allergies, some broader policies apply. For example, as noted earlier, food allergy might be considered a disability under the ADA. In fact, in 2009, the U.S. Department of Justice (DOJ) received a complaint about violations of the ADA public accommodations provision at Lesley University in Cambridge, Massachusetts, related to students with celiac disease and/or food allergy. After concluding that violations had occurred, the DOJ entered into an agreement with the university "to ensure that its students with celiac disease and other food allergies can fully and equally enjoy the university's meal plan and food services" (DOJ, 2012). This was a key decision that will guide any future decision regarding implementation and enforcement of the ADA public accommodations provision.

Other Policies

Until recently, no specific guidelines had been developed on recommended practices to manage and prevent food allergy in higher education.

With this goal in mind, the Food Allergy Research Education College Food Allergy Program[13] was launched in 2014. The program provides the first guideline with details about processes that must be in place at a college or university to ensure safety. The guideline helps officials develop uniform policies to successfully manage food allergy in this setting. It addresses all aspects of college life that are relevant to food allergy, including dining services, health services, resident life, social well-being, disability accommodations, and emergency services. It emphasizes the need for comprehensive policies (e.g., a clear process for requesting accommodations), emergency response plans, process transparency and documentation, individual confidentiality, effective outreaching, staff training, and methods for assessment. The program is very flexible, being sensitive to the varying resources among colleges and universities. The program is being tested in 12 colleges and universities with the hope that others will join.

As a pilot program, some barriers have already been identified (Haas, 2015), such as the challenges of gathering accurate information about food allergens in food and food ingredients from food manufacturers, gathering adequate resources for implementation of the guideline, and identifying practical measures of success.

FOOD ALLERGIES AND THE TRAVEL INDUSTRY

Flying with Food Allergies[14]

Patients with food allergy can have serious reactions to small quantities of an allergen and, as previously discussed, allergen avoidance is currently the only management approach to minimize the risk of an allergic reaction. When flying, avoidance might appear more difficult because spending hours in a closed environment might increase the risk of contact with a food allergen when food is served or other passengers bring food. This perceived higher risk can exacerbate anxiety in passengers with food allergy. Although peanut has become a center of focus in research and in the media, any food allergy can be a concern to a flyer.

Few data are available on the percentage of food allergy reactions

[13] The Food Allergy Research Education College Food Allergy Program was developed in partnership with other organizations (the National Foundation for Celiac Awareness; the National Association of College & University Food Services) and food allergy experts, college and university representatives, and industry representatives. The program, including the guidelines and other resources for prospective and current students with food allergy, can be found at http://www.foodallergy.org/resources-for/colleges-universities/college-food-allergy-program (accessed January 6, 2017).

[14] Considerations while traveling on other modes of transport should be the same, especially if food is served to travelers.

among those with food allergies while flying. In a 2008 study, Comstock et al. reported that in a sample of 471 individuals with peanut, tree nut, or seed allergy, approximately 9 percent (41 individuals) reported an allergic reaction to food while on board an airplane. Six of these reactions were serious and potentially life-threatening (Comstock et al., 2008). Similar findings emerged from an earlier study that interviewed participants in the National Registry of Peanut and Tree Nut Allergy. Within a total of 3,704 registry participants, 62 reported a reaction associated with airline travel, with reaction severity correlating with exposure route (i.e., ingestion led to the most severe reaction, with inhalation and skin contact resulting in progressively less severe reactions) (Sicherer et al., 1999). In 2008, Greenhawt et al. tracked 150 self-reported reactions to peanut or tree nut on an airline. Of these reactions, 33 percent were reported with symptoms consistent with anaphylaxis but only 10 percent (15 individuals) of the total number of individuals that reported a reaction were treated with epinephrine (Greenhawt et al., 2009). And 48 percent of individuals in the study reported changing flying behavior in response to their reaction. In a survey of 850 physicians who had been asked to provide medical assistance during in-flight medical episodes, no cases relating to peanut allergy were reported (Rayman, 2002). One case report also has been published. In this report, a woman age 19 years experienced anaphylaxis during a transcontinental flight after eating a meal that was reported to have been cooked in peanut oil (Brady and Bright, 1999). Because this individual had a past medical history of asthma, allergic rhinoconjunctivitis, and urticaria related to peanuts, she had medications with her to treat allergic reactions.

Environmental Exposure to Food Allergens

In addition to the risk of exposure through accidental ingestion of an allergen, travelers on airplanes also may worry about being exposed to an allergenic food through contact with particles through skin or by breathing aerosolized allergens. Although no studies have addressed the risk of exposure and reaction on an actual commercial airline flight, studies have been completed to determine whether contact by skin exposure or inhalation can cause an allergic reaction in individuals with a peanut allergy (see Box 8-1).

Based on these limited studies and reported cases on environmental exposure to food allergens, the risk of a severe reaction from aerosolized food allergens appears to be very low, except for children with both asthma and food allergies.[15] Likewise, the risk from skin exposure is low. However, similar to other settings, individuals still need to be cautious about the

[15] Occupational exposure to food allergens is not included in this report.

potential for severe reactions in an airplane environment in the case, for example, of accidental transfer from the hand to the mouth if the seats or other contact areas are not carefully cleaned.

Current Management of Food Allergies During Air Travel

Relevant Federal Policies on Flying with Food Allergy

The Americans with Disabilities Act and the Air Carrier Access Act The Federal Aviation Act of 1958[16] was intended to ensure "safe and adequate service" on airlines, but it primarily addressed fair prices and did not address disabilities. In 1986, the Supreme Court found that Section 504 of the Rehabilitation Act, the first U.S. protection for people with disabilities that led to the 1990 ADA, applies only to accommodations in the airport, not on airlines, as airlines do not receive federal funding.[17] Subsequently, the court found that the ADA also does not apply to airlines (Francoeur, 2015). The Air Carrier Access Act[18] (ACAA) of 1986 covers all domestic and most international flights and instituted much stricter regulation regarding serving passengers with disabilities. The ACAA uses the same definition of disability as the ADA, and the U.S. Department of Transportation (DOT) was given authority[19] to make regulations enforcing the ACAA. Applying the ACAA to passengers with a food allergy could imply the following:

- The cost of accommodating special needs of passengers with food allergy will not be passed on by the airlines to passengers.
- Epinephrine is allowed on board in a medical kit, but flight attendants may not use this without a doctor on board or without calling down to a doctor on the ground.
- Passengers are allowed to bring epinephrine on the airplane as long as it had been prescribed.
- Medical certificates are not necessary to prove that an individual has a food allergy.

[16] Public Law 726, 85th Cong., 2d sess. (August 23, 1958).

[17] The Paralyzed Veterans brought a case under Section 504 of the Rehabilitation Act, arguing that paralyzed veterans were entitled to certain rights when traveling on an airline (*U.S. Department of Transportation v. Paralyzed Veterans*, 477 U.S. 597 [Supreme Court, 1986]).

[18] Public Law 435, 99th Cong., 2d sess. (October 2, 1986).

[19] Nondiscrimination on the Basis of Disability in Air Travel, 14 CFR Part 382, 2003.

However, passengers can actually do very little if they feel discriminated against for having a food allergy. The contract of carriage[20] limits passengers from filing a lawsuit against an airline for failure to make accommodations. Even if a passenger can file a complaint with a Complaint Resolution Officer or with the DOT, the DOT is able to fine an airline or take it to court only if there is a *pattern* of discrimination. Passengers cannot receive any compensation in such cases (Francoeur, 2015). Data pertaining to disability-related complaints filed to the DOT for all United States and foreign air carriers are helpful for passengers to determine which airlines have the most allergy-related complaints against them.[21] In 2014, a total of 968 allergy-related complaints were filed with the DOT. However, these complaints are not separated by allergy, so it is likely that some allergy complaints were not food-related.

Department of Transportation and Related Agencies Appropriations Act of 2000 and Buffer Zones In 1998, to deal with an increasing concern over food allergic reactions on planes, the DOT suggested that airlines create buffer zones. As a result of backlash followed this suggestion, Congress passed the Department of Transportation and Related Agencies Appropriations Act of 2000[22] which states that no federal funds can be used to require airlines to provide peanut-free buffer zones or limit the distribution of peanuts on airlines until a peer-reviewed study could show that peanut protein circulating in the air could cause harm (Francoeur, 2015). In 2010, the DOT issued a new proposal to the public in which they offered three suggestions regarding peanuts on flights:

1. Ban peanuts completely on flights.
2. Ban peanuts on flights with a peanut allergic passenger.
3. Create buffer zones.

The DOT soon backed down from this 2010 proposal when reminded about the 2000 Appropriations Act. Until the 2000 Appropriations Act is modified, airlines will be legally allowed to make their own policies regarding food allergy without any instructions from the DOT. As a result, each

[20] The contract of carriage is an agreement that passengers automatically enter any time they purchase a ticket from an airline. The contract of carriage is often either printed in fine print on the paper ticket or is found on the airline's website. This agreement limits a passenger's right to sue a carrier for damages, and courts have held that this is a binding contract whether or not a passenger has read it in its entirety.

[21] These data can be found on the DOT's website: https://www.transportation.gov/airconsumer/2015-report-disability-related-air-travel-complaints-received-2014 (accessed January 6, 2017).

[22] Public Law 69, 106th Cong., 1st sess. (October 9, 1999).

airline has developed its own policies.[23] As examples, some airlines warn passengers that they are unable to guarantee no nut dust in the air but they will attempt to accommodate them by not serving nut-containing snacks when a passenger at risk of an allergic reaction is on board. Some also recommend that passengers with nut allergies take precautions by flying early in the day and reading the labels. Other airlines have implemented buffer zones whereby peanuts are not served within two rows of a passenger with food allergies.

Food safety policies Airlines, similar to railroads and other transportation services, are managed under the Interstate Travel Program, which governs Interstate Conveyance Sanitation and is authorized by the Public Health Service Act. It is enforced by the FDA, not by the states.[24] However, in airplanes, with the more recent practice of receiving prepackaged food, rather than preparing food on board, informing the consumers about allergens in foods is no different than it is in a retail stores. In that way, firms (caterers and commissaries) who provide food for these transportation services are not subject to FALCPA or the FDA Food Safety Modernization Act[25] (FSMA), the federal laws regulating food safety and food allergy labels, unless they prepared and distributed food that was packaged and sold in interstate commerce and need to carry a label. As a result, airline menus (which are typically prepared 1 year in advance) and meals are required to be labeled for allergens on U.S. carriers, but this requirement is not currently being enforced. Policies enforcing the labeling of food allergens for meals served on airplanes are only currently being finalized. The FDA Food Code (see above and Annex) also applies to airline caterers. Finally, these U.S. regulations pertain only to flights that depart from the United States jurisdiction. For example, an U.S. carrier on a flight from Germany to the United States would not have to comply with FALCPA.

In contrast, European Union Allergen Legislation Regulation No. 1169/2011 on The Provision of Food Information to Consumers,[26] which was published in October 2011 and became effective in December 2014, requires labeling information for prepacked food to include an ingredients list, including allergens, and a quantitative indication of ingredients. This regulation applies "to all foods intended for the final consumer, including foods delivered by mass caterers" and applies to "catering services provided by transport undertakings when the departure takes place on the territories

[23] See www.dot.gov/airconsumer/nuts-airlines-policies (accessed January 6, 2017).

[24] Interstate Conveyance Sanitation. Code of Federal Regulations, Title 21, Part 1250.

[25] Public Law 353, 111th Cong., 2d sess. (January 4, 2011).

[26] See http://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX%3A32011R1169 (accessed July 2, 2016).

of the Member States to which the Treaties apply." This regulation also covers crew food and requires that allergens be labeled on catered and nonprepacked foods as well. When allergens are present, they must either be listed on the packaging information or available by asking a crew member. If this information is available verbally, it must be indicated on a label attached to the food, or on a menu, ticket, or label that is readily discernible by an intending purchaser at the place where the intending purchaser chooses that food (FSA, 2015).

The *World Food Safety Guidelines*[27] from the International Flight Services Association has information on allergen labeling and management, and some airlines may require caterers to report allergens to airline staff but it is unclear whether this is mandatory or optional guidance.

Policies about medical emergencies training of personnel As already mentioned, epinephrine is indicated if a person has an anaphylactic reaction due to a food allergy. The Federal Aviation Administration (FAA) has required an emergency medical kit in domestic passenger planes since 1986. Under the current rule, the kit must contain two single-dose vials of epinephrine injection (1:1,000 dilution) or the equivalent, and two single-dose vials of epinephrine injection (1:10,000 dilution) or the equivalent. The 1:10,000 vials are labeled for the treatment of cardiac arrest. However, the 1:1,000 vials, which would be typically used for severe food allergic reactions, are not labeled specifically for this use. In addition, the FAA does not mandate that epinephrine auto-injectors be available on board. In response, the American Academy of Pediatrics is currently advocating the FAA to require the inclusion of epinephrine auto-injectors in the medical kits on aircrafts and to work with the FAA on procedures for the use of auto-injectors, recommendations for doses, and replacement of old medication. In addition, in July 2015, bipartisan legislation[28] was introduced to require the FAA to initiate rule-making to update the emergency medical kits contents with appropriate pediatric medications and equipment, including an epinephrine auto-injector.

Flight attendants and other crew members have first-aid training. However, the airlines do not mandate that a crew member respond to an emergency, such as anaphylaxis, occurring on a plane. As mentioned above, they are not allowed to use medical kits (including epinephrine) unless a doctor is on board or they have received permission from a doctor on the ground. The Aviation Medical Assistance Act of 1998[29] protects persons

[27] See http://www.ifsanet.com/?page=World_Guidelines (accessed July 2, 2016).

[28] Airplane Kids in Transit Safety Act of 2015 or Airplane KITS Act of 2015, HR 3379, 114th Cong., 1st sess. (July 29, 2015).

[29] Public Law 170, 105th Cong., 2d sess. (April 24, 1998).

providing assistance in the case of an in-flight emergency as long as they are medically qualified. As mentioned above, however, the epinephrine vials in a plane's emergency medical kit are not labeled for allergic use and so it is possible that a person who is unfamiliar with allergy would not know that epinephrine can and should be used in the case of anaphylaxis.

Another approach to managing emergencies is to divert the plane. Although pilots have broad discretion to divert an airplane in an emergency, they have to consider cost (which can range anywhere from $3,000 to $100,000 [Gendreau and DeJohn, 2002]), proximity to an airport, advice of medical team, and the ability to land safely. One study analyzed the records of in-flight emergency calls from five domestic and international airlines from January 2008 to October 2010. This study found that in total 11,920 in-flight medical emergencies resulted in calls to medical professionals on the ground and 265 of these calls were related to an allergic reaction (Peterson et al., 2013). Of the 265 calls, 12 required aircraft diversion, 40 required transportation to a hospital upon landing, 8 required hospital admission, and no deaths occurred. The authors did not indicate how many of these reactions were food-related.

Research on Mitigating Risk

The committee did not find any studies on approaches to mitigate risk conducted in an airplane setting, although one study, which assessed the effectiveness of cleaning agents for allergen removal (Perry et al., 2004), could apply to airlines. The researchers found that on a flat surface such as a table, dish soap does not remove peanut protein Ara h 1. However, other cleaners did effectively remove peanut protein Ara h 1 from a table surface. Soap and water were able to remove Ara h 1 from hands, but hand sanitizer was not adequate for this purpose. The authors were not able to detect airborne allergen in a simulated environment, suggesting that the risk from contact and airborne exposures to peanut protein is very small. Although the findings were promising, the Enzyme-Linked Immunosorbent Assay (ELISA) test used to identify the peanut protein was specific for Ara h 1 protein; other peanut allergenic proteins could have been present but not detectable. In addition, some detergents and sanitizers can interfere with ELISA detection of allergen residues, for example, by denaturing the proteins. Therefore, the findings from this study, although interesting, would need to be re-evaluated under a different study design to ensure that the ELISA method does not interfere with the results.

Greenhawt et al. studied international in-flight experiences to determine the efficacy of risk-mitigation behaviors by food-allergic passengers (Greenhawt et al., 2013). They found that the following contributed to lower odds of risk of reaction: requesting a buffer zone, requesting an

announcement to not eat peanut items, request for a peanut-free meal, wiping tray table, bringing own food, and avoiding airline blanket/pillow. No association was reported for preboarding; sitting in a particular area; wiping the seat belt, arm rest, or seat back; or asking the airline to not distribute snacks containing peanut.

OTHER SETTINGS

Many settings where food is served in any community present health risks for consumers with food allergies, but only a few are presented in detail here because of their particular relevance: food service and retail, day care centers and educational institutions, and air travel (and other modes of transportation). However, in other settings, food is prepared and served for specific populations. These include camps, social gatherings, prisons and jails, military bases, hospitals, and senior homes. The committee did not explore these settings but, just like other cafeterias, it is reasonable to suggest that they also are considered food establishments under the U.S. Food Code and therefore should meet its food allergy provisions.

OVERALL CONCLUSIONS

In general, tools that can assist in achieving safety in settings of concern relate to policies (either implemented and enforced by the individual setting or by federal, state, or local government) combined with precautionary behaviors from the side of those at risk of having an allergic reaction. In general, however, only a few federal policies directly or indirectly apply to food allergies at the settings of concern described in this chapter (e.g., a recent federal policy allowing schools to stock epinephrine to manage severe allergic reactions). For the most part, however, oversight of places where food is prepared or served is left to the state and local government, such as the voluntary adoption of the FDA Food Code for food establishments. Unfortunately, many states follow Food Code versions before 2013, which do not include important provisions relevant for food allergies that are now in effect.

In regard to individual settings, such as schools or restaurants, studies showing internal policies, knowledge, and practices to manage food allergies are scarce. The data available would indicate that many improvements are feasible that would likely contribute to preventing and managing severe allergic reactions. For example, studies about food service settings suggest that staff may not have a good understanding of the nuances of food allergy management or how to prepare a safe meal. The 2013 FDA Food Code suggests the need for awareness and training, but this is not mandated. Only a few states have laws regarding approaches to food allergy and very few

mandate training of employees. Training programs are available but have generally not been grounded in evidence. High employee turnover, varying education levels, and language barriers represent additional challenges.

Another example of needed improvements that are feasible is in educational settings. In early care and education and school settings, U.S. Food Code regulations could be followed. Also, voluntary guidelines exist for K-12 schools (i.e., the CDC Guideline, FAMPP), and some federal and state laws are specific to children participating in federal nutrition programs and those who have an individualized education program (IEP).[30] However, gaps in managing food allergies exist. First, because schools are not reporting in a systematic fashion the occurrence of severe reactions or the number of children with IEPs due to a food allergy diagnosis, the scope of the problem in schools is unknown. Second, it is also clear from reviewing the literature and policies, that schools and other educational settings do not have sufficient staff trained in first aid and, in particular, in food allergy anaphylaxis first aid training, which creates a serious problem for being capable of managing severe food allergy reactions. Finally, the degree to which states adhere to laws that allow stocking of epinephrine is not monitored, which hinders the ability to develop best practices and evaluate their effectiveness.

As children begin to transition into adulthood and may engage in risk-taking behaviors, it is critical to have policies in place to help ensure that their food allergies can be managed. No specific federal or state policies for higher education campuses directly address food allergies. Several policies, however, such as the ADA are important for college and university students and indirectly support food allergy prevention and management.

In all settings where food is prepared or served, most severe reactions will occur by oral exposure and not from exposure to dust particles. Therefore, the committee concluded that policies, such as mandating a buffer zone or prohibiting serving allergens in airplanes or in schools, are not based on current knowledge. Patients and caregivers can take precautions to minimize the risk, such as making sure those in charge (e.g., teachers, restaurant servers, flight crew) are informed about a person's food allergy, wiping tray tables, or requesting an allergen-free meal as appropriate. However, other policies that could be effective at preventing or treating the rare severe reactions do not exist in those settings of concern. For example, policies enforcing the labeling of food allergens for meals served on airplanes are only currently being finalized. Also, although epinephrine vials

[30] An individualized education program is a plan that lays out an educational program designed to meet the needs of a child with special needs. Ideally, it is developed collaboratively among the parents and school staff. See http://www.parentcenterhub.org/repository/iep-overview (accessed January 6, 2017).

are included in an airplane first aid kit, the availability of epinephrine in a dose to treat food anaphylaxis is not required. Likewise, medically trained personnel in these settings need to be able to recognize signs and symptoms of a severe food allergic reaction and treat with epinephrine.

Policies are not the only approach to food safety. Students in particular, but also those with risk of food allergy and their caregivers in general, need to be provided with the information that empowers them to make their own appropriate decisions about safety. For students, given the nature of campus life, institutions of higher education have the potential to be key providers of information about food options and nutrition and available resources (e.g., dietitians, health care service, or on-campus accommodations) that can help to meet their food allergy needs. In practice, health care providers offer food-allergic individuals variable advice about avoidance diets and the need to avoid completely the specific allergenic food(s) (Turner et al., 2016). Moreover, advice from food allergy advocacy groups, the Internet, and other sources also may be inconsistent. Therefore, health care professionals (see Chapter 6), public health authorities (see Chapter 5), and food allergy advocacy groups should be trained to offer consistent, evidence-based advice on allergen risks, including allergen avoidance diets.

In response to its task, the committee developed specific recommendations for ways to assure that appropriate guidance and education is in place to create a safe public environment for individuals with food allergy. In doing so, the committee recognized that its task did not include recommendations for therapeutic intervention or clinical management of food allergies.

RECOMMENDATIONS

Training Food Industry Personnel

The committee recommends that food industry leaders provide the necessary resources for integrating food allergy training (e.g., food allergen identification and preventive controls, effective risk communication with customers) into existing general food safety and customer service training for employees at all levels and stages in the food industry, as appropriate, encompassing processing, retail food and grocery stores, restaurants, and other food service venues.

Training for employees could be offered through, for example, supporting conferences, workshops, or webinars to share best practices related to allergen preventive controls, food allergen risk communication, and other food allergen safety topics. State health departments could develop a certification process for allergy aware-

ness and management in restaurants modeled after the letter grading system that rates their food safety performance.

Implementing Improved Policies and Practices to Prevent the Occurrence of Severe Reactions

The committee recommends that all state, local, and tribal governmental agencies adopt the 2013 Food and Drug Administration Food Code, which includes provisions for food establishments on preventing food allergic reactions. Working in collaboration with other stakeholders, the agencies also should propose that the next Food Code requires that the person in charge in food establishments pass an accredited food safety certification program that includes basic food allergy management in order to decrease or prevent the risk of food allergen exposure. In addition, agencies should develop guidance on effective approaches to inform consumers with food allergies in food service establishments.

Guidance on effective approaches to inform consumers with food allergens in food service establishments could include menu designations of allergens and posters, and other forms of displaying information about food allergens in food establishments.

The committee recommends that, within the next year, relevant federal agencies (e.g., the Food and Drug Administration [FDA], the Centers for Disease Control and Prevention [CDC], the Federal Aviation Administration) convene a special task force that includes participants from the medical community, food companies, and advocacy stakeholder groups to establish and implement policy guidelines to:

- **Assure emergency epinephrine capabilities are in place for children and adults in public venues, including schools, early care and education facilities, and on-board airlines;**
- **Provide standardized food allergy and anaphylaxis first aid training (e.g., identification of major food allergens, signs and symptoms of allergic reactions, and emergency treatment protocols) to appropriate school and university health staff, early care and education providers, and on-board flight crews; and**
- **Implement education standards for responding to and managing food allergy emergencies in schools and early care and education facilities (e.g., CDC Food Allergy Guidelines) and on airlines.**

The committee recommends that the FDA continue to work together with other relevant federal, state, and local agencies to develop and implement labeling policies specific to allergenic ingredients in packaged and prepared foods that are distributed through airlines and other public venues, including schools and early care and education facilities.

RESEARCH NEEDS

Allergic reactions occur among children attending early care and education settings, schools, camps, or college, as well as among children and adults while traveling or eating at a food establishment and may include persons without a prior diagnosis. Although anecdotal reports describe severe reactions, well-documented estimates of such reactions in each setting are not available. Also, although federal and local policies exist, such as the FDA Food Code, no studies have been conducted on the extent to which regulatory policies have been implemented and the impact of those policies on management or prevalence of food allergy.

The obstacles for consumers with food allergy in restaurants, food establishments, and during travel include lack of communication between the consumer and staff and lack of knowledge about ensuring safety for consumers with food allergies. Limited programs exist for education and more studies are needed to create and validate food allergy educational materials and programs.

Best practices for managing food allergies in settings of concern where food is served have not been studied. For example, management plans for food allergy in early care and education settings, schools, camps, or other places where children are served food include providing instructions for safe meals, recognizing and managing reactions, and assigning roles and responsibilities. These plans require different strategies according to age of the child, skill level of the supervising adults, and cultural or socioeconomic context, but these factors have not been extensively studied and a paucity of data exist upon which to base best practices.

To fill gaps in knowledge in this area, studies should be conducted to accomplish the following objectives:

- Monitor the number of food allergic reactions that occur in various settings where food is served, particularly in early care and education settings, schools, camps, and food establishments, and in additional settings of concern, including restaurants, cafeterias, grocery stores, and commercial airliners (or other commercial means of travel).

- Monitor the degree to which states adhere to the FDA Food Code and other laws and regulations with a food allergy component (e.g., the number of children with IEPs[31] due to food allergy) so that best practices are developed and their effectiveness in the prevention of severe reactions and management of food allergies is evaluated.
- Define best practices regarding food allergy management (e.g., epinephrine storage) at settings where food is served, particularly in early care and education settings, schools, camps, and food establishments in additional settings of concern, including restaurants, cafeterias, grocery stores, and commercial airliners (or other commercial means of travel). The experiences of other countries where management practices have been standardized should be considered.
- Develop and implement evidence-based, effective training programs for relevant personnel at settings where food is served, particularly in early care and education settings, schools, camps, and food establishments in additional settings of concern, including restaurants, cafeterias, grocery stores, and commercial airliners (or other commercial means of travel). The experiences of other countries where effective training programs have been standardized should be considered.
- Identify and explain risks associated with environmental exposures to food allergens through skin contact or inhalation.

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[31] In public schools, students with a disability may qualify for an IEP, under federal special education funding through the Individuals with Disabilities Education Act (IDEA) of 1975, and may receive special education and related services. See more at http://www.foodallergyawareness.org/civil-rights-advocacy/schools-2/individualized_education_program_(iep)-2/#sthash.F4dKKnbV.dpuf (accessed January 6, 2017).

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ANNEX 8: 2013 FOOD CODE (FOOD ALLERGY PROVISIONS)

1.1 Definitions

Major Food Allergen. (1) "Major food allergen" means: (a) Milk, EGG, FISH (such as bass, flounder, cod, and including crustacean shellfish such as crab, lobster, or shrimp), tree nuts (such as almonds, pecans, or walnuts), wheat, peanuts, and soybeans; or (b) A FOOD ingredient that contains protein derived from a FOOD, as specified in Subparagraph (1)(a) of this definition. (2) "Major food allergen" does not include (a) Any highly refined oil derived from a FOOD specified in Subparagraph (1)(a) of this definition and any ingredient derived from such highly refined oil; or (b) Any ingredient that is exempt under the petition or notification process specified in the Food Allergen Labeling and Consumer Protection Act of 2004 (Public Law 108-282).

Chapter 2 Management and Personnel

2-1 Supervision

Responsibility

2-101.11 Assignment

(A) Except as specified in ¶ (B) of this section, the PERMIT HOLDER shall be the PERSON IN CHARGE or shall designate a PERSON IN CHARGE and shall ensure that a PERSON IN CHARGE is present at the FOOD ESTABLISHMENT during all hours of operation.

Knowledge

2-102.11 Demonstration

Based on the RISKS inherent to the FOOD operation, during inspections and upon request the PERSON IN CHARGE shall demonstrate to the REGULATORY AUTHORITY knowledge of foodborne disease prevention, application of the HAZARD Analysis and CRITICAL CONTROL POINT principles, and the requirements of this Code. The PERSON IN CHARGE shall demonstrate this knowledge by:

(C) Responding correctly to the inspector's questions as they relate to the specific FOOD operation. The areas of knowledge include:

(9) Describing FOODS identified as MAJOR FOOD ALLERGENS and the symptoms that a MAJOR FOOD ALLERGEN could cause in a sensitive individual who has an allergic reaction

Duties

2-103.11 Person in Charge*

The PERSON IN CHARGE shall ensure that:

(M) EMPLOYEES are properly trained in FOOD safety, including FOOD allergy awareness, as it relates to their assigned duties;

Chapter 3 Food

3-6 FOOD IDENTITY, PRESENTATION, AND ON-PREMISES LABELING

Labeling

3-602.11 Food Labels

(B) Label information shall include:

(5) The name of the FOOD source for each MAJOR FOOD ALLERGEN contained in the FOOD unless the FOOD source is already part of the common or usual name of the respective ingredient.

Chapter 4 Equipment, Utensils, and Linens

4-602.11

(A) EQUIPMENT FOOD-CONTACT SURFACES and UTENSILS shall be cleaned:

(1) Except as specified in ¶ (B) of this section, before each use with a different type of raw animal FOOD such as beef, FISH, lamb, pork, or POULTRY;

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*"Person in charge" means the individual present at a FOOD ESTABLISHMENT who is responsible for the operation at the time of inspection.

(2) Each time there is a change from working with raw FOODS to working with READY-TO-EAT FOODS;

(3) Between uses with raw fruits and vegetables and with TIME/TEMPERATURE CONTROL FOR SAFETY FOOD;

(4) Before using or storing a FOOD TEMPERATURE MEASURING DEVICE;

(5) At any time during the operation when contamination may have occurred

(B) Subparagraph (A)(1) of this section does not apply if the FOOD-CONTACT SURFACE or UTENSIL is in contact with a succession of different types of raw MEAT and POULTRY each requiring a higher cooking temperature as specified under § 3-401.11 than the previous type.*

* 4-602.11(B) was amended in the 2013 Food Code. It changes the cleaning and sanitizing frequency for food contact surfaces or utensils that are in contact with a raw animal food that is a major food allergen such as fish, followed by other types of raw animal foods. With this change, the exception to existing subparagraph (A)(1) found in ¶ (B) now applies only to raw meat and poultry.

Annex 3 Public Health Reasons/Administrative Guidelines

Restaurant and retail food service managers need to be aware of the serious nature of food allergies, including allergic reactions, anaphylaxis, and death; to know the eight major food allergens; to understand food allergen ingredient identities and labeling; and to avoid cross-contact during food preparation and service. The 2008 Conference of Food Protection (CFP) passed Issue 2008-III-006 which provided that food allergy awareness should be a food safety training duty of the Person in Charge. Accordingly, the Person in Charge's Duties under paragraph (M) were amended to assure the food safety training of employees includes food allergy awareness in order for them to safely perform duties related to food allergies.

9

Research Needs

This report represents the first review by the National Academies of Sciences, Engineering, and Medicine of the field of food allergy. The committee's review identified a broad array of pressing questions that need to be addressed through new research in order to understand the scope and the underlying scientific mechanisms of food allergy; improve the management and treatment of food allergic children and adults and ultimately identify ways to prevent or cure food allergy; and inform policy and regulatory decisions concerning food production, labeling, and marketing. The implementation and vigorous pursuit of such a research agenda will constitute an important component of charting the "roadmap to safety" needed by the food allergic community (see Chapter 10). The following research questions were identified during the work of the committee and are organized to follow the report chapters, rather than according to priorities.

MECHANISMS OF FOOD ALLERGY (CHAPTER 2)

Conducting research related to the mechanistic processes underlying food allergy is essential in making significant advances to develop better methods to prevent disease or reduce its severity; predict, diagnose, and monitor disease; and optimally manage and treat, and ultimately to cure, food allergy. These mechanistic processes include disease predispositions, origins and onset, normal and disordered oral tolerance to foods, factors that contribute to disease severity, and variation in individual responses to different forms of therapy. In exploring mechanisms of action, including mechanisms of food allergy etiology, the committee recognizes the value

of animal models. However, a discussion of the benefits and limitations of using animal models is beyond the scope of this report. The readers are referred to some excellent reviews on the topic (e.g., Bogh et al., 2016; Van Gramberg et al., 2013).

One of the most prominent hypotheses for how food allergy develops—the dual-allergen hypothesis—proposes that environmental exposure to food allergens through the skin early in life can lead to allergy, while consumption of these foods during a developmentally appropriate period early in life results in tolerance. Under this hypothesis, children who avoid allergens in their diet but are still exposed to them in the environment might be more likely to develop an allergy than those not exposed. Supporting this hypothesis are data suggesting that early dietary introduction of peanut products may confer protection against peanut allergy as well as data suggesting that loss of function of filaggrin, a protein important for epithelial structure, confers a risk for food sensitization. However, many questions remain about the mechanisms by which sensitization and tolerance occur and about which elements of the immune system represent the most important contributors to the severity of food allergy or the establishment of tolerance (see Chapter 5). For example, studies have shown that biochemical indicators of tolerance include a reduction in allergen-specific immunoglobulin E (IgE) production, decreased allergen-IgE-induced basophil activation, increased allergen-specific IgG4, and induction of T regulatory (Treg) cells or anergic T cells. However, some of the data are conflicting and more studies are needed to better understand the role of these factors in food allergy.

During the perinatal period, interactions between the developing microbiota and the immune system at the cellular and molecular levels are likely influenced by environmental factors that can, in turn, influence health outcomes. Although the potential relationships between exposure to microbes early in life and the onset of food allergies have been explored, specific changes in the microbial profile of individuals, their particular interactions with the immune system, and how these interactions might be associated with food allergy have not been studied in depth.

To fill gaps in knowledge in this area, studies should be conducted to accomplish the following objectives:

- Elucidate the molecular and cellular mechanisms that account for the differences between innate tolerance versus food sensitization and between food sensitization versus food allergy.
- Identify the mechanisms, in patients with food allergies, for acquiring tolerance to the offending food allergen, without therapeutic intervention, as well as for responding to therapeutic interventions

by developing transient desensitization versus sustained unresponsiveness versus true tolerance to the offending food allergens.
- Define how particular products and functions of mast cells, basophils, and other effector cells can contribute to the signs and symptoms of food allergic reactions, including anaphylaxis, and identify factors that may contribute to individual variation in the pathophysiological responses to such products.
- Study the role of immunoglobulins other than IgE, such as IgG4 or IgA, and of effector cells in addition to mast cells and basophils, in modulating (i.e., enhancing or reducing) food allergic responses.
- Identify and describe the roles of the skin and intestinal barriers in protecting individuals from developing food sensitization or a food allergy, and identify ways in which protective aspects of barrier function can be enhanced and factors that diminish barrier function be reduced.
- Examine the interactions between the microbiota and the host immune system that may favor or protect against the development of a food allergy, and define the extent to which the microbiota or its products can be manipulated to enhance resistance to the development of food allergy.

PREVALENCE AND COST OF FOOD ALLERGIES (CHAPTER 3)

One of the committee's recommendations is to perform well-designed and adequately powered studies to estimate the true prevalence of food allergy (see Chapter 3). In addition, the committee concluded that better methods to collect information about anaphylaxis reactions are needed. Estimates of the various costs of food allergy are needed as well. For example, the Centers for Disease Control and Prevention has developed tools to estimate the costs associated with some chronic diseases, such as arthritis. Medical expenditures for managing food allergy place financial burdens on society, as well as on the individuals affected and their caregivers. Additional costs relate to quality of life, productivity in school or at work, and food recalls. Estimates on cost burden are necessary for prioritizing research and resources, and for effectively advocating for implementation of practices and policies that will reduce those costs. These estimates should include the costs to society, such as those related to health care and productivity losses due to absenteeism, the costs to families and patients in terms of lost quality of life, and costs to the food industry due to food recalls.

The following research needs are warranted to improve data on severe reactions and on cost estimates:

- Evaluate various methods of collecting national data on food allergy severe reactions such as by leveraging the existing surveillance systems (e.g., the National Health and Nutrition Examination Survey or the National Electronic Injury Surveillance System) or by developing a Web-based reporting system for anaphylaxis in the community.
- Collect and analyze data to estimate the economic and social costs of food allergy based on current prevalence of both mild and severe reactions and on objective measures of costs, such as data on medical expenses and time lost from school and work. Collect these data on different ethnicities and socioeconomic strata. The costs to industry due to food recalls and implementation of allergen control strategies also should be estimated.

RESEARCH ON DIAGNOSIS AND PROGNOSIS (CHAPTER 4)

Diagnosis of food allergy is complex, currently requiring expertise in assessing the medical history, understanding allergen cross-reactivity, understanding eliciting factors that may alter reactivity, selecting and interpreting imperfect tests, and possibly conducting a medically supervised oral food challenge (OFC) test. The OFC is currently the best diagnostic test to confirm an allergy, but it is time-consuming, expensive, carries risks (e.g., the risk of triggering an allergic reaction), and is often deferred due to patient and physician concerns. Therefore, the OFC is underused. In addition, commonly available simple allergy tests (serum-specific IgE antibody tests or skin prick tests [SPTs]) have limitations that can result in misdiagnosis, primarily overdiagnosis, requiring procedures such as OFCs to confirm a proper diagnosis. For example, currently available, simple diagnostic tests that are often used to diagnose IgE-mediated food allergies, the serum food-specific IgE test and the SPT, actually diagnose sensitization, not food allergy. A variety of diagnostic tests, such as component resolved diagnostics, the basophil activation test, and many others, are emerging or under study and may better inform diagnosis, prognosis, severity, and threshold.

To fill gaps in knowledge in this area, studies should be conducted to accomplish the following objectives:

- Optimize the currently available diagnostic tests and validate methods, such as OFC (including in special contexts, such as OFC in infants and young children), as well as pursue additional novel tests to improve diagnosis, prognosis, determination of severity of disease, and assessment of antigen thresholds, and to monitor host responses. These tests will be valuable in assessing the effectiveness and durability of interventions, such as immunotherapy. These

studies should include all affected patient populations (ages, sexes, ethnicities, comorbidities, socioeconomic strata), should consider the role of eliciting factors (such as exercise and infections), and also should be assessed in those circumstances where interventions are being applied to the patient (immunotherapeutic strategies as they become available).

- Comprehensively examine the utility, cost-effectiveness of, and barriers to testing, especially regarding the OFC, with a goal of maximizing the use of appropriate tests.
- Examine and assess educational approaches and tools to improve physician and health care provider education about both the natural history of food allergies and the appropriate approaches to use to diagnose food allergies.
- Study the utility of emerging technologies in the area of "omics" methodologies (e.g., genomics, epigenomics, metabolomics). In particular, identify reliable and clinically useful biomarkers for the following important goals:
  - Assessing the severity of a food allergy (e.g., to identify those at high risk for anaphylaxis)
  - Evaluating and monitoring responses to therapy (e.g., immunotherapy)
  - Predicting prognosis (e.g., predicting severity)
  - Identifying populations at risk of developing a food allergy so that they can be included when conducting research on prevention and management strategies and on public health guidelines
  - Diagnosing food allergy in individuals and populations (e.g., for collecting data on prevalence)

RESEARCH ON RISK DETERMINANTS AND PREVENTION (CHAPTER 5)

Considerations for Study Designs

Studies on the etiological factors associated with food allergies frequently present methodological flaws due to various reasons, including lack of accounting for confounding factors (e.g., breastfeeding), use of inaccurate food allergy measures (e.g., self-reporting), or disregard for the fact that different populations (e.g., those at high risk of developing a food allergy) might respond differently to the various risk factors. For example, due to a variety of differential gene-environment factors (e.g., genetics, epigenetics, microbiomes, and other pre- and postnatal environmental factors), populations will respond differently to interventions. Also, the etiology

and early life onset of food allergy seems to be multifactorial, and collecting specimen for future analyses would be advantageous. Future research design on etiological determinants should consider the following:

- Conduct longitudinal birth cohort studies that explore the effects of environmental factors during critical developmental windows (in utero, infancy, and early childhood) on food allergy.
- Couple relevant prenatal, perinatal, and early childhood epidemiological and clinical data with appropriate biospecimen collections (e.g., serum, cord blood, breast milk) for current and future biomarker analyses.
- Design studies so that the responses to various exposures of individuals and populations at high risk and low risk of developing food allergy can be differentiated.
- Use the currently accepted gold standard—double-blind, placebo-controlled OFCs (employing standard dosing protocols and scoring systems, so that the results of various studies can better be compared)—as the food allergy outcome in research intervention studies until a simpler reliable method to measure food allergy is identified and validated.
- Account for the potential influence of confounding factors, in addition to age, sex, and geography, such as breastfeeding, composition of breast milk, dietary intake, other allergic disorders in the patient or family history (particularly atopic dermatitis), genetic susceptibility, presence of dogs or cats in the household, number of siblings, history of antibiotic usage, and exposure to agents or practices that might impair skin barrier function.
- Engage patients or groups representing patients so that research designs may take into consideration potential socio-psychological, cultural, and behavioral considerations.

Overall Research Needs

Many genetic and environmental factors could contribute to the onset of sensitization and to food allergy. For the majority of factors reviewed by the committee, some, but largely insufficient or inconsistent, evidence exists at this time about their association with sensitization or food allergy. Nevertheless, health care providers, patients, and their caregivers still need clear prevention approaches and authoritative and clear public health guidelines. Therefore, research needs to continue to support or refute the contribution of these factors to food sensitization or food allergy. The committee recognizes, though, that for other factors direct or indirect evidence is lacking and research is not currently warranted (e.g., food additives). Although

some public health guidelines have been developed to guide practices of health care providers and individuals, efforts have not been undertaken to assess the impact of such public health guidelines on practices related to food allergy and on prevalence of food allergy. Prospective studies and behavioral research should be conducted to accomplish the following objectives:

- Examine risk factors for food allergies in all populations (ages, sexes, ethnicities, comorbidities, socioeconomic strata), especially in those populations that might have been underrepresented in past research.
- Gain insights about the behaviors of those with (or at risk of) food allergy and their caregivers as well as about the impact of public health guidelines on health care providers and individuals' practices.
- Examine the etiology of the rising prevalence of food allergy within the past two decades, which could identify new targets for allergy prevention and treatment. For example, what changes have occurred in food preparation and consumption behavior in communities and what is their potential relationship to the increase in food allergies? What changes may have occurred in the use of agents (such as detergents) or practices (such as in personal hygiene) that might contribute to impaired skin barrier function?
- Elucidate, through prospective studies, the role of environmental factors and gene-environment interactions in the atopic march and the development of food allergy. For example, do specific factors increase the risk of an individual progressing from eczema to food allergy?
- Explore potentially unidentified risk factors that may influence food allergy. For example, although the data available to date have not shown evidence of a relationship, it is plausible that maternal and early childhood adiposity and metabolic disorders could be risk factors for food allergy development.
- Using prospective birth cohort studies, evaluate the effects of multiple early life factors (individually and in combination) and of possible gene-environmental interactions in the development and prevention of food allergy in order to inform the design of specific randomized controlled trials (RCTs).
- Identify the best practices to engage patients and their families in the planning stages of research studies so that patients' and families' concerns are considered, and assess the value of using these approaches.

Specific Research Needs

In addition, high-quality prospective studies and RCTs are needed on specific risk determinants for which some evidence exists about their effect on food allergy related to the most plausible hypotheses to make meaningful conclusions. These studies should be conducted to accomplish the following objectives:

The Microbial Hypothesis

- Determine, using well-designed prospective studies, the role of mode of birth delivery (vaginal, emergency versus elective cesarean section) and early life microbiome composition on the development of food allergy.
- Assess, through well-designed prospective studies, potential links between food allergy and antibiotic exposure in children (studies should include information on the type, dose, and frequency of antibiotic exposure).
- Determine whether pet ownership is related to food allergy by using well-designed prospective studies.
- Assess, with RCTs, the potential benefits of prebiotics and probiotics to prevent the onset of food allergy.

Allergen Avoidance and Exposure

- Elucidate the relationship, if any, between breastfeeding and the onset of food allergy (may also influence through microbiome modulation) with well-designed prospective studies and take into account the potential effect of differences in breast milk composition.
- Determine, with RCTs, whether consuming or eliminating or avoiding specific allergenic foods during pregnancy and lactation has any benefits.
- Conduct RCTs, similar to the Learning Early About Peanut study, to determine whether early introduction of peanut products has benefit in individuals other than high-risk infants, who were studied in the original trial.
- Examine early introduction of allergenic foods in addition to peanut to determine whether this approach is beneficial in preventing the development of food allergy.

Nutrition Immunomodulation Hypothesis

- Assess, with RCTs, the potential role of specific nutrients, such as vitamin D, folate, or fatty acids, in preventing food allergy.

RESEARCH ON HEALTH CARE SETTINGS AND OTHER SETTINGS (CHAPTERS 6, 7, AND 8)

Health Care Settings

Food allergy management primarily requires avoiding the trigger allergen(s), but this approach requires extreme care; knowledge of cross-contact, hidden ingredients, and the effect of processing; and knowledge of ingredients through label reading and other methods. It is prone to accidents resulting in allergic reactions. Numerous obstacles arise for food-allergic consumers attempting to obtain safe meals outside the home. Surveys among individuals with food allergy, caregivers, and health care providers reveal deficiencies in food allergy knowledge and concerns about accidents, especially among adolescents and young adults. Only limited programs are available for educating individuals, caregivers, and health care providers on strategies to obtain and provide safe meals outside the home, with few validated programs and limited information on implementation. In addition, validated, evidence-based dietary guidance is lacking for those avoiding allergens, such as milk or multiple foods. Knowledge about potential interventions that health professionals could use to improve individual psychosocial status, such as to improve quality of life or alleviate anxiety, also is lacking.

In regard to management, some areas of research need further study. For example, no means are currently available to reliably predict severity of anaphylaxis, which would be valuable for health care providers, individuals with food allergy, and their caregivers. In terms of managing anaphylaxis, underuse of epinephrine, the primary treatment for anaphylaxis, is common but the reasons are unknown. In addition, the fixed doses of epinephrine in auto-injectors may not be appropriate for infants or for individuals with obesity. Also, medications used as primary and adjunctive therapy for anaphylaxis (e.g., epinephrine dosing, bronchodilators, antihistamines, corticosteroids) have not been studied. Standardized emergency plans for individuals that can be used by caregivers at home or school also do not exist.

To address those gaps in knowledge, the following research areas should be pursued on all affected populations (ages, sexes, ethnicities, comorbidities, socioeconomic strata), especially on underrepresented populations:

- Determine the effectiveness of evidence-based guidelines and evidence-based educational programs on food allergy management, including avoidance of allergens and emergency management of allergic reactions and anaphylaxis, for health care providers and for patients, particularly for high-risk groups.
- Assess the following management issues:
  - The effectiveness of approaches other than strict allergen avoidance
  - The role of food allergy in other chronic allergic conditions
  - The identification of means to recognize clinically relevant versus nonrelevant allergen cross-reactivity
- Identify risk factors and biomarkers of food-induced anaphylaxis, particularly to identify individuals at high risk of severe reactions.
- Assess the safety and efficacy of adjunctive therapies for anaphylaxis, especially bronchodilators, antihistamines, and corticosteroids.
- Devise safe and effective therapies for food allergy, including those that can induce long-term desensitization and tolerance (i.e., sustained remission), and ideally a true cure.
- Improve understanding of the nutritional needs of persons on food allergen avoidance diets, how best to determine their need for dietitian evaluation/management, and how to develop evidence-based medical nutrition therapy.
- Evaluate whether consulting with a dietitian or a mental health professional improves quality of life and understand barriers to referring patients to dietitians or mental health professionals.
- Explore the best means to identify and intervene about psychosocial concerns associated with managing food allergy.
- Identify best practices for providing a uniform written emergency action plan for anaphylaxis. Consider using the recent American Academy of Pediatrics guidelines as the reference for a best practice study.
- Determine the proper dose of epinephrine in infants less than 10 kg and in individuals with obesity.
- Characterize risks associated with nonoral allergen exposures (e.g., skin-exposure and inhalation).

Risk Assessment and Factors Affecting Allergic Reactions to Foods

Some allergenic foods have higher potency and cause more severe reactions than do others. Likewise, evidence indicates that changes in proteins during food processing can contribute to their allergenicity, but these changes and their effects are not the same for all allergenic proteins. The relationship between specific protein characteristics (e.g., structure, sensitiv-

ity to heat, and digestibility) and specific processing conditions and potency needs to be elucidated so it can be considered when designing research studies and when prescribing prevention approaches for individuals.

In addition to age and geographical differences, circumstantial factors might modify the severity of a food allergy reaction and the level of allergen needed for a reaction in an individual. The effect of exercise on experiencing a food allergy reaction has been reported and it is well recognized. However, for other factors, such as alcohol or medication use, biological cycles, psychological factors, stress, and concomitant allergen exposures, anecdotes are the main source of information. Identifying the factors that can modify the severity of allergic reactions and defining their influence on whether an allergic reaction is experienced upon exposure to a food allergen or in changing the specific eliciting dose are key pieces of information needed to provide advice to individual patients (see Chapters 6 and 7).

To fill gaps in knowledge in this area, studies should be conducted to accomplish the following objectives:

- Strengthen current knowledge about: food allergen risk assessment and management, including continued assessment of threshold doses for individual allergens; single dose oral challenges for confirmation of threshold doses; the development, application, and improvement of parametric dose-distribution modeling approaches for allergen risk assessment; food consumption patterns of food-allergic populations; and improved methods for detecting allergen residues in food matrices.
- Study the mechanisms that make some food proteins more allergenic than others and the effects of food processing methods and other ingredients on their allergenicity and thresholds.
- Study the possible effects of augmentation factors on threshold doses (e.g., exercise, alcohol) or on modifying the severity of reactions, and the mechanisms underlying such effects.

Managing Food Allergies in Food Establishments, Food Service, Schools, and When Traveling

Allergic reactions occur among children attending early care and education settings, schools, camps, or college, as well as among children and adults while traveling or eating at a food establishment and may include persons without a prior diagnosis. Although anecdotal reports describe severe reactions, well-documented estimates of such reactions in each setting are not available. Also, although federal and local policies exist, such as the Food and Drug Administration (FDA) Food Code, no studies have been conducted on the extent to which regulatory policies have been imple-

mented and the impact of those policies on management or prevalence of food allergy.

The obstacles for consumers with food allergy in restaurants, food establishments, and during travel include lack of communication between the consumer and staff and lack of knowledge about ensuring safety for consumers with food allergies. Limited programs exist for education and more studies are needed to create and validate food allergy educational materials and programs.

Best practices for managing food allergies in settings of concern where food is served have not been studied. For example, management plans for food allergy in early care and education settings, schools, camps, or other places where children are served food include providing instructions for safe meals, recognizing and managing reactions, and assigning roles and responsibilities. These plans require different strategies according to age of the child, skill level of the supervising adults, and cultural or socioeconomic context, but these factors have not been extensively studied and a paucity of data exist upon which to base best practices.

To fill gaps in knowledge in this area, studies should be conducted to accomplish the following objectives:

- Monitor the number of food allergic reactions that occur in various settings where food is served, particularly in early care and education settings, schools, camps, and food establishments, and in additional settings of concern, including restaurants, cafeterias, grocery stores, and commercial airliners (or other commercial means of travel).
- Monitor the degree to which states adhere to the FDA Food Code and other laws and regulations with a food allergy component (e.g., the number of children with individualized education programs[1] due to food allergy) so that best practices are developed and their effectiveness in the prevention of severe reactions and management of food allergies is evaluated.
- Define best practices regarding food allergy management (e.g., epinephrine storage) at settings where food is served, particularly in early care and education settings, schools, camps, and food establishments in additional settings of concern, including restaurants, cafeterias, grocery stores, and commercial airliners (or other

[1] In public schools, students with a disability may qualify for Individualized Education Program, under federal special education funding through the Individuals with Disabilities Education Act (IDEA) of 1975, and may receive special education and related services. See more at: http://www.foodallergyawareness.org/civil-rights-advocacy/schools-2/individualized_education_program_(iep)-2/#sthash.F4dKKnbV.dpuf (accessed January 6, 2017).

commercial means of travel). The experiences of other countries where management practices have been standardized should be considered.

- Develop and implement evidence-based, effective training programs for relevant personnel at settings where food is served particularly in early care and education settings, schools, camps, and food establishments in additional settings of concern, including restaurants, cafeterias, grocery stores, and commercial airliners (or other commercial means of travel). The experiences of other countries where effective training programs have been standardized should be considered.
- Identify and explain risks associated with environmental exposures to food allergens through skin contact or inhalation.

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10

Final Comments: A Roadmap to Safety

Food allergy is an important chronic disease that can occur in any age group but mainly affects infants and children, some of our most vulnerable populations. For individuals with food allergy and caregivers, food allergy has effects that extend beyond health to quality of life. Food allergy can be life threatening. It has been estimated to cost an overall $24.8 billion annually, including direct medical costs and other costs borne by the family (Gupta et al., 2013). Despite these concerns and general awareness among some in the public, the nation as a whole has not yet devoted adequate resources and efforts to address this important chronic disease.

As explained in Chapter 1, the committee was not charged with developing clinical guidelines but, where appropriate, it states its support for clinical guidelines and recommends that health care providers follow guidelines as they are updated with scientific evidence. The committee was tasked with the following: developing a framework for future directions in understanding food allergy and its impact on individuals, families, and communities; recommending steps to increase public awareness of food allergy; promoting research on both disease causation and management; and informing preventive approaches to food allergy. In their deliberations and recommendations, the committee greatly benefited from information gathered during public sessions, and it is particularly grateful to the advisory panel that so generously came to public meetings and provided their unique perspectives and expectations. Although obviously a cure for food allergies will not result from a scientific report, this committee hopes that its recommendations will generate the ideas and incentives to promote the research needed for an eventual cure. Until that happens, many policies,

practices, and behaviors could be changed to substantially improve food safety, which would enhance the health and quality of life of individuals with food allergy and their caregivers and save lives. The committee's review of information in leading journals and through the public sessions has underscored the conclusion that solutions are not the responsibility of individuals with food allergy and their caregivers alone. Solutions to food allergy and a roadmap to greater safety will emerge from the efforts of many stakeholders working collaboratively toward the same unifying goal of managing food allergies, and, ultimately, developing safe, effective therapies.

IMPLICATIONS OF AN ECOLOGICAL-DEVELOPMENTAL MODEL

In its consideration of the evidence and recommendations for a roadmap to greater safety, the committee adopted an ecological-developmental perspective (see Figure 10-1). This approach had multiple implications for the work of the committee in delineating the issues, organizing the evidence, drawing conclusions, and making recommendations, and for multifaceted efforts to communicate their conclusions. This perspective underscores the importance of a multidisciplinary and multisystem approach to evaluating the evidence and forming recommendations, calling on the viewpoints of experts and stakeholders representing a range of ecological contexts.

An ecological-developmental model highlights the importance of *developmental timing,* both for exposures and also for safety planning. The committee considered distinct issues focused on the different developmental periods—prenatal, infancy, early childhood, primary school-age, adolescence, adulthood, and older years. The nature of the human organism changes during each of these periods of development, affecting vulnerability to food allergy (see Chapter 5). The nature of the food context changes as well, for an individual does not control his or her food intake during the very early stages of life. Choices by parents and caregivers, as well as the quality and type of food available will be crucial. Later on in development, children not only will have more choices in what they eat and be less influenced by the restrictions posed on them earlier in life. They also will be more influenced by contexts outside the family, including peers, schools, social media, and mass media (see Chapter 8). The roles of families and schools also are influenced by the food industry, dietary recommendations by health care providers and informal "experts," as well as by policies about food allergy from the community, culture, or government. Thus, in prenatal development and early life, key contexts for addressing food allergy include the immediate prenatal environment of the mother, caregiving, home, and early care and education settings, and the larger contextual environments comprising health care provider advice, policies for food

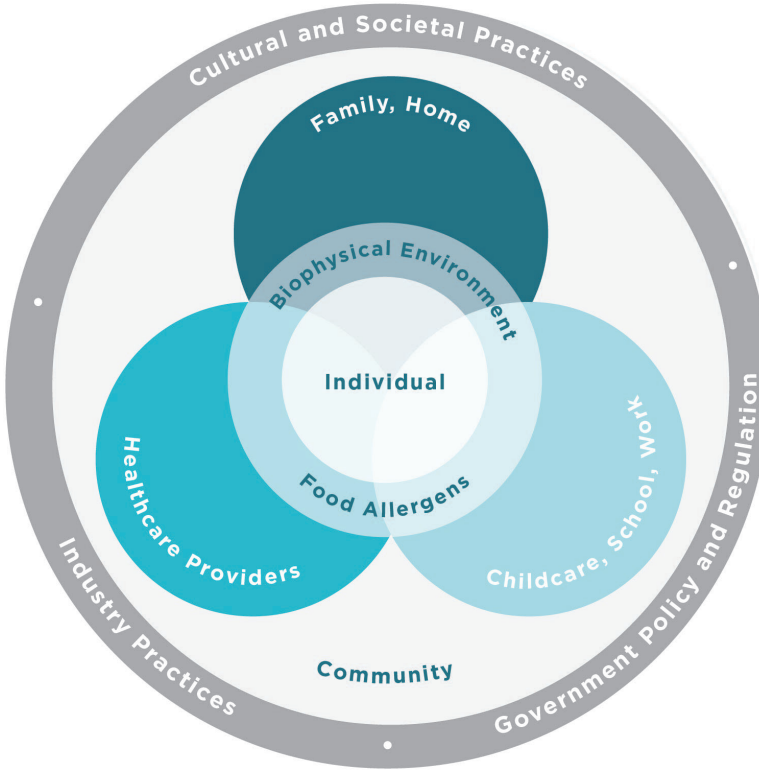

FIGURE 10-1 Ecological-developmental model for food allergies. Different systems that an individual interacts with are depicted as proximal (e.g., food, biophysical environment) and distal (e.g., industry, government).
NOTES: **Industry practices** refers to all the manufacturing processes and allergen control plans followed during food production, distribution, preparation or cooking, and serving. They also refer to mandatory and voluntary labeling of food allergens and to recall procedures followed when a product is contaminated with a food allergen. **Cultural and societal practices** refer to the particular diets and foods of regions and countries. **Biophysical environment** refers to the external proximal environment (e.g., air) while **Individual** refers to all systems internal to a developing human, including genome, epigenome, proteome, metabolome, central nervous system, immune system, microbiomes, and many other self-regulatory systems involved in adaptation and sustaining life. **Health care providers** include the persons (e.g., physicians, dieticians) and the institutions that protect individual and public health. **Child care, school, work** includes all proximal settings that interact with an individual at different life stages. Finally, **family, home** refers to the system of people, relationships, routines, and practices occurring at home. Interactions (e.g., communication, physical contact) occur between and among all those systems and the individual to support (or not) food safety.

allergy safety in early care and education settings, the food industry, and societal policies. Later in life, individuals need knowledge and skills to make their own choices pertinent to food allergy in the broad contexts of everyday life, including schools, workplaces, playgrounds and recreational settings, restaurants, and transportation systems (Chapters 7 and 8).

THE ROADMAP TO SAFETY

Although it is not yet possible to prevent the onset of food allergy (due to lack of a clear understanding of all the relevant genetic and environmental factors) or completely prevent food allergic reactions, multiple improvements could be achieved in the short term with relatively small feasible actions.

The committee conceptualized the answers to the statement of task as articulating a roadmap to safety with key actions (see Figure 10-2). In mapping the road to greater public safety regarding food allergy, it is essential to recognize the roles of multiple systems (and their actors within) at multiple organizational levels in private and public life and their complex interactions, as depicted in Figure 10-1. The committee selected specific settings (and their interactions with others, such as governments or health providers) for their relevance to safety in food allergy: food establishments, early care and education settings, schools, higher education, and the travel industry. In its review, the committee found deficiencies in existing practices or policies in these various settings. Likewise, lack of information or misinformation among the general public and even individuals with food allergy themselves need to be amended. Presentations from the advisory panel to the committee and published statements from individuals with food allergy or their caregivers (see Chapter 1) corroborate the committee's findings related to these deficiencies.

The committee's roadmap to safety consists of a multifaceted undertaking that involves the effort of many stakeholders in the different arenas and includes the following actions: (1) obtain accurate prevalence estimates, (2) use proper diagnostic methods and provide evidence-based health care, (3) identify evidence-based prevention approaches, (4) improve education and training of all stakeholders, including health care providers, individuals with food allergy, caregivers, food industry leaders and employers, and others, (5) implement improved policies and practices that prevent and treat severe reactions, and (6) expand research programs related to better diagnostics, effective management and prevention practices, including food allergy therapies and attempts to devise a cure.

The first major action on the road to greater safety is collecting better information about prevalence. Reliable data on the prevalence of food allergy are crucial to inform further advances in food allergy safety and also

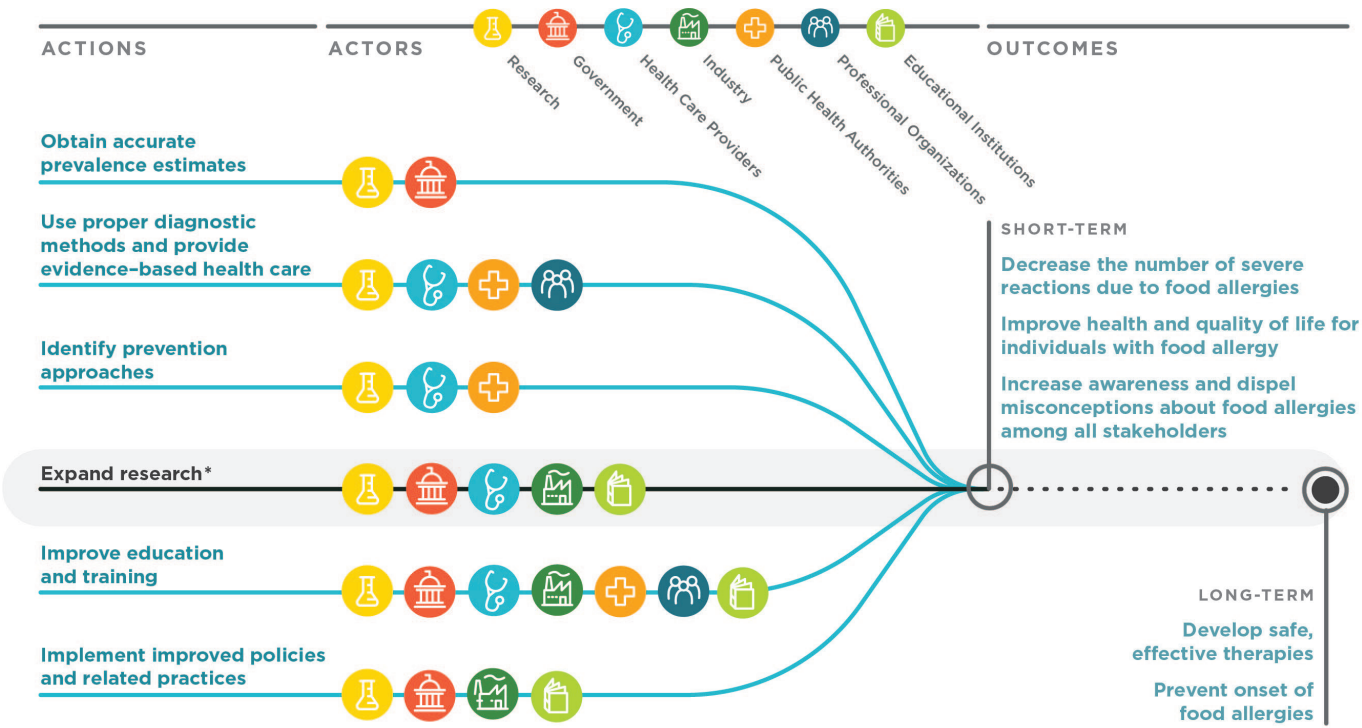

FIGURE 10-2 Roadmap to food allergy safety in six actions.
*Research is needed to achieve all other actions and to reach the short- and long-term goals (see Chapter 9 for all specific areas of research). The actors represent the primary stakeholders that will be involved in implementing the actions.

to prioritize food allergies in the context of other public health diseases. Prevalence data also are crucial to define the major allergens and to explore risk factors that might differentially affect specific populations. With this in mind, the committee has recommended collecting food allergy prevalence data in a systematic manner.

The second major action on the road to safety is improving the quality of diagnosis and providing evidence-based health care. As recently articulated by the National Academies of Sciences, Engineering, and Medicine report *Improving Diagnosis in Health Care* (NASEM, 2015), getting the right diagnosis is a key aspect of health care, informing all subsequent health care decisions. That report recognizes that "diagnostic errors can lead to negative health outcomes, psychological distress, and financial costs" and possibly inappropriate or unnecessary treatment (NASEM, 2015, p. 19). In the context of food allergy, proper diagnosis is a challenging activity. It is, however, particularly important given the many misunderstandings about food allergy and the consequences, including death, of a misdiagnosis. Therefore, the committee recommends proper use of current diagnostic methods and identification of better methods in the future.

The third action is defining evidence-based prevention approaches. Many hypotheses have been proposed to explain food allergy etiology (e.g., microbial hypothesis, dual-exposure hypothesis) but none is confirmed yet. Because of their importance in designing prevention approaches, particularly for individuals who carry a genetic predisposition, the committee concluded that understanding the risk determinants is another important element of the road to safety. In this regard, the committee recommends that guidelines be updated with emerging scientific findings. Also, recognizing the weaknesses in current studies and the inconsistencies in findings, the committee outlined research needs related to specific risk determinants and made recommendations for improving study designs, including expanding study participant populations to include all ages, ethnicities, and socioeconomic strata.

The fourth action to greater safety, the committee concluded, is improved education and training of all stakeholders, including health care providers, industry leaders, and employers as appropriate, in recognizing and managing the disease and/or preventing severe reactions. On the one hand, public health and clinical guidelines already exist on how to diagnose, prevent, and manage food allergy (e.g., Guidelines supported by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health and published by the American Academy of Allergy, Asthma & Immunology). These Guidelines should continue to be updated as new information emerges. The Guidelines are not only meant for all health care providers but also include valuable information for individuals with food allergy and their caregivers as they attempt to manage food allergy in their

homes and various settings. Updating the Guidelines as soon as relevant information emerges is an essential action to prevent and treat reactions. On the other hand, little information is available on the extent to which these evidence-based clinical and public health guidelines are used by health care providers and others. In this digital age, consumers rely on sources of information other that the health care providers, augmenting the possibilities for misunderstanding about a chronic disease for which fundamental data are still emerging. For this reason, it becomes even more important that advice from the health care providers is clear and consistent and based on the most current scientific findings.

Guidelines also are essential for other stakeholders. For example, existing government-led guidelines for early care and education centers and schools (e.g., CDC, 2013) provide excellent starting points for preventing allergic reactions in those settings. Likewise, industry-led guidelines for the food manufacturing (GMA, 2009) or food retail (FMI, 2016) industry as well as training curricula (NRA, 2016) for food service establishments have been developed. Although the committee did not review these food industry guidelines, such guidelines, when complete and scientifically based, can assist industry personnel in understanding food allergy, controlling food allergen cross-contact contamination, and communicating with consumers about their allergies and potential risks. The guidelines for early care and education programs and schools or for the food industry represent best current practices and were developed based on the sound judgement of experts and current scientific knowledge. They are a key component for minimizing risks in settings of concern.

Training in food allergy and appropriate preventive emergency response actions is another critical action to this component of the roadmap to safety. When severe food allergy reactions occur due to accidents, insufficient or inappropriate responses can lead to unnecessary loss of lives. It is well known among the medical community that epinephrine is a safe, adequate treatment for anaphylaxis. However, epinephrine is not always used due to lack of availability, lack of knowledge about on how to administer, or unfounded safety concerns. More extensive emergency training is needed for many more in the community. It is obvious, that although it will not be possible to prevent all severe food allergy reactions for all individuals, much more could be done to decrease the current burden. Overall, the committee concluded that a fundamental need exists to train many stakeholders (e.g., health care providers, industry, consumers at risk, and ultimately the general public) on how to prevent and treat severe food allergy reactions.

The fifth important action is to develop and implement policies and related practices that help to prevent and to properly treat severe reactions. Among them, improved labeling is highlighted by the committee as a key action not only to improve risk communication and safety for consumers,

but also to assist the food industry with applying a labeling system for food products that is based on risk. The implementation of the mandatory labeling rule Food Allergen Labeling and Consumer Protection Act of 2004 and the 2013 Food and Drug Administration Food Code, which provides advice from the Food and Drug Administration (FDA) for uniform systems and practices that address the safety of food sold in food establishments, serves to protect the consumer from severe reactions. Yet, in other important areas, such as preventing the possibility of cross-contamination during food processing, no regulation has been enacted that aims to protect consumers by providing them with information about potential risks. The current voluntary labeling of packaged foods that warns consumers of potential contamination (e.g., "may contain X") has resulted only in confusion for consumers and industry alike and bears no relationship to risk. In this regard, the committee recommends that the food industry and federal government work together toward a risk-based labeling system. Adoption of the FDA Food Code by all states is another important policy recommendation. The 2013 FDA Food Code includes provisions on preventing food allergic reactions but it has not been adopted by all states.

Additional policies highlighted by the committee focus on safety at settings of concern such as early care and education centers and school settings, from early childhood preschool through college or university. The committee recognized the need to ensure that appropriate guidance and education is in place to create a safe public environment for individuals with food allergy. To that effect, the committee recommends that relevant federal agencies (e.g., the FDA, the Centers for Disease Control and Prevention, the Federal Aviation Administration) convene a special task force to establish and implement policy guidelines.

Finally and critical to future improvements in food allergy safety, the committee has identified a list of research priorities as the sixth action in the road to safety. Key questions about diagnostics, mechanisms, risk determinants, and management require greater research efforts. The committee recommends priorities for research based on those that showed promise for advancing and refining management approaches, including the development of safe and effective therapies and, ultimately, a cure.

As a whole, this report, including its conclusions and recommendations, is intended to provide a roadmap to greater safety for individuals with food allergy, for stakeholders at multiple levels, in families, communities, industries, and the nation as a whole. Although more research is needed, the committee concluded that sufficient evidence is available now to guide these stakeholders to make changes and take actions toward greater safety that will improve the health and quality of life of many individuals with food allergy, and all those who have a stake in their health and well-being. In general, stakeholders in charge of implementing recommendations

should consider the experiences of other countries where management practices (e.g., training of stakeholders or developing anaphylaxis plans) have been standardized.

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NASEM (National Academies of Sciences, Engineering, and Medicine). 2015. *Improving diagnosis in health care*. Washington, DC: The National Academies Press.

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Appendix A

Open Session Agendas

The committee held data-gathering sessions that were open to the public in Washington, DC, on June 22, 2015, and August 31-September 1, 2015. The open session agendas for the public meetings and a workshop are presented below:

Committee on Food Allergies: Global Burden, Causes, Treatment, Prevention, and Public Policy

Keck Center of the National Academies
500 Fifth Street NW, Washington, DC
Room 201

MONDAY, JUNE 22, 2015

OPEN SESSION

11:30-11:35 a.m. Welcome and Introductions
Virginia Stallings and Committee

11:35 a.m.-12:30 p.m.	**Sponsor Perspectives on the Study** *Mary Jane Marchisotto, Food Allergy Research & Education* *Stefano Luccioli & Patricia Hansen, Center for Food Safety and Applied Nutrition, Food and Drug Administration* *Daniel Rotrosen, National Institute of Allergy and Infectious Diseases, National Institutes of Health* *Charlsia Fortner, Food and Nutrition Service, U.S. Department of Agriculture* *Bob Parker, National Peanut Board*
12:30-1:30	Lunch Break Cafeteria on the Third Floor
1:30-2:30	**Sponsor Perspectives on the Study** *Tia Rains, Egg Nutrition Center* *Barbara Blakistone, National Fisheries Institute* *Ari Mayer Mackler, International Tree Nut Council Nutrition Research & Education* *Jill Nicholls, National Dairy Council* *Alison Kretser, International Life Sciences Institute North America* *Meryl Bloomrosen, Asthma and Allergy Foundation of America*
2:30-3:00	Questions from the Committee
3:00-3:15	Break
3:15-3:30	Discussion with Advisory Panel *Bryan Bunning* *Monika Biller Harris* *Dan Cicero* *Karen Hemmerdinger* *Jill Mindlin* *Caroline Moassessi* *Karin Tegila*
3:30 p.m.	End of Open Session

Committee on Food Allergies: Global Burden, Causes, Treatment, Prevention, and Public Policy

Public Workshop
August 31-September 1, 2015

Keck Center of the National Academies
500 Fifth Street NW, Washington, DC
Room 100

Workshop Goals

- Review current knowledge, research, and trends in food allergy
- Explore strategies for understanding, measuring, preventing, and diagnosing food allergy
- Identify public settings of concern for individuals with food allergy
- Evaluate approaches to address the unique needs and challenges of individuals with food allergy
- Discuss existing food allergy legislation and regulatory issues

MONDAY, AUGUST 31, 2015

12:15-12:40 p.m. Registration and Check-In

12:40-12:45 Welcome Remarks
Virginia Stallings, Committee Chair

Session I: Context, Basic Mechanisms, and Diagnostics
Moderator: Stephen Galli

12:45-1:05 Food Allergies in Socioecological Contexts of Human Adaptation and Development
Ann Masten, University of Minnesota

1:05-1:35 Mechanisms of Food Allergy
Wayne Shreffler, Massachusetts General Hospital

1:35-1:55	Cellular and Molecular Diagnostics and Prognostics in Food Allergy *Kari Nadeau, Stanford University School of Medicine*
1:55-2:10	Panel Discussion
	Session II: Early Determinants of Food Allergy Moderator: Anna Maria Siega-Riz
2:10-2:30	Genetic and Epigenetics Effects for Allergy-Related Diseases and Traits *Liming Liang, Harvard School of Public Health*
2:30-2:50	Infant Gut Microbial Markers of Food Sensitization at Age 1 *Anita Kozyrskyj, Pediatrics, University of Alberta*
2:50-3:10	Nutritional and Lifestyle Early Life Determinants *Katie Allen, Murdoch Children's Research Institute*
3:10-3:30	Panel Discussions
3:30-3:50	Break
	Session III: Prevention and Urgent Care of Food Allergy Moderator: Hugh Sampson
3:50-4:25	Food Allergy Prevention (Peanuts) *Gideon Lack, King's College London/St. Thomas' Hospital*
4:25-4:45	Research on Early Introduction of Hen's Egg and Cow's Milk *Johanna Bellach, Charité Hospital, University of Berlin*
4:45-5:05	Emergency Anaphylaxis Management: Opportunities for Improvement *Ronna Campbell, Mayo Clinic*
5:05-5:25	Panel Discussion
5:25 p.m.	Adjourn

TUESDAY, SEPTEMBER 1, 2015

7:30-7:55 a.m.	Coffee, Tea, and Juice Served
7:55-8:00	Welcome Remarks *Virginia Stallings, Committee Chair*
	Session IV: International Perspectives Moderator: Virginia Stallings
8:00-8:25	Food Allergy in Japan *Motohiro Ebisawa, World Allergy Organization/ Sagamihara National Hospital*
8:25-8:50	Management of Food Allergy in Europe—an Overview Using Germany as an Example *Johanna Bellach, Charité University Hospital Berlin*
8:50-9:15	Food Allergies in Australia/Food Advisory Labeling *Katie Allen, Murdoch Children's Research Institute*
9:15-9:35	Break
	Session V: Patient-Centered Concerns Moderator: Scott Sicherer
9:35-9:55	Reimbursement/Insurance *Paul Campbell, Amplify Public Affairs*
9:55-10:15	Causes, Treatment, Prevention, and Public Policy: A Psychological Perspective on Food Allergy *Audrey DunnGalvin, University College Cork*
10:15-10:35	Primary Care Management of Food Allergy and General Public Knowledge and Beliefs *Ruchi Gupta, Northwestern University Feinberg School of Medicine; Ann & Robert H. Lurie Children's Hospital of Chicago*
10:35-10:55	Challenges in Managing Food Allergy in Vulnerable Groups *Hemant Sharma, Children's National Medical Center*

10:55-11:25	Dietary Intake and Nutritional Status *Marion Groetch, Jaffe Food Allergy Institute, Icahn School of Medicine at Mount Sinai*
11:25-11:55	Panel Discussion
11:55 a.m- 12:55 p.m.	Lunch Cafeteria on Third Floor

Session VI: Food Industry and Regulatory Environment
Moderator: Stephen Taylor

12:55-1:15	Bioguided Food Processing *Bruce German, University of California*
1:15-1:35	State and National Policymaking on Food Allergies: Changes Sweeping (some of) the Nation *Lynn Morrison, Washington Health Advocates*
1:35-1:55	Assessing Risks of Exposure to Allergens from Foods *Joe Baumert, University of Nebraska*
1:55-2:15	The Allergen Journey: Developing Best Practice Solutions for Industry *Sue Estes, Pepsico*
2:15-2:45	Practical Regulatory Issues *Steven Gendel, IEH Laboratories and Consulting Group*
2:45-3:15	Panel Discussion
3:15-3:30	Break

Session VII: Public Settings of Concern
Moderator: Wesley Burks

3:30-3:50	Food Allergy Management in the School Setting *Sally Schoessler, Allergy and Asthma Network*
3:50-4:10	Food Allergies in Higher Education

	Lindsay Haas, University of Michigan
4:10-4:30	Food Allergies: Bridging the Accommodation Gap in Food Service *David Crownover, National Restaurant Association*
4:30-4:50	Food Marketing/Retail *Hilary Thesmar, Food Marketing Institute*
4:50-5:10	Flying with Food Allergies: Concerns and Opportunities *Laurel Francoeur, Attorney and Food Allergy Advocate*
5:10-5:40	Panel Discussion
5:40-6:00	Public Comment *Karin Teglia* *Bryan Bunning* *Lianne Mandelbaum* *Kristen Spotz* *Rachel Clark* *Scott Riccio* *Meryl Bloomrosen*
6:00 p.m.	Closing Remarks and Adjourn *Virginia Stallings*

Appendix B

Food Allergy Prevalence Literature Search Strategy

Two literature searches were conducted to assess the current prevalence of food allergy both nationally and internationally, including overall population prevalence, food-induced anaphylaxis, and the prevalence of allergy to specific foods. The searches were conducted in the online databases Medline and EMBASE and were not limited by country. Peanut, nut, milk, wheat, egg, soy, fish, shellfish, and sesame were included in the initial search. An additional search was conducted that included the previous foods as well as specific types of fish (tuna, salmon, cod), molluscs (clams), nuts (almond, macadamia nut, Brazil nut, pecan, cashew, pine nut, chestnut, pistachio, hazelnut, walnut), seeds (sesame, mustard, sunflower, poppy, pumpkin), coconut, litchi, lupin, fruits, and vegetables. Articles were excluded if they were written in a language other than English, had nonhuman subjects, or were case studies/series, notes, conference abstracts, nonsystematic reviews, or opinion pieces. The searches yielded 767 unduplicated articles. The abstracts of these articles were then screened for food allergy or anaphylaxis population prevalence estimates. Of these, 707 articles did not provide an estimate and were excluded, leaving 60 articles for full text review. These were supplemented by 13 articles suggested by committee members or found through reference mining. This process is illustrated in Figure B-1, and the search terms used are listed in Tables B-1 and B-2. A summary of studies that reported prevalence of food allergy is found in Table B-3. Summary tables of systematic reviews on the prevalence of food allergy are found in Table B-4.

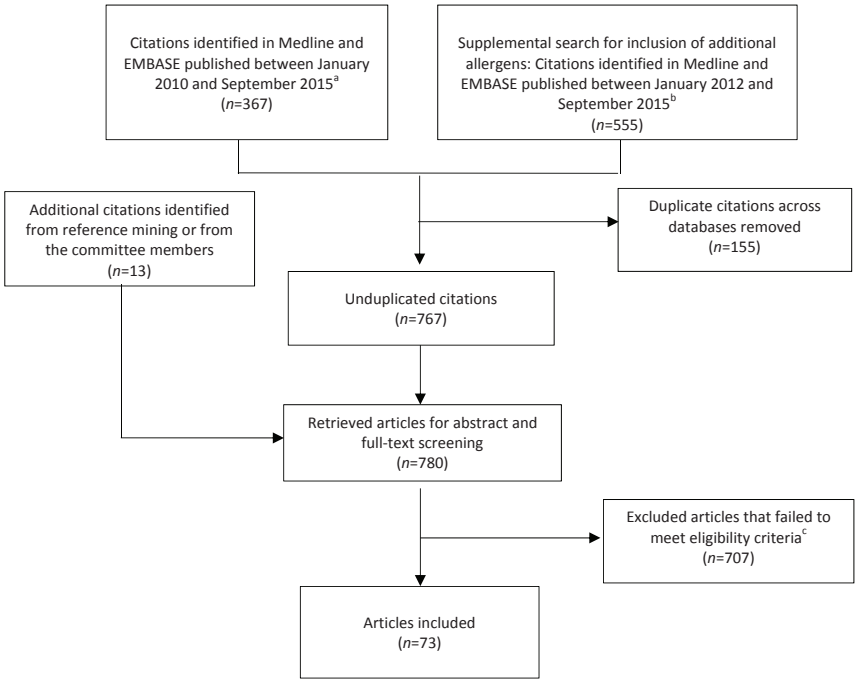

FIGURE B-1 Literature search and selection process.

[a] Search was designed to capture studies measuring the prevalence of food allergy and anaphylaxis to peanut, nut, milk, wheat, egg, soy, fish, shellfish, or sesame, and was not limited by country.

[b] Supplemental search was designed to capture studies measuring the prevalence of food allergy and anaphylaxis to additional allergens not included in initial search (see text for complete list) and was not limited by country.

[c] Articles were excluded if they did not give food allergy or anaphylaxis population prevalence estimates.

TABLE B-1 Search Terms to Identify Relevant Literature on Global Prevalence of Food Allergy for Medline and EMBASE

Search Number	Search Terms
	a. Medline Search
1	Food hypersensitivity/
2	Peanut hypersensitivity/
3	Nut hypersensitivity/
4	Milk hypersensitivity/
5	Wheat hypersensitivity/
6	Egg hypersensitivity/
7	Soybean allergy.mp
8	Soy allergy.mp
9	Fish allergy.mp
10	Shellfish allergy.mp
11	Sesame allergy.mp
12	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13	Prevalence/
14	Anaphylaxis/
15	Life threatening food allergy.mp
16	13 or 14 or 15
17	12 and 16
	b. EMBASE Search
1	Food allergy/
2	Food allergen/
3	Peanut allergy/
4	Nut allergy/
5	Milk allergy/
6	Wheat allergy/
7	Egg allergy/
8	Soy allergy.mp
9	Soybean allergy.mp
10	Fish allergy.mp
11	Shellfish allergy.mp
12	Sesame allergy.mp
13	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14	Prevalence/
15	Anaphylaxis/
16	Food allergy prevalence.mp
17	Life threatening food allergy.mp
18	14 or 15 or 16 or 17
19	13 and 18

NOTES: Search terms were mapped to Subject Headings when available; otherwise searched as Keyword (.mp). Searches limited to 2010 to Current.

TABLE B-2 Search Terms to Identify Relevant Literature on Global Prevalence of Food Allergy to Additional Allergens for Medline and EMBASE

Search Numbers	Search Terms
	a. Medline
1	Prevalence/
2	limit 1 to (English language and humans and yr="2012 -Current")
3	Incidence/
4	limit 3 to (English language and humans and yr="2012 -Current")
5	Hypersensitivity/
6	limit 5 to (English language and humans and yr="2012 -Current")
7	Food Hypersensitivity/
8	limit 7 to (English language and humans and yr="2012 -Current")
9	Skin Tests/
10	Immunoglobulin E/
11	2 or 4
12	6 or 8 or 9 or 10
13	11 and 12
14	Milk/
15	13 and 14
16	Egg Hypersensitivity/
17	13 and 16
18	Milk Hypersensitivity/
19	13 and 18
20	Fishes/
21	Tuna/
22	Salmon/
23	Gadiformes/
24	20 or 21 or 22 or 23
25	13 and 24
26	Nut Hypersensitivity/
27	Prunus/
28	Macadamia/
29	Bertholletia/
30	Carya/

TABLE B-2 Continued

Search Numbers	Search Terms
31	Anacardium/
32	Nuts/
33	Pistacia/
34	Corylus/
35	Juglans/
36	pine nut.mp.
37	chestnut.mp.
38	26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37
39	13 and 38
40	Peanut Hypersensitivity/
41	13 and 40
42	Wheat Hypersensitivity/
43	13 and 42
44	Soybeans/
45	13 and 44
46	Seeds/
47	Sesamum/
48	Mustard Plant/
49	Helianthus/
50	Papaver/
51	Cucurbita/
52	46 or 47 or 48 or 49 or 50 or 51
53	13 and 52
54	Cocos/
55	13 and 54
56	Litchi/
57	13 and 56
58	Lupinus/
59	13 and 58
60	Fruit/
61	Vegetables/
62	Fragaria/

continued

TABLE B-2 Continued

Search Numbers	Search Terms
63	60 or 61 or 62
64	13 and 63
65	Mollusca/
66	Bivalvia/
67	65 or 66
68	13 and 67
	Results from 15, 17, 19, 25, 39, 41, 43, 45, 53, 55, 57, 59, 64, and 68 combined
	b. EMBASE Search
1	Prevalence/
2	limit 1 to (human and English language and yr="2012 -Current")
3	incidence/
4	limit 3 to (human and English language and yr="2012 -Current")
5	hypersensitivity/
6	limit 5 to (human and English language and yr="2012 -Current")
7	food allergy/
8	limit 7 to (human and English language and yr="2012 -Current")
9	skin test/
10	immunoglobulin E/
11	2 or 4
12	6 or 8 or 9 or 10
13	11 and 12
14	milk allergy/
15	egg allergy/
16	fish/
17	salmon/
18	tuna/
19	Atlantic cod/
20	Crustacea/
21	shellfish/
22	shrimp/
23	lobster/
24	crab/
25	mollusc/

TABLE B-2 Continued

Search Numbers	Search Terms
26	clam/
27	nut allergy/
28	almond/
29	Macadamia/
30	Brazil nut/
31	pecan/
32	cashew nut/
33	pine nut.mp.
34	chestnut/
35	hazelnut/
36	pistachio/
37	walnut/
38	peanut allergy/
39	wheat allergy/
40	soybean/
41	plant seed/
42	sunflower/
43	sesame/
44	Papaver/
45	mustard/
46	squash/
47	coconut/
48	lychee/
49	lupin/
50	fruit/
51	vegetable/
52	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51
53	13 and 52

NOTES: Search terms were mapped to Subject Headings when available; otherwise searched as Keyword (.mp). Searches limited to human studies, English language, and published 2012 to Current.

TABLE B-3 Summary of Food Allergy Prevalence Studies

Reference	Country	Study Design	Number Invited or Eligible Participants	Participation Rate N (%)
Grabenhenrich et al., 2016	Europe	Cross-sectional	N/A	1,970 (reports of anaphylaxis)
McGowan et al., 2016	US	Cross-sectional	N/A	NHANES III (1988-1994): 4,995 NHANES (2005-2006): 2,901
Xepapadaki et al., 2016	Europe	Cohort	12,049	9,336 (77%)
Datema et al., 2015	Europe	Cross-sectional	Not indicated	731
Le et al., 2015	Europe (The Netherlands)	Cross-sectional	6,600	3,864 (59%)

Age of Participants	Food Allergens	Method of Outcome Assessment	Estimated Prevalence of Food Allergy, % (95% CI)
<18 years	Hen egg, cow milk, nuts	Report of anaphylaxis in the European Anaphylaxis Registry	Food-related anaphylaxis: 66% of reports
6-19 years	Peanut, milk, egg, shrimp	sIgE	Food sensitization NHANES III: 24.3 (22.1-26.5) NHANES 2005-2006: 21.6 (19.5-23.7) Shrimp sensitization NHANES III: 11.2 (10.0-12.5) NHANES 2005-2006: 6.1 (4.5-7.7)
2 years	Hen egg	sIgE, SPT, DBPCOFC	Mean raw incidence: 0.84 (0.67-1.03) Adjusted mean incidence: 1.23 (0.98-1.51) (Adjusted for eligible children who were not challenged)
Mean age: 32.3 ± 14.8 (SD) years	Hazelnut	SPT sIgE DBPCOFC (N=124)	77.4 83.7 70.2
20-54 years	Hen egg, cow milk, peanut, hazelnut, celery, apple, peach, fish, or shrimp	Self-report Clinical evaluation, medical history, sIgE DBPCOFC	10.8 4.1 3.2

continued

TABLE B-3 Continued

Reference	Country	Study Design	Number Invited or Eligible Participants	Participation Rate N (%)
Schoemaker et al., 2015	Europe	Cohort	12,049	9,336 (77%) 358 eligible for DBPCOFC; 248 agreed to at least 1 challenge
Soller et al., 2015	Canada	Cross-sectional	12,762 households	5,734 households/ 15,022 individuals (45%) (full participants) 524 households (4%) (partial participants)
Winberg et al., 2015	Sweden	Cohort	Not indicated	2,612 (96%)

Age of Participants	Food Allergens	Method of Outcome Assessment	Estimated Prevalence of Food Allergy, % (95% CI)
12 and 24 months	Cow milk	Parent-report, clinical examination, sIgE or SPT, DBPCOFC	Raw incidence: 0.54 (0.41-0.70) Adjusted incidence: 0.74 (0.56-0.97) (Adjusted for children who were eligible but not challenged, were placebo reactors, or who had inconclusive challenge outcomes, or who were lost to follow up)
Adults and children	Peanut, tree nuts, fish, shellfish, sesame, milk, egg, wheat, and/or soy	Self-report, convincing history, physician diagnosis	Self-reported food allergy to any food Full participants: 6.4 (6.0-6.8) (unweighted) 7.5 (6.9-8.1) (weighted) Partial participants: 2.1 (1.4-2.9) (unweighted)
11-12 years	Milk, egg, cod, wheat	Parent-report	Reported food allergy: 4.8 (4-6)
		Clinical evaluation + sIgE	Clinically evaluated food allergy: 1.4 (1-2)
		DBPCOFC	DBPCOFC-proven food allergy: 0.6 (0-1)

continued

TABLE B-3 Continued

Reference	Country	Study Design	Number Invited or Eligible Participants	Participation Rate N (%)
Bunyavanich et al., 2014	US	Cohort study	1,277	616 (48.2)
Burney et al., 2014	Europe	Cross-sectional	28,269	17,366 (54.6)
Gaspar-Marques et al., 2014	Portugal	Cross-sectional	2,228	1,225 (55.0) participated 1,217 (54.6) included in analysis
Salo et al., 2014	US	Cross-sectional	10,348	10,348
Wood et al., 2014	US	Cross-sectional (patient survey)	1,651	1,059 (64%)

Age of Participants	Food Allergens	Method of Outcome Assessment	Estimated Prevalence of Food Allergy, % (95% CI)
7-10 years	Peanut	Self-reported symptoms, sIgE levels, clinical information, and combinations of these variables	Self-reported food allergy: 4.6 (2.9-6.3) Clinical food allergy based on sIgE: 5.0% (3.5-7.1) Peanut sIgE ≥0.35 kU/L and prescribed epi auto-injector: 4.9 (3.2-6.7) Peanut sIgE ≥14 kU/L: 2.9 (1.6-4.3) Peanut sIgE ≥14 kU/L and prescribed epi auto-injector: 2.0 (0.9-3.2)
20-54 years	Various	Self-report, physician diagnosis, sIgE (≥0.35 kU_A/L)	Self-report: 21.0 Physician diagnosis: 4.4 IgE to any foods: 15.81
0-3 years 4-6 years	Various	Self-report	*Ever had a food allergy* 0-3 years: 8.6 (6.4-11.5) 4-6 years: 12.1 (10.0-14.7) Total: 10.8 (9.1-12.6) *Current food allergy* 0-3 years: 4.7 (3.1-7.0) 4-6 years: 6.4 (4.9-8.4) Total: 5.7 (4.6-7.2)
≥1 year	Egg white, cow milk, peanut, shrimp	sIgE	Prevalence of food sensitization: 28
Adults (median age 52 years)	Not specified	Self-report of anaphylaxis to food	Reported anaphylaxis: 31

continued

TABLE B-3 Continued

Reference	Country	Study Design	Number Invited or Eligible Participants	Participation Rate N (%)
Kaya et al., 2013	Turkey	Cross-sectional	11,233	10,096 (89.9)
Gupta et al., 2012	US	Cross-sectional	40,104	38,465 (96)
Gupta et al., 2011, 2013	US	Cross-sectional	40,104	38,480 (96)

Age of Participants	Food Allergens	Method of Outcome Assessment	Estimated Prevalence of Food Allergy, % (95% CI)
11-15 years	Various	Parent-report Confirmation by: clinical history, sIgE, SPT, OFC, DBPCOFC	Lifetime parent-reported: 11.3 (10.7-11.9) Parent-reported point prevalence: 3.6 (3.2-3.8) Confirmed food allergy: 0.15 Confirmed peanut: 0.05 Confirmed tree nut: 0.05
0-17 years	All allergens (peanut, shellfish, milk, fin fish, egg, tree nuts, wheat, soy)	Parent report of physician diagnosis, sIgE, SPT, OFC, reaction history	Urban centers: 9.8 (8.6-11.0) Metro cities: 9.2 (8.4-10.1) Urban outskirts: 7.8 (7.0-8.6) Suburban areas: 7.6 (6.9-8.2) Small towns: 7.2 (5.7-8.6) Rural areas: 6.2 (5.6-6.8) P<0.0001
0-17 years	Egg, fin fish, milk, peanut, shellfish, soy, tree nuts, wheat, or strawberry	Parent report of physician diagnosis, sIgE, SPT, OFC, reaction history	All allergens: 8.0 (7.7-8.3) Egg: 0.8 (0.7-0.9) Fin fish: 0.5 (0.4-0.6) Milk: 1.7 (1.5-1.8) Peanut: 2.0 (1.8-2.2) Shellfish: 1.4 (1.2-1.5) Soy: 0.4 (0.3-0.4) Tree nuts: 1.0 (0.9-1.2) Wheat: 0.4 (0.3-0.5) Strawberry: 0.4 (0.4-0.5)

continued

TABLE B-3 Continued

Reference	Country	Study Design	Number Invited or Eligible Participants	Participation Rate N (%)
Osborne et al., 2011	Australia	Cohort	3,898	2,848 (73)
Sicherer et al., 2010	US	Cross-sectional	12,658 households	5,300 households (13,534 subjects) (42)
Venter et al., 2010	UK	Cohort	Cohort A: 1,456 Cohort B: 2,858 Cohort C: 969	Cohort A: 1,218 (84) Cohort B: 1,273 (44) Cohort C: 891 (92)
Ben-Shoshan et al., 2009	Canada	Cross-sectional	8,039	(64)
Branum and Lukacs, 2009	US	Cross-sectional	Not indicated	Not indicated

NOTE: CI = confidence interval; DBPCOFC = double-blind, placebo-controlled oral food challenge; IgE = immunoglobulin E; N/A = not applicable; OFC = oral food challenge; SE = standard error; sIgE = food-specific serum IgE; SPT = skin prick test; UK = United Kingdom; US = United States.

Age of Participants	Food Allergens	Method of Outcome Assessment	Estimated Prevalence of Food Allergy, % (95% CI)
12 months	Raw egg, peanut, sesame, shellfish, or cow milk	SPT, DBPCOFC Shellfish and milk: no food challenge performed	Overall prevalence (raw egg, peanut or sesame): 10.4 (9.3-11.5) Raw egg: 8.9 (7.8-10.0) Peanut: 3.0 (2.4-3.8) Sesame: 0.8 (0.5-1.1)
<18 years	Peanut, tree nuts, sesame	Self-report	Peanut: 1.4 (1.0-1.9) Tree nuts: 1.1 Sesame: 0.1 (0-0.2)
3-4 years	Peanut	Cohort A: clinical history Cohorts B and C: SPT and clinical history or OFC	Cohort A: 0.5 Cohort B: 1.4 Cohort C: 1.2
K-grade 3 students	Peanut	Clinical history, SPT, sIgE, DBPCOFC	1.62 (1.31-1.98)
0-17 years	Not indicated	Parent-report	3.9 ± 0.3 (SE)
	Peanut, egg, milk, shrimp (in children ≥6 years)	sIgE	Proportion estimate ± SE sIgE (peanut): 9.3 ± 0.8 sIgE (egg): 6.7 ± 0.6 sIgE (milk): 12.2 ± 0.9 sIgE (shrimp): 5.2 ± 0.6
		Food allergy-related ambulatory care visits to hospital facilities and physician offices and hospitalizations	317,000 (95% CI: 196,000-438,000) visits per year

TABLE B-4 Prevalence of Food Allergy: Systematic Review Summaries

Author, year	McWilliam et al., 2015
Aims/Key questions	To provide a comprehensive, up-to-date systematic review of the population prevalence of tree nut allergy in children and adults, including details of all individual tree nuts in various regions of the world
Study eligibility criteria	Inclusion criteria: • Types of studies: Population, cross-sectional, and cohort studies. • Types of participants: Adults and children; no age restrictions. • Primary outcomes: All forms of allergic reactions (primary and secondary IgE-mediated and non-IgE-mediated reactions) were included. All tree nut allergy outcomes were included for both individual and combined tree nut allergies. Included eligible studies that reported tree nut allergy based on self-report, sensitization (sIgE or SPT), OFC/DBPCOFC or convincing clinical history. Exclusion criteria: • Types of studies: Reviews, case reports, and studies without full-text. • Types of participants: Selected patient groups or those performed in hospital or allergy clinic settings.
Literature search dates or year range	January 1996 to December 2014
Number of food allergy studies included	36
Synthesis methods	Summary tables, narrative text, meta-analysis

TABLE B-4 Continued

Key findings	Confirmed food allergy: Seven studies (all in children) using OFC (or convincing recent history of allergic reaction together with positive allergen-specific IgE) to determine a prevalence range of 0-1.6%. Probable food allergy: Nine studies combined self-reported food allergy with additional objective assessment (e.g., specific details regarding doctor diagnosis or sensitization details [sIgE/SPT]) and were classified as probable food allergy for this review. The overall probable tree nut allergy prevalence range was 0.05-4.9%, with only one study reporting adult data. Self-reported food allergy: Twenty studies based on self-report found tree nut allergy prevalence range was wider for adults (0.18-8.9%) and those studies including both adults and children (0.4-11.4%) than for those studies including only children (0-3.8%). Overall self-reported tree nut allergy prevalence ranged from 0 to 11.4%. Pollen-associated food allergy: Prevalence estimates that included pollen-associated food allergy reactions to tree nut were significantly higher (8-11.4%) and were predominantly from Europe. Geographic Differences: Prevalence of individual tree nut allergies varied significantly by region, with hazelnut the most common tree nut allergy in Europe; walnut and cashew the most common in the US; and Brazil nut, almond, and walnut the most common in the UK.
Limitations	Small number of studies reporting challenge-confirmed tree nut allergy prevalence. Unable to pool the prevalence estimates due to the large heterogeneity between the studies. Data are largely limited to European, US, and UK studies.
AMSTAR rating	
An a priori design?	Y
Duplicate study selection and data extraction?	Y
Comprehensive literature search?	Y
Status of the publication as an inclusion criterion?	Y (limited to English-language articles)
List of studies (included and excluded) provided?	Y/N (no list of excluded studies)
Characteristics of included provided?	Y
Scientific quality of the included studies assessed and reported?	Y
Scientific quality used in formulating conclusions?	Y

continued

TABLE B-4 Continued

Methods used to combine the findings appropriate?	Y
Likelihood of publication bias assessed?	N
Conflict of interest (COI) stated?	Y/N (COI of the systematic review authors was provided but not provided for included studies)

Author, year	Umasunthar et al., 2015
Aims/Key questions	To quantify the risk of anaphylaxis for food-allergic people
Study eligibility criteria	Inclusion criteria: • Study design: Prospective or retrospective registries, databases or cohort studies. • Participants: People with a medically diagnosed food allergy or a defined population where an assumed population rate of food allergy could be applied. • Follow-up: To enable calculation of total person-years of observation, the authors included studies that specified either total population and duration of data collection or anaphylaxis incidence rate. • Outcomes: The authors included reports of number of food anaphylaxis events during the follow-up period. Anaphylaxis determined by self-report, medical coding, or anaphylaxis admission to hospital. Exclusion criteria: • Food-allergic reactions reported were not anaphylactic, or severity was not defined. • Time period not defined. • Population in which food anaphylaxis cases occurred could not be quantified.
Literature search dates or year range	January 1946 to September 5, 2012
Number of food allergy studies included	34
Synthesis methods	Summary tables, narrative text, meta-analysis

TABLE B-4 Continued

Key findings	Self-reported food anaphylaxis in food allergic people: • Based on data from 10 studies, meta-analysis gave an incidence of 4.93 (95% CI: 2.78-8.74; range 0.60-57.89) per 100 person-years for people ages 0-19 years. • For peanut allergic people meta-analysis of data from four studies gave an incidence rate of 2.64 (95% CI: 1.13-6.17; range 1.64-8.90) per 100 person-years. Medically coded food anaphylaxis in food-allergic people: • Based on nine studies, the incidence rate was 0.14 per 100 person-years (95% CI: 0.05-0.35; range 0.01-1.28). • Based on nine studies, the incidence rate for people ages 0-19 years was 0.20 (95% CI: 0.09-0.43; range 0.01-2.55; sensitivity analysis 0.08-0.39). • In sensitivity analysis using different estimated food allergy prevalence, the incidence varied from 0.11 to 0.21 per 100 person-years. • The incidence rate of up to 7.00 per 100 person-years has been reported for children ages 0-4 years. Hospital admission due to food anaphylaxis in food-allergic people: • Based on four studies, the incidence rate was 0.09 (95% CI: 0.01-0.67; range 0.02-0.81) per 1,000 person-years. • Based on eight studies, the incidence rate for people ages 0-19 years was 0.20 (95% CI: 0.10-0.43; range 0.04-2.25). • Based on six studies, the incidence rate for children agse 0-4 years was 0.50 (95% CI: 0.26-0.93; range 0.08-2.82).
Limitations	High heterogeneity between study results, possibly due to variation in study populations, anaphylaxis definition, and data collection methods. Some uncertainty exists about the precision of the risk estimates, so mean estimates should be interpreted with caution. The rate of self-reported anaphylaxis varied widely across studies. Study quality was generally rated as low for studies of self-reported anaphylaxis. It is likely that studies of self-reported anaphylaxis overestimate the true incidence of anaphylaxis. The rate of medically coded anaphylaxis also varied widely between studies. These data may underestimate food anaphylaxis occurrence.

continued

TABLE B-4 Continued

AMSTAR rating	
An a priori design?	Y
Duplicate study selection and data extraction?	Y
Comprehensive literature search?	Y
Status of the publication as an inclusion criterion?	Y
List of studies (included and excluded) provided?	Y/N (no list of excluded studies)
Characteristics of included provided?	Y
Scientific quality of the included studies assessed and reported?	Y
Scientific quality used in formulating conclusions?	Y
Methods used to combine the findings appropriate?	Y
Likelihood of publication bias assessed?	Y
Conflict of interest stated?	Y/N (COI of the systematic review authors was provided but not provided for included studies)

Author, year	Katz et al., 2014
Aims/Key questions	To identify the adjusted prevalence of IgE-mediated soy allergy in children and perform a secondary analysis of the impact of age (less than and more than 6 months).
Study eligibility criteria	Inclusion criteria: • Types of studies: analytical transversal studies, studies of cases and controls, cohort studies, and clinical trials. • Types of participants: infants and children up to 19 years old, including newborns. • Primary outcomes: prevalence of sensitization or allergy to soy identified by clinical manifestations, parent reports, serum concentrations of sIgE, SPT, or an OFC. Exclusion criteria: • Types of studies: narrative reviews; studies of people older than age 19 years; studies lacking sufficient congruence and/or yield between what was described in the objectives and what was reported.
Literature search dates or year range	1909 to March 2013
Number of food allergy studies included	40
Synthesis methods	Summary tables, meta-analysis

TABLE B-4 Continued

Key findings	Ten studies reported OFC-proven soy protein allergy in the general population (i.e., the referred population). Quality of evidence was low or moderate. • The weighted prevalence for the general population: 0.27 (95% CI: 0.1%-0.44%) (N/total=4/1,946) • The weighted prevalence for the referred population: 1.9 (95% CI: 1.1%-2.7%) (N/total=35/1,807) • The weighted prevalence for atopic children: 2.7 (95% CI: 1.8%-3.3%) (N/total=19/708) Six studies reported the prevalence of self-reported soy allergy in the general population. The quality of evidence was low. • The prevalence was 0.2 (95% CI: 0.0%-0.30%) (N/total=39/19,732) Twelve studies reported the prevalence of allergy to soy after the use of infant formula with soy-based protein. Quality of evidence was low to moderate. • The weighted prevalence of OFC-proven soy allergy was 2.5% (95% CI: 2.1%-8.3%) (N/total=18/720) Six studies reported prevalence of self-reported soy allergy after use of soy-based formula. Quality of evidence was moderate except for one study. • Weighted prevalence was 4.4% (95% CI: 0%-5.6%) (N/total=108/2,439)
Limitations	All four positive cases of OFC-proven soy allergy in the general population originated from one study. Cutaneous signs were noted in only one of these cases.

AMSTAR rating	
An a priori design?	Y
Duplicate study selection and data extraction?	Y
Comprehensive literature search?	Y
Status of the publication as an inclusion criterion?	Y
List of studies (included and excluded) provided?	Y/N (no for excluded studies)
Characteristics of included provided?	Y
Scientific quality of the included studies assessed and reported?	Y
Scientific quality used in formulating conclusions?	Y
Methods used to combine the findings appropriate?	Y
Likelihood of publication bias assessed?	Y
Conflict of interest stated?	N

continued

TABLE B-4 Continued

Author, year	Keet et al., 2014
Aims/Key questions	To determine the prevalence of self-reported food allergy in children in the US, and explore sources of variation in prevalence estimates, including case definition, changes over time, and racial/ethnic differences.
Study eligibility criteria	Inclusion criteria: • Types of studies: national surveys; population-based original reports. • Types of participants: US general population; children. • Primary outcomes: self-reported food allergy. Exclusion criteria: • Types of studies: studies without individual level data; abstracts only. • Types of participants: adults.
Literature search dates or year range	Up to February 2012
Number of food allergy studies included	27 survey administrations (20 survey administrations were used in the meta-regression)
Synthesis methods	Summary tables, narrative text, meta-analysis with meta-regression

TABLE B-4 Continued

Key findings	Seven surveys reported self-reported food allergy (National Maternal and Infant Health Survey; NHANES III; National Survey of Children's Health 2003 and 2007; NHIS 1997-2011; NHANES 2007-2008 and 2009-2010). Prevalence: It appears that the prevalence of self-reported food allergy is between 3 and 6 percent. Prevalence (current versus ever): Compared to estimates of prevalence of self-reported current food allergy, the prevalence of self-reported history of food allergy ever was considerably higher, even after adjusting for year of study (difference: 2.5 percentage points between current and ever/time undefined food allergy, 95% CI: 1.5%-3.4%; P<0.001 for all children). Change over time: The self-reported prevalence of food allergy among children was estimated to have increased by 1.2 percentage points per decade during 1988-2011 (95% CI: 0.7%-1.6%). Racial/ethnic differences: The rate of increase in self-reported food allergy prevalence varied significantly by race/ethnicity; the estimated increase in food allergy prevalence per decade among Black children was 2.1 percentage points (95% CI: 1.5%-2.7%) compared to 1.2 percentage points among Hispanics (95% CI: 0.7%-1.7%) and 1.0 percentage points (95% CI: 0.4%-1.6%) among whites (P=0.01 for comparison of trends between blacks and whites, and P=0.04 for comparison between blacks and Hispanics).
Limitations	Surveys included in meta-regression were limited to those conducted by the CDC. The studies have too much heterogeneity to calculate a summary measure of food allergy prevalence. All outcomes were based on self-report.
AMSTAR rating	
An a priori design?	Y
Duplicate study selection and data extraction?	Y
Comprehensive literature search?	Y
Status of the publication as an inclusion criterion?	Y (English-only)
List of studies (included and excluded) provided?	Y/N (no list of excluded studies)
Characteristics of included provided?	Y
Scientific quality of the included studies assessed and reported?	Y
Scientific quality used in formulating conclusions?	Y
Methods used to combine the findings appropriate?	Y

continued

TABLE B-4 Continued

Likelihood of publication bias assessed?	Y
Conflict of interest stated?	Y/N (COI of the systematic review authors was provided but not provided for included studies)
Author, year	Nwaru et al., 2014
Aims/Key questions	To provide up-to-date estimates of the prevalence of allergy to cow milk, egg, wheat, soy, peanut, tree nuts, fish, and shellfish in Europe.
Study eligibility criteria	Inclusion criteria: • Types of studies: Systematic reviews and meta-analyses, cohort studies, case-control studies, cross-sectional studies, and routine health care studies published in Europe. • Types of participants: All ages; population-based. • Primary outcomes: Allergy to cow milk, egg, wheat, soy, peanut, tree nuts, fish, and shellfish. Assessments based on self-report, SPT, sIgE, OFC/DBPCOFC, or convincing clinical history (i.e., outcomes confirmed by a convincing clinical judgment by a physician without food challenge). Exclusion criteria: • Types of studies: Review and discussion papers, non-research letters and editorials, case studies and case series, animal studies, and all randomized controlled trials.
Literature search dates or year range	January 2000 to September 30, 2012
Number of food allergy studies included	65 (based on 50 primary studies)
Synthesis methods	Summary tables, narrative text, meta-analysis
Key findings	Self-reported food allergy: The overall pooled estimates for all age groups of self-reported lifetime prevalence of allergy to cow milk, egg, wheat, soy, peanut, tree nuts, fish, and shellfish were 6.0% (95% CI: 5.7%-6.4%), 2.5% (2.3%-2.7%), 3.6% (3.0%-4.2%), 0.4% (0.3%-0.6%), 1.3% (1.2%-1.5%), 2.2% (1.8%-2.5%), and 1.3% (0.9%-1.7%), respectively. Food-challenge-defined food allergy: The prevalence of food-challenge-defined allergy to cow milk, egg, wheat, soy, peanut, tree nuts, fish, and shellfish was 0.6% (0.5%-0.8%), 0.2% (0.2%-0.3%), 0.1% (0.01%-0.2%), 0.3% (0.1%-0.4%), 0.2% (0.2%-0.3%), 0.5% (0.08%-0.8%), 0.1% (0.02%-0.2%), and 0.1% (0.06%-0.3%).

TABLE B-4 Continued

Limitations	Significant heterogeneity between the studies. Limited generalizability (limited to European studies published after 2000).
AMSTAR rating	
An a priori design?	Y
Duplicate study selection and data extraction?	Y
Comprehensive literature search?	Y
Status of the publication as an inclusion criterion?	Y
List of studies (included and excluded) provided?	Y/N (no list of excluded studies)
Characteristics of included provided?	Y
Scientific quality of the included studies assessed and reported?	Y
Scientific quality used in formulating conclusions?	Y
Methods used to combine the findings appropriate?	Y
Likelihood of publication bias assessed?	N
Conflict of interest stated?	Y/N (COI of the systematic review authors was provided but not provided for included studies)
Author, year	Greenhawt et al., 2013
Aims/Key questions	To understand the racial and ethnic disparities in food allergy in the US.
Study eligibility criteria	Inclusion criteria: • Types of studies: English-language articles with data from the US and research that presented original data related to racial/ethnic disparity in reported or diagnosed food allergy (including food sensitization), prevalence, treatment, or clinical course. Exclusion criteria: • Types of studies: Systematic reviews, meta-analyses, abstracts, gray literature, and non-US studies.
Literature search dates or year range	Not provided
Number of food allergy studies included	20
Synthesis methods	Summary tables, narrative text

continued

TABLE B-4 Continued

Key findings	None of the studies used OFC/DBPCOFC to assess food allergy.
	In 12 studies, blacks (primarily children) had significantly increased adjusted odds of food sensitization or significantly higher proportion or odds of food allergy by self-report, discharge codes, or clinic-based chart review than did white children.
Limitations	Major differences in study methodology and reporting precluded calculation of a pooled estimate of effect.
	Food allergy outcomes were measured indirectly.
	Low AMSTAR rating.
AMSTAR rating	
An a priori design?	Y
Duplicate study selection and data extraction?	Y
Comprehensive literature search?	N (did not state the literature search dates or range)
Status of the publication as an inclusion criterion?	N
List of studies (included and excluded) provided?	Y/N (list of excluded studies not provided)
Characteristics of included provided?	Y
Scientific quality of the included studies assessed and reported?	N
Scientific quality used in formulating conclusions?	N
Methods used to combine the findings appropriate?	N
Likelihood of publication bias assessed?	N
Conflict of interest stated?	Y/N (COI of the systematic review authors was provided but not provided for included studies)

TABLE B-4 Continued

Author, year	Lee et al., 2013
Aims/Key questions	To summarize the current literature on food allergy in Asia and compare it with Western populations.
Study eligibility criteria	Inclusion criteria: • Types of studies: Reviews, epidemiological/prevalence studies, clinical studies, anaphylaxis studies, case series/reports. • Types of participants: Asian populations. • Outcomes: Food allergy determined by self-report, SPT, food elimination testing, DBPCOFC, convincing history, food avoidance, sIgE, physician diagnosis, or OFC. Exclusion criteria: • Types of studies: Articles from the Middle East and Turkey; non-English studies.
Literature search dates or year range	January 2005 to December 2012
Number of food allergy studies included	53
Synthesis methods	Summary table, narrative text
Key findings	The overall prevalence of food allergy in Asia is somewhat comparable to the West. However, the types of food allergy differ in order of relevance. Shellfish is the most common food allergen from Asia. The prevalence of peanut allergy in Asia is extremely low compared to the West. Among young children and infants, egg and cow milk allergy are the two most common food allergies, with prevalence data comparable to Western populations. Wheat allergy, though uncommon in most Asian countries, is the most common cause of anaphylaxis in Japan and Korea, and is increasing in Thailand.
Limitations	Low AMSTAR rating
AMSTAR rating	
An a priori design?	Y
Duplicate study selection and data extraction?	N
Comprehensive literature search?	N (did not supplement the database searches)
Status of the publication as an inclusion criterion?	N
List of studies (included and excluded) provided?	Y/N (did not include list of excluded studies)

continued

TABLE B-4 Continued

Characteristics of included provided?	Y/N (not for all 53 studies)
Scientific quality of the included studies assessed and reported?	N
Scientific quality used in formulating conclusions?	N
Methods used to combine the findings appropriate?	Not applicable (findings were not combined)
Likelihood of publication bias assessed?	N
Conflict of interest stated?	N

Author, year	Panesar et al., 2013
Aims/Key questions	To understand and describe the epidemiology of anaphylaxis from any cause in Europe and describe how these characteristics vary by person, place, and time.
Study eligibility criteria	Inclusion criteria: • Types of studies: Systematic reviews and/or meta-analyses, cohort studies, cross-sectional studies, case-control studies, and routine health care studies. • Primary outcomes: Incidence, prevalence, and trends over time of anaphylaxis in Europe. Exclusion criteria: • Types of studies: Reviews, discussion papers, nonresearch letters and editorials, case studies, and case series plus animal studies.
Literature search dates or year range	January 1, 2000, to September 30, 2012
Number of food allergy studies included	49 (3 included in meta-analysis) Only 10 were food allergy studies and none of these was in the meta-analysis
Synthesis methods	Summary tables, narrative text, meta-analysis
Key findings	Meta-analysis yielded a pooled estimated prevalence of anaphylaxis, due to any cause, of 0.3% (95% CI 0.1%-0.5%). Ten studies found that the proportions of food allergy reactions that resulted in anaphylaxis ranged from 0.4% to 39.9%. One study of 163 children found the food allergens that most commonly resulted in anaphylaxis were cow milk (29%), hen egg (25%), hazelnut (5%), peanut (4%), kiwi (4%), walnut (4%), pine nut (3%), fish (3%), wheat (2%), soy (2%), shrimp (2%), apricot (2%), and sesame (2%).

TABLE B-4 Continued

Limitations	No discussion of how food allergy was determined. Very few studies were on food allergy. Limited to European populations.	
AMSTAR rating		
An a priori design?		Y
Duplicate study selection and data extraction?		Y
Comprehensive literature search?		Y
Status of the publication as an inclusion criterion?		Y
List of studies (included and excluded) provided?		Y
Characteristics of included provided?		Y
Scientific quality of the included studies assessed and reported?		Y
Scientific quality used in formulating conclusions?		Y
Methods used to combine the findings appropriate?		Y
Likelihood of publication bias assessed?		N
Conflict of interest stated?		Y/N (COI of the systematic review authors was provided but not provided for included studies)
Author, year	Umasunthar et al., 2013	
Aims/Key questions	To estimate the incidence of fatal food-induced anaphylaxis for people with food allergy and relate this to other mortality risks in the general population.	
Study eligibility criteria	Inclusion criteria: • Study design: Registries, databases, or cohort studies including ≥1 case of fatal food anaphylaxis. • Participants: A defined population where an assumed population rate of food allergy could be applied. • Follow-up: To enable calculation of total person-years of observation, the authors included studies that specified either total population and duration of data collection or anaphylaxis incidence rate. • Outcomes: Reports of number of fatal food anaphylaxis events during the follow-up period. Exclusion criteria: • Fatalities neither probably nor definitely due to anaphylaxis, in the judgment of the original study authors. • Time period not defined. • Population in which food anaphylaxis cases occurred could not be quantified.	

continued

TABLE B-4 Continued

Literature search dates or year range	January 1946 to September 5, 2012
Number of food allergy studies included	13
Synthesis methods	Summary table, meta-analysis
Key findings	Meta-analysis estimates the incidence rate of fatal food anaphylaxis in a food-allergic person as: • 1.81 (95% CI: 0.94-3.45; range 0.63-6.68) per million person-years (micromorts) based on 10 studies • 3.25 (95% CI: 1.73-6.10; range 0.94-15.75) micromorts in those ages 0 to 19 based on 10 studies • 2.13 (95% CI: 1.09-4.16; range 1.03-8.77) micromorts for peanut allergy based on seven studies In sensitivity analysis with different estimated food allergy prevalence, the incidence varied from 1.35 to 2.71 per million person-years.
Limitations	Study quality was mixed, and study results had high heterogeneity, possibly due to variation in food allergy prevalence and data collection methods. Study authors were unable to exclude the possibility of a systematic bias operating across different studies, in either the acquisition and coding of fatal food anaphylaxis data or the estimation of food allergy prevalence.
AMSTAR rating	
An a priori design?	Y
Duplicate study selection and data extraction?	Y
Comprehensive literature search?	Y
Status of the publication as an inclusion criterion?	Y
List of studies (included and excluded) provided?	Y/N (list of excluded studies was not provided)
Characteristics of included provided?	Y
Scientific quality of the included studies assessed and reported?	Y
Scientific quality used in formulating conclusions?	Y
Methods used to combine the findings appropriate?	Y
Likelihood of publication bias assessed?	Y
Conflict of interest stated?	Y/N (COI of the systematic review authors was provided but not provided for included studies)

TABLE B-4 Continued

Author, year	Chafen et al., 2010
Aims/Key questions	To systematically review the evidence on the prevalence of food allergies.
Study eligibility criteria	Inclusion criteria: • The initial inclusion criteria were broad and included prior systematic reviews, meta-analyses, or both, and studies presenting original data related to the prevalence, diagnosis, management, or prevention of food allergy. After assessing the relative quantities of studies on these topics, the authors restricted studies of prevalence to those with population-based samples (and systematic reviews of such studies); studies of diagnostic tests to those that presented sufficient data to calculate both sensitivity and specificity, had a prospective, defined study population, and used food challenge as a criterion standard; and studies of management and prevention to those that were either controlled trials (both randomized and nonrandomized) or systematic reviews.
Literature search dates or year range	January 1988 to September 2009
Number of food allergy studies included	6 studies on prevalence of food allergy
Synthesis methods	Narrative text

continued

TABLE B-4 Continued

Key findings	One meta-analysis on incidence and prevalence. • The pooled estimate of prevalence of cow milk allergy was 3.5% (95% CI: 2.9%-4.1%) by self-report; 0.6% to 0.9% from SPT, sIgE, and DBPCOFC. • The pooled estimates (%, 95% CI) for self-report and other methods were: 1.3% (95% CI: 1.0%-1.6%) versus 0.3% to 0.9% (egg); 0.75% (95% CI: 0.6%-0.9%) versus 0.75% (peanut); 0.6% (95% CI: 0.5%-0.7%) versus 0.2% to 0.3% (fish); and 1.1% (95% CI: 1.0%-1.2%) versus 0.6% (shellfish). Three population-based studies on change in prevalence over time in the UK, Canada, and the US. • The UK study found the parent-reported prevalence of peanut allergy increased from 0.5% in 1989 to 1.0% in 1994-1996 (P=0.20), and the prevalence of IgE antibodies increased from 1.1% to 3.3% (P=0.001). • In Canada, prevalence of peanut allergy was 1.5% in 2000-2002 and increased to 1.63% in 2005-2007 (non-significant difference) (based on parent-report, SPT, sIgE, and food challenge). • In the US, authors estimated that 3.3% of US children had food allergies in 1997 versus 3.9% in 2007 (statistically significant difference). Overall Findings: • Food allergy affects more than 1% to 2% but less than 10% of the population. • It is unclear whether the prevalence of food allergies is increasing.
Limitations	• Heterogeneity in the criteria used for the diagnosis of food allergy made comparisons of prevalence across studies dependent on the methods used for the diagnosis and prevented data pooling. • Authors were unable to perform formal evaluations for publication bias due to the heterogeneity of the included studies.

AMSTAR rating	
An a priori design?	Y
Duplicate study selection and data extraction?	Y
Comprehensive literature search?	Y
Status of the publication as an inclusion criterion?	Y (limited to English-only articles)
List of studies (included and excluded) provided?	N
Characteristics of included provided?	N
Scientific quality of the included studies assessed and reported?	Y
Scientific quality used in formulating conclusions?	Y

TABLE B-4 Continued

Methods used to combine the findings appropriate?	Not applicable (findings on prevalence were not combined)
Likelihood of publication bias assessed?	N
Conflict of interest stated?	Y/N (COI of the systematic review authors was provided but not provided for included studies)

Author, year	Zuidmeer et al., 2008
Aims/Key questions	To assess the prevalence of allergies to plant food according to the different subjective and objective assessment methods.
Study eligibility criteria	Inclusion criteria: • Types of studies: Population-based cross-sectional and cohort studies. • Primary outcomes: Food allergy (OFC/DBPCOFC), food sensitization (SPT, sIgE), or perceived food allergy (parent-/self-report). Exclusion criteria: • Types of studies: Case-control studies; studies in selected patient groups (e.g., asthma or eczema patients); studies performed in clinical settings; studies that had enriched study samples with patients with allergy (for further clinical studies); or articles that did not report the sample size.
Literature search dates or year range	January 1990 to December 2006
Number of food allergy studies included	36 (33 publications)
Synthesis methods	Summary tables, meta-analysis

continued

TABLE B-4 Continued

Key findings	Based on 4 studies using food challenge tests, the prevalence of allergy to fruits ranged from 0.1% to 4.3%. Based on 2 studies using food challenge tests, the prevalence of allergy to vegetables ranged from 0.1% to 0.3%. Based on 3 studies using food challenge tests, the prevalence of allergy to nuts ranged from 0.1% (almond) to 4.3% (hazelnut). Both for challenge tests and for sensitization assessed by SPT, the highest prevalence estimates of more than 4% were found for hazelnut. Two studies from the UK and one from Germany reported positive wheat challenge tests in children with a prevalence as high as 0.5%. In adults, the prevalence of sensitization to wheat (assessed by IgE) was >3% in several studies. In adults and adolescents, the highest prevalence estimates of allergy to soy were found in three Swedish studies (sensitization assessed by IgE as high as almost 3%). Studies from all other countries showed prevalences well below 1% regardless of method used or age group. Meta-analyses showed significant heterogeneity between studies regardless of food item or age group. In adults, there was significant heterogeneity (P<0.001) among the seven studies regarding perception of allergy caused by fruits (summary prevalence estimate, 1.22%; 95% CI: 0.82%-1.63%), vegetables (six studies: 0.98%; 95% CI: 0.52%-1.45%), and wheat (five studies: 0.40%; 95% CI: 0.21%-0.59%), as well as for sensitization against wheat (assessed by IgE in five studies: 2.08%; 95% CI: 0.87%-3.29%). Similarly, among studies in children, the heterogeneity was significant (P<0.001) for perception of allergy caused by tree nuts (five studies: 0.52%; 95% CI: 0.20%-0.85%) or soy (seven studies: 0.34%; 95% CI: 0.12%-0.56%), whereas the heterogeneity was of a lower level but still significant (P=5.016) among the five studies assessing sensitization against wheat by SPT (0.43%; 95% CI: 0.16%-0.70%).

TABLE B-4 Continued

Limitations	Few studies used OFC or DBPCOFC to determine food allergy. Meta-analysis was done only when five or more studies were available, so, due to the lack of studies using OFC or DBPCOFC, meta-analysis was done only for studies that determined food allergy by SPT, sIgE, or self-report. The authors could not rule out that studies were missed, particularly from non-European or non-American journals. The comparison of prevalence estimates from different studies is hampered by using different types of prevalence. A limitation of the interpretation of findings on allergic sensitization may be that positive IgE or SPT results to plant-derived foods can be a result of cross-reactivity to pollen. Consequently, the prevalence of food allergy may rise or fall with the presence of the sensitizing pollen in the study area, which depends on the season and climate and may vary from year to year. Fairly low AMSTAR rating.
AMSTAR rating	
An a priori design?	Y
Duplicate study selection and data extraction?	Y (study selection)/ Not clear for data extraction
Comprehensive literature search?	N (searched only one database)
Status of the publication as an inclusion criterion?	N
List of studies (included and excluded) provided?	Y/N (no list of excluded studies)
Characteristics of included provided?	Y
Scientific quality of the included studies assessed and reported?	N
Scientific quality used in formulating conclusions?	N
Methods used to combine the findings appropriate?	Y
Likelihood of publication bias assessed?	N
Conflict of interest stated?	Y/N (COI of the systematic review authors was provided but not provided for included studies)

continued

TABLE B-4 Continued

Author, year	Rona et al., 2007
Aims/Key questions	To assess the prevalence of food allergy by performing a meta-analysis according to the method of assessment used.
Study eligibility criteria	Inclusion criteria: • Primary outcomes: Self-reported symptoms, specific IgE positive, specific skin prick test positive, symptoms combined with sensitization, and food challenge studies. Exclusion criteria: • Types of studies: Studies restricted to the prevalence of food allergy in groups with asthma, eczema, or allergic rhinitis and those performed in selected patients in a clinical setting. Also excluded studies using a case control design if it did not provide a prevalence estimate for the community, and duplicate publications. Excluded articles when the original community sample was enriched with a sample including patients, or the sample size was not provided.
Literature search dates or year range	January 1990 to December 2005
Number of food allergy studies included	51
Synthesis methods	Narrative text, summary tables, meta-analysis
Key findings	The studies showed marked heterogeneity regardless of type of assessment or food item considered, and in most analyses this persisted after age stratification. Self-reported prevalence of food allergy varied from 1.2% to 17% for milk, 0.2% to 7% for egg, 0% to 2% for peanuts and fish, 0% to 10% for shellfish, and 3% to 35% for any food. Prevalence of food allergy determined by OFC or DBPCOFC: • The prevalence for fish was near 0% (based on two studies). • The prevalence for milk varied from 0% to 3% (based on seven studies). A marked heterogeneity was observed for milk in preschool children, the only group for which sufficient studies were available for useful analysis. • The prevalence for egg varied from 0% to 1.7% (based on three studies). • The prevalence for any food varied from 1% to 10.8% (based on six studies). Meta-analysis results were presented graphically in this paper.

TABLE B-4 Continued

Limitations	In the overall estimate of the prevalence of food allergy related to food challenge, the authors were unable to omit positive challenges to nonallergic food hypersensitivity; thus, these estimates may give an overestimate of prevalence. Marked heterogeneity among studies.	
AMSTAR rating		
An a priori design?		Y
Duplicate study selection and data extraction?		Y
Comprehensive literature search?		Y
Status of the publication as an inclusion criterion?		N
List of studies (included and excluded) provided?		Y/N (list of excluded studies not provided)
Characteristics of included provided?		N
Scientific quality of the included studies assessed and reported?		N
Scientific quality used in formulating conclusions?		N
Methods used to combine the findings appropriate?		Y
Likelihood of publication bias assessed?		N
Conflict of interest stated?		Y/N (COI of the systematic review authors was provided but not provided for included studies)

NOTE: CDC = Centers for Disease Control and Prevention; CI = confidence interval; DBPCOFC = double-blind, placebo-controlled oral food challenge; IgE = immunoglobulin E; NHANES = National Health and Nutrition Examination Survey; NHIS = National Health Interview Survey; sIgE = food-specific serum IgE; SPT = skin prick test; UK = United Kingdom; US = United States.

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Appendix C

Risk Determinants Literature Search Strategy

Electronic literature searches of published systematic reviews (from 2010 to September 2015) and primary studies (from 2012 to September 2015) indexed in Medline, Cochrane Database of Systematic Reviews, EMBASE, and ISI Web of Science were conducted. For systematic reviews, a broad search was conducted to identify all systematic reviews with or without meta-analysis from 2010 onward related to food allergies or food sensitizations without restrictions to any interventions or exposures. For primary studies, search strategies in European Academy of Allergy & Clinical Immunology (EAACI) (de Silva et al., 2014) and Marrs et al. systematic reviews (Marrs et al., 2013) were adopted. The EAACI search strategies were developed to identify all randomized controlled trials, quasi-randomized controlled trials, controlled clinical trials, controlled before-and-after studies, interrupted time series studies, and prospective cohort studies that were primarily concerned with preventing sensitization to food(s) and/or the development of food allergy. The Marrs et al. search strategy was intended to capture any study designs describing food allergy or sensitization overall and to individual foods (milk, egg, peanut, tree nuts, fish, wheat, sesame, shellfish, and seafood) combined with search terms of factors that directly or indirectly influence microbial exposure (Marrs et al., 2013). All searches were restricted to human studies that were published in the English language from 2012 onward. Duplicate citations across databases were removed before screening. Medline searches conducted for this report for systematic reviews and individual studies are in Table C-1. Medline searches were used to develop the search strategies for the EMBASE and Web of Science databases.

Abstrackr software (abstrackr.cebm.brown.edu), Endnote, and Microsoft Excel were used to manage the search outputs, screening, and data abstraction. After a training session to ensure understanding of the inclusion and exclusion criteria, title/abstract screening was conducted independently by two reviewers using a screening form that listed the inclusion and exclusion criteria and allowed selection of reasons for exclusion. A third reviewer reconciled the discrepant title/abstract selections. Full-text articles of all accepted title/abstracts were then retrieved and screened by one reviewer based on the study eligibility criteria. Second-level screening of full text articles was conducted by two reviewers and differences reconciled by a third reviewer. Boxes C-1 and C-2 list the study inclusion and exclusion criteria, respectively. Figure C-1 illustrates the study selection flow. Summary tables for the systematic reviews and studies selected for the evidence-based review are included in Tables C2-C6.

TABLE C-1 Medline Search Strategy to Identify Relevant Literature

Search Number	Search Terms
	a. Systematic Reviews Search Strategy
1	exp food hypersensitivity/ or exp egg hypersensitivity/ or exp milk hypersensitivity/ or exp nut hypersensitivity/ or exp peanut hypersensitivity/ or exp wheat hypersensitivity/
2	(food$ adj2 (allergy$ or hypersensitivity)).mp.
3	((milk or egg$ or shellfish or fish or nut$ or peanut$ or wheat or soybean$ or seasame or seafood$) adj1 (allerg$ or hypersensitivity or sensitization)).mp.
4	(sensitization or hypersensitivity).mp.
5	(food$ or diet$).mp.
6	4 and 5 (13121)
7	1 or 2 or 3 or 6 (15068)
8	(rat or rats or cow or cows or chicken? or horse or horses or mice or mouse or bovine or animal?).ti.
9	exp animals/not humans.sh.
10	8 or 9
11	7 not 10
12	MEDLINE.tw.
13	systematic review.tw.
14	meta analysis.pt.
15	or/12-14
16	11 and 15
17	limit 16 to (English language and yr="2010 -Current")
	b. Primary Studies: EAACI Search Strategy
1	exp food hypersensitivity/ or exp egg hypersensitivity/ or exp milk hypersensitivity/ or exp nut hypersensitivity/ or exp peanut hypersensitivity/ or exp wheat hypersensitivity/
2	(food$ adj2 (allergy$ or hypersensitivity)).mp.
3	((milk or egg$ or shellfish or fish or nut$ or peanut$ or wheat or soybean$ or seasame or seafood$) adj1 (allerg$ or hypersensitivity or sensitization)).mp.
4	(sensitization or hypersensitivity).mp.
5	(food$ or diet$).mp.
6	4 and 5 (13121)
7	1 or 2 or 3 or 6 (15068)
8	(rat or rats or cow or cows or chicken? or horse or horses or mice or mouse or bovine or animal?).ti.

continued

TABLE C-1 Continued

Search Number	Search Terms
9	exp animals/ not humans.sh.
10	8 or 9
11	7 not 10
12	randomized controlled trial.pt.
13	controlled clinical trial.pt.
14	randomized.ab.
15	placebo.ab.
16	clinical trials as topic.sh.
17	randomly.ab.
18	trial.ti.
19	or/16-22
20	intervention?.ti. or (intervention? adj6 (clinician? or collaborat$ or community or complex or DESIGN$ or doctor? or educational or family doctor? or family physician? or family practitioner? or financial or GP or general practice? or hospital? or impact? or improv$ or individuali?e? or individuali?ing or interdisciplin$ or multicomponent or multi-component or multidisciplin$ or multidisciplin$ or multifacet$ or multi-facet$ or multimodal$ or multimodal$ or personali?e? or personali?ing or pharmacies or pharmacist? or pharmacy or physician? or practitioner? or prescrib$ or prescription? or primary care or professional$ or provider? or regulatory or regulatory or tailor$ or target$ or team$ or usual care)).ab.
21	(pre-intervention? or preintervention? or "pre intervention?" or postintervention? or postintervention? or "post intervention?").ti,ab.
22	(hospital$ or patient?).hw. and (study or studies or care or health$ or practitioner? or provider? or physician? or nurse? or nursing or doctor?).ti,hw.
23	demonstration project?.ti,ab.
24	(pre-post or "pre test$" or pretest$ or posttest$ or "post test$" or (pre adj5 post)).ti,ab.
25	(pre-workshop or post-workshop or (before adj3 workshop) or (after adj3 workshop)).ti,ab.
26	trial.ti. or ((study adj3 aim?) or "our study").ab.
27	(before adj10 (after or during)).ti,ab.
28	("quasi-experiment$" or quasiexperiment$ or "quasi random$" or quasirandom$ or "quasi control$" or quasicontrol$ or ((quasi$ or experimental) adj3 (method$ or study or trial or design$))).ti,ab,hw.
29	("time series" adj2 interrupt$).ti,ab,hw.

TABLE C-1 Continued

Search Number	Search Terms
30	(time points adj3 (over or multiple or three or four or five or six or seven or eight or nine or ten or eleven or twelve or month$ or hour? or day? or "more than")).ab.
31	pilot.ti.
32	Pilot projects/
33	(clinical trial or controlled clinical trial or multicenter study).pt.
34	(multicentre or multicenter or multi-centre or multi-center).ti.
35	random$.ti,ab. or controlled.ti.
36	(control adj3 (area or cohort? or compare? or condition or design or group? or intervention? or participant? or study)).ab. not (controlled clinical trial or randomized controlled trial).pt.
37	comment on.cm. or review.ti,pt. or randomized controlled trial.pt.
38	or/24-41
39	exp cohort studies/
40	cohort$.tw.
41	controlled clinical trial.pt.
42	epidemiologic methods/
43	exp case-control studies/
44	(case$ and control$).tw.
45	or/43-48
46	11 and 19
47	11 and 38
48	11 and 45
49	or/46-48
50	limit 49 to yr="2012 -Current"
51	limit 50 to "review articles"
52	50 not 51
	c. Primary Studies: Marrs et al. Search Strategy
1	Measles/ or measles.mp,
2	exp Mumps/ or mumps.mp,
3	Whooping Cough/ or whooping cough.mp,
4	exp Pneumonia/ or pneumonia.mp,
5	exp Chickenpox/ or chickenpox.mp,
6	hepatitis/ or hepatitis a/ or exp hepatitis b/

continued

TABLE C-1 Continued

Search Number	Search Terms
7	Hepatitis A/ or exp Hepatitis B/
8	hepatitis.mp,
9	exp Herpes Simplex/ or herpes simplex.mp,
10	exp Rubella/ or rubella.mp,
11	exp Helicobacter pylori/ or helicobacter pylori.mp,
12	exp Tuberculosis/ or tuberculosis.mp,
13	exp Mycobacterium bovis/
14	exp Helminthiasis/
15	helminthiasis.mp,
16	exp Helminths/
17	helminths.mp,
18	exp Necator americanus/
19	Necator americanus.mp,
20	exp Trichuris/ or trichuris.mp,
21	exp Ascaris lumbricoides/ or Ascaris lumbricoides.mp,
22	exp Schistosomiasis/ or Schistosomiasis.mp,
23	exp Enterobius/
24	enterobius vermicularis.mp,
25	exp Bacterial Infections/
26	bacterial infection*.mp,
27	or/1-26
28	hygiene/ or skin care/
29	hygiene.mp,
30	hygiene hypothesis.mp,
31	exp Anthroposophy/
32	anthroposoph*.mp,
33	Child Day Care Centers/
34	day care.mp,
35	Siblings/
36	sibling*.mp,
37	Birth Order/
38	birth order.mp,
39	nurser*.mp,

TABLE C-1 Continued

Search Number	Search Terms
40	agriculture/ or animal husbandry/
41	agriculture.mp,
42	farming.mp,
43	farms.mp,
44	farm.mp,
45	Animals, Domestic/
46	pets.mp,
47	pet.mp,
48	Cats/
49	cats.mp,
50	cat.mp,
51	Dogs/
52	dog.mp,
53	dogs.mp,
54	exp Endotoxins/
55	endotoxin*.mp,
56	exp Probiotics/
57	probiotic*.mp,
58	lactobacillus.mp,
59	exp Lactobacillus/
60	intestinal microflora.mp,
61	mycobacterium vaccae.mp,
62	Prebiotics/
63	pre-biotic*.mp,
64	prebiotic*.mp,
65	pro-biotic*.mp,
66	exp Anti-Bacterial Agents/
67	antibiotic*.mp,
68	Disinfectants/ or disinfectant.mp,
69	vaccination.mp,
70	vaccinat*.mp,
71	unpasteuri* milk.mp,
72	unpasteuri* cow* milk.mp,

continued

TABLE C-1 Continued

Search Number	Search Terms
73	pasteuri* milk.mp,
74	pasteuri* cow* milk.mp,
75	raw milk.mp,
76	raw cow* milk.mp,
77	unhomogeni* milk.mp,
78	unhomogeni* cow* milk.mp,
79	un-pasteuri* milk.mp,
80	un-homogeni* milk.mp,
81	or/28-80
82	27 or 81
83	exp food hypersensitivity/ or exp egg hypersensitivity/ or exp milk hypersensitivity/ or exp nut hypersensitivity/ or exp peanut hypersensitivity/ or exp wheat hypersensitivity/
84	(food$ adj2 (allergy$ or hypersensitivity)).mp.
85	((milk or egg$ or shellfish or fish or nut$ or peanut$ or wheat or soybean$ or seasame or seafood$) adj1 (allerg$ or hypersensitivity or sensitization)).mp,
86	(sensitization or hypersensitivity).mp,
87	(food$ or diet$).mp,
88	86 and 87
89	83 or 84 or 85 or 88
90	88 and 89
91	Cesarean Section/
92	caesarian section.mp,
93	cesarian section.mp,
94	mode of delivery.mp,
95	microbiota.mp,
95	82 or 91 or 92 or 93 or 94 or 95
96	90 and 95
97	limit 96 to “review articles”
98	96 not 97
99	limit 98 to yr=“2012 -Current”

BOX C-1
Study Inclusion Criteria

Studies that reported food allergy or sensitization outcomes, including
- Food challenge outcomes,
- Physician-diagnosed food allergy,
- Reported doctor diagnosis of food allergy,
- Food sensitization diagnosed by either skin prick testing (SPT) or elevated food-specific serum immunoglobulin E (sIgE) levels, and
- Self-reported food allergies or sensitizations.

Study designs of interest:
- Systematic reviews with or without meta-analysis
- Randomized controlled trials
- Quasi-randomized controlled trials and controlled clinical trials (defined as studies where the comparison group is not fully randomized)
- Controlled before-and-after studies (only where a clearly defined comparison group is available prospectively) and interrupted time series studies
- Prospective cohort studies
- Interrupted time series studies
- Case-control studies
- Cross-sectional studies

Determinants and prevention factors of interest:
- Preconception factors
- Lactation
- Food introduction
- Microbiome/prebiotics/probiotics
- Hygiene hypothesis related factors (parity, living environment, pets, siblings, cesarean section delivery, prenatal and postnatal antibiotics use),
- Nutrient factors: vitamin D, fatty acid profiles (e.g., omega-3), folic acid
- Maternal dietary intake during pregnancy, lactation, child, adult
- Infant breastfeeding versus formula feeding
- Genetics, epigenetics (gene-environment interactions)
- Epithelial barrier function

BOX C-2
Study Exclusion Criteria

Studies seeking to prevent potential manifestations of food allergy (e.g., atopic eczema/dermatitis or asthma) but not including an explicit diagnosis of sensitization to food or food allergy or studies investigating celiac disease were excluded, as well as management guidance documents, narrative reviews, letters to the editor, commentaries, studies that used animal or in vitro models, ecological studies, and studies of transplant patients.

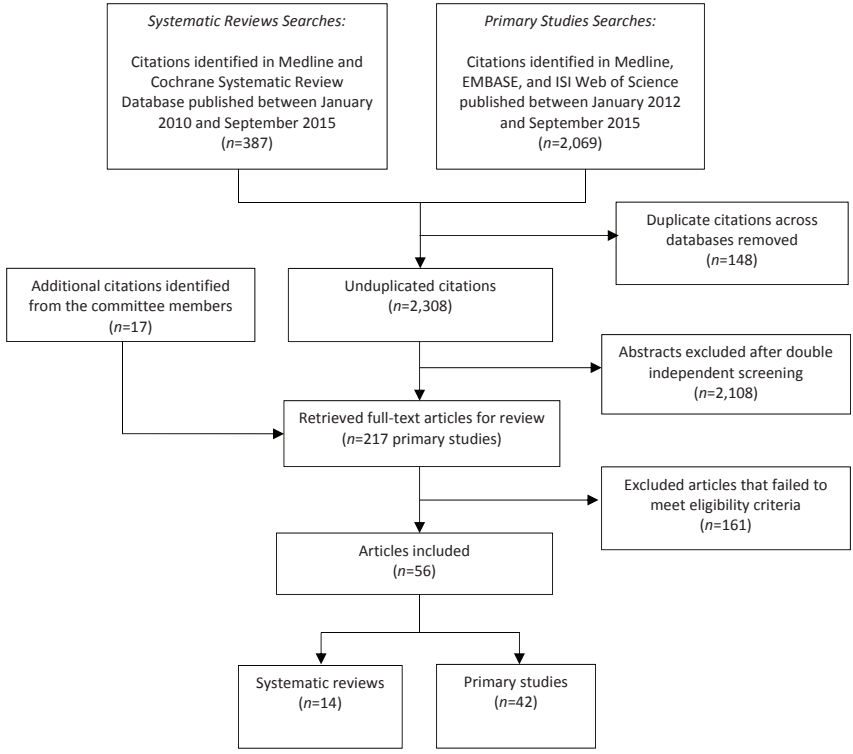

FIGURE C-1 Literature search and study selection process.

TABLE C-2a BEGINS ON THE NEXT PAGE

TABLE C-2a Microbial Exposure Hypothesis (Randomized Controlled Trials)

Author, Year	Study Design, Country	Population	N	Age When Outcome Was Ascertained
Prebiotics/Probiotics				
Ivakhnenko and Nyankovskyy, 2013	Randomized controlled trial (formula feeding) + 1 BF group (nonrandomized), Ukraine	Healthy, term newborns	80 BF infants; 160 formula fed infants (80 formula enriched with the specific mixture of oligo-saccharides; 80 standard formula)	18 months

NOTE: BF = breastfed; CI = confidence interval; GI = gastrointestinal; OFC = oral food challenge.

[a] **Bold** indicates statistical significance at P<0.05. Results were reported as odds ratio (95% confidence interval) unless otherwise noted. Adjusted results were extracted in the summary table unless otherwise noted.

Food Allergy or Sensitization Outcome Definition	Exposure	Odds Ratio[a] (95% CI) of Food Allergy	Comments
Allergic reactions to food (not defined) Allergic reactions to cow milk protein (not defined) GI symptoms of food allergy (not defined)	BF (group 1) versus formula enriched with oligosaccharides (scGOS/lcFOS; 9:1; 8 g/L) (group 2) versus standard formula (group 3)	Allergic reactions to food: **2/51 (3.92%) versus 3/62 (4.84%) versus 9/53 (16.98%); P<0.05** Allergic reactions to cow milk: **1/51 (1.96%) versus 2/62 (3.23%) versus 8/53 (15.09%); P<0.05** GI symptoms of food allergy: **1/51 (1.96%) versus 2/62 (3.23%) versus 7/53 (13.21%); P<0.05**	51 (63.7%), 62 (77.5%), and 53 (66.3%) infants in groups 1, 2, and 3, respectively, completed the study. Analysis was done in completers only. Duration and exclusivity of BF were not measured. Food allergy not confirmed by OFC.

TABLE C-2b Microbial Exposure Hypothesis (Observational Studies)

Author Year	Study Design, Country	Population	N	Age When Outcome Was Ascertained
Prebiotics/Probiotics				
Loo et al., 2014	Long-term follow-up of a RCT, Singapore	Asian infants at risk for allergic disease	226	3-5 years
West et al., 2013	Long-term follow-up of an RCT, Sweden	Healthy, term infants with no prior allergic manifestations	121	8-9 years
Route of Delivery				
McGowan et al., 2015	Prospective cohort, Baltimore, Boston, New York City, St. Louis	Children from the Urban Environment and Childhood Asthma (URECA) study	516	1-5 years

Food Allergy or Sensitization Outcome Definition	Exposure	Odds Ratio[a] (95% CI) of Food Allergy	Comments
Ever had food allergy (history of convincing symptoms of food allergy and the presence of IgE allergen) since year 3	Intervention: Cow milk formula supplemented with probiotics (BL999 and LPR) from birth to age 6 months (N=117) Control: Cow milk formula supplemented without probiotics (N=109)	RR=1.1 (0.1-17.0)	245 infants were randomized; 220 (87%) completed 5-year follow-up. The analysis was done in 226 children (number of dropouts by groups was not reported).
IgE-associated food allergy	Intervention: Infant cereals with addition of probiotics (LF19 1×10^8 CFU per serving) from 4 to age 13 months (N=59) Control: Infant cereals without addition of probiotics (N=62)	1.05 (0.14-7.73)	171/179 randomized infants completed the trial; 121 children in the long-term follow-up. More children in the placebo group received antibiotics during intervention than probiotic group (32.3% versus 16.9%, P=0.05). Unadjusted analysis.
Food allergy (N=51) or sensitization (N=286): sIgE to milk, egg, peanut; clinical history	(1) Caesarean section (food allergy versus not allergic) (2) Caesarean section (food sensitized versus not sensitized)	(1) 23.5% versus 31.6%; P=0.31 (2) 31.5% versus 30.9%; P=0.96	Unadjusted analysis.

continued

TABLE C-2b Continued

Author Year	Study Design, Country	Population	N	Age When Outcome Was Ascertained
Peters et al., 2015	Prospective cohort, Australia	Infants from the HealthNuts study	5,276	1 year
Grimshaw et al., 2014	Prospective nested case-control study, UK	Cases: all infants with food allergy by age of 2 years from the Prevalence of Infant Food Allergy (PIFA) study Controls: age-matched controls from the PIFA study	123 (41 with food allergy; 82 controls)	1-2 years
Luccioli et al., 2014	Prospective cohort, US	Children who participated in the Infant Feeding Practices Study (IFPS) II	1,363	6 years

Food Allergy or Sensitization Outcome Definition	Exposure	Odds Ratio[a] (95% CI) of Food Allergy	Comments
IgE-mediated food allergy = positive OFC in the presence of positive test of sensitization (SPT ≥2 mm or sIgE ≥0.35 kua/L). Separate analysis for single egg allergy (9% of the cohort), multiple food allergies predominantly peanut (3% of the cohort), and multiple food allergies predominantly egg (2% of the cohort), comparing to no allergic disease at baseline.	Caesarean section versus vaginal birth	Single egg allergy: 1.02 (0.81-1.29) Multiple food allergies - peanut: 1.24 (0.86-1.78) Multiple food allergies - egg: 0.93 (0.56-1.60)	5,142 infants underwent SPT to egg, peanut, or sesame and 1,089 infants were eligible for hospital assessment, of whom 908 participated in OFC.
Food allergy determined by SPT, physical exam, clinical history, sIgE, DBPCOFC	Birth by caesarean section (cases versus controls)	31.7% versus 24.4%; P=0.255	Unadjusted analysis except for pet ownership.
Physician-diagnosed food allergy as reported by parent	Caesarean section versus vaginal birth	1.37 (0.84-2.21)	

continued

TABLE C-2b Continued

Author Year	Study Design, Country	Population	N	Age When Outcome Was Ascertained
Depner et al., 2013	Prospective cohort, Austria, Finland, France, Germany, Switzerland	Children from the Protection against Allergy-Study in Rural Environments (PASTURE) birth cohort	686	Birth to 1 year
Pele et al., 2013	Prospective cohort, France	Respondents to the 2-year follow-up FFQ of the PELAGIE mother–child cohort study	1,487	2 years
Pyrhonen et al., 2013	Retrospective cohort study, Finland	Children identified from the South Karelian Allergy Research Project (SKARP), a population-based study comprising all children of a given age range and living in the same province.	3,181	1-4 years

Food Allergy or Sensitization Outcome Definition	Exposure	Odds Ratio[a] (95% CI) of Food Allergy	Comments
sIgE to food allergens (hen egg, cow milk, peanut, hazlenut, carrot, wheat flour)	Caesarean section	1.18 (0.69-2.03)	793 (378 farm and 415 nonfarm) children were included in the analyses, of whom 686 were included in IgE to food allergens model.
Mother-reported food allergy in children (N=136): 37 had a medical diagnosis of cow milk allergy, 41 had a medical diagnosis of food allergy, and 22 of both, while 36 children had no doctor's diagnosis	Cesarean section (yes versus no)	8.7% versus 9.1%; P=0.10	Nonrespondents (N=1,496) were younger at the birth of the child, less educated, and more likely to smoke. These factors were considered as covariates in the paper. Unadjusted analysis results only.
Physician-diagnosed allergic manifestations: positive specific IgE test, SPT, open food challenge (did not specify which foods)	Caesarean section	1.15 (0.80-1.63)	Large nonresponse rate.

continued

TABLE C-2b Continued

Author Year	Study Design, Country	Population	N	Age When Outcome Was Ascertained
Dowhower Karpa et al., 2012	Retrospective case-control study, US	Cases: children visiting an allergy specialty clinic for a food allergy–related concern who were also born at the institution's medical center. Age- and sex-matched controls: children visiting primary care practice who were also born at the institution's medical center.	99 case; 192 controls	No data
Antibiotics Use				
Grimshaw et al., 2014	Prospective nested case-control study, UK	Cases: all infants with food allergy by age of 2 years from the PIFA study Controls: age-matched controls from the PIFA study	123 (41 with food allergy; 82 controls)	1-2 years

Food Allergy or Sensitization Outcome Definition	Exposure	Odds Ratio[a] (95% CI) of Food Allergy	Comments
ICD-9-CM coding consistent with food-related allergic reactions and a confirmed presence of food allergies documented by either a positive serum specific IgE test or positive SPT	Caesarean (cases versus controls)	32.2% versus 33.9%; P=0.79	Retrospective chart review. Possible selection bias. Unadjusted analysis results only.
Food allergy determined by SPT, physical exam, clinical history, sIgE, double-blind placebo controlled food challenge	Maternal antibiotic use (cases versus controls)	No significant associations during or after pregnancy or while breastfeeding	Unadjusted analysis except for pet ownership.

continued

TABLE C-2b Continued

Author Year	Study Design, Country	Population	N	Age When Outcome Was Ascertained
Metsala et al., 2013	Prospective nested case-control study, Finland	Cases: infants who had received a special reimbursement for the cost of special infant formulas based on diagnosed cow milk allergy. Controls: randomly selected and matched for date of birth, sex, and the hospital district of birth.	16,237 case-control pairs	0-2 years
Dowhower Karpa et al., 2012	Retrospective case-control study, US	Cases: children visiting an allergy specialty clinic for a food allergy-related concern who were also born at the institution's medical center. Age-and-sex matched controls: children visiting primary care practice who were also born at the institution's medical center.	99 case; 192 controls	No data

Food Allergy or Sensitization Outcome Definition	Exposure	Odds Ratio[a] (95% CI) of Food Allergy	Comments
Pediatric certification of cow milk allergy based on clinical exam, symptoms, elimination diet, SPT, and elevated serum-specific IgE or open challenge test	(1) Maternal use of antibiotics before pregnancy (2) Maternal use of antibiotics during pregnancy (3) Child's use of antibiotics from birth to 1 month	(1) **1.26 (1.20-1.33)** (2) **1.21 (1.14-1.28)** (3) **1.71 (1.59-1.84)**	
ICD-9-CM coding consistent with food-related allergic reactions and a confirmed presence of food allergy documented by either a positive serum specific IgE test or positive SPT	(1) Neonatal antibiotics (cases versus controls) (2) Peripartum antibiotics (cases versus controls)	(1) 16.2% versus 12.5%; P=0.39 (2) 28.3% versus 28.1%; P=1.0	Retrospective chart review. Possible selection bias. Unadjusted analysis results only.

continued

TABLE C-2b Continued

Author Year	Study Design, Country	Population	N	Age When Outcome Was Ascertained
Exposure to Animals				
Martin et al., 2015	Prospective cohort, Australia	Infants from the HealthNuts study	4,453 (2,795 without eczema; 1,903 with eczema)	1 year
Peters et al., 2015	Prospective cohort, Australia	Infants from the HealthNuts study	5,276	1 year

Food Allergy or Sensitization Outcome Definition	Exposure	Odds Ratio[a] (95% CI) of Food Allergy	Comments
SPT or sIgE, OFC (egg white, peanut, sesame) or parent report of recent immediate-type reaction	(1) Pet dog among infants without eczema; among infants with eczema	(1) 0.9 (0.6-1.5); 0.7 (0.5-0.9)	Same cohort as Peters et al., 2015, but different analyses and outcome definitions. [Note: cesarean section results were not extracted for this study because for this factor the analysis was unadjusted.]
	(2) Pet cat among infants without eczema; among infants with eczema	(2) 0.9 (0.5-1.6); 0.6 (0.4-0.8)	
IgE-mediated food allergy = positive OFC in the presence of positive test of sensitization (SPT ≥2 mm or sIgE ≥0.35 kua/L). Separate analysis for single egg allergy (9% of the cohort), multiple food allergies, predominantly peanut (3% of the cohort), and multiple food allergies predominantly egg (2% of the cohort), compared to no allergic disease at baseline.	(1) Dogs allowed inside the home versus no dogs	(1) Single egg allergy: 0.76 (0.56-1.05) Multiple food allergies - peanut: **0.40 (0.21-0.73)** Multiple food allergies - egg: 0.59 (0.26-1.34)	5,142 infants underwent SPT to egg, peanut or sesame and 1,089 infants were eligible for hospital assessment, of whom 908 participated in OFC.
	(2) Dogs outside only versus no dogs	(2) Single egg allergy: **1.56 (1.10-2.21)** Multiple food allergies - peanut: 0.82 (0.44-1.54) Multiple food allergies - egg: 0.39 (0.13-1.18)	
	(3) Pet cats versus no dogs	(3) Single egg allergy: 0.80 (0.57-1.12) Multiple food allergies - peanut: 0.83 (0.47-1.47) Multiple food allergies - egg: 0.86 (0.38-1.91)	

continued

TABLE C-2b Continued

Author Year	Study Design, Country	Population	N	Age When Outcome Was Ascertained
Grimshaw et al., 2014	Prospective nested case-control study, UK	Cases: all infants with food allergy by age of 2 years from the PIFA study Controls: age-matched controls from the PIFA study	123 (41 with food allergy; 82 controls)	1-2 years
Stelmach et al., 2014	Prospective cohort, Poland	Children from the Polish Mother and Child Cohort Study (REPRO_PL cohort)	501	1-2 years
Depner et al., 2013	Prospective cohort, Austria, Finland, France, Germany, Switzerland	Children from the Protection against PASTURE birth cohort	686	Birth to 1 year
Goldberg et al., 2013	Prospective case-cohort study, Israel	Cases: IgE-cow milk allergy children identified from a cohort study (Katz, 2010) Controls: healthy children randomly chosen from the cohort	66 cases 156 controls	2-3 years

Food Allergy or Sensitization Outcome Definition	Exposure	Odds Ratio[a] (95% CI) of Food Allergy	Comments
Food allergy determined by SPT, physical exam, clinical history, sIgE, DBPCOFC	Pet ownership (yes versus no)	1.275 (0.49-3.33)	
Food allergy ever diagnosed by doctor according to international guidelines	Pets at home during pregnancy (yes versus no)	**1.48 (1.02-2.16)**	Frequency of cleaning was not associated with food allergy and was dropped out from multivariate model.
sIgE to food allergens (hen egg, cow milk, peanut, hazlenut, carrot, wheat flour)	(1) Early contact with sheep, goats, hares (2) Farming	(1) 0.92 (0.75-1.13) (2) **2.11 (1.33-3.34)**	793 (378 farm and 415 nonfarm) children were included in the analyses, of whom 686 were included in IgE to food allergens model.
IgE-mediated cow milk allergy defined by a suggestive history of an immediate response, a positive SPT response, and, in most cases, a positive challenge result to cow milk protein	Pets in home (cases versus controls)	26.2% versus 30.1%; P=0.72	Unadjusted analysis.

continued

TABLE C-2b Continued

Author Year	Study Design, Country	Population	N	Age When Outcome Was Ascertained
Pele et al., 2013	Prospective cohort, France	Respondents to the 2-year follow-up FFQ of the PELAGIE mother–child cohort study	1,487	2 years
Koplin et al., 2012	Prospective cohort, Australia	Infants from the HealthNuts study	4,963	1 year

NOTE: CI = confidence interval; DBPCOFC = double-blind, placebo-controlled oral food challenge; FFQ = food frequency questionnaire; IgE = immunoglobulin E; OFC = oral food challenge; RAST = radioallergosorbent test; RR = relative risk; sIgE = food-specific serum IgE; SPT = skin prick test; UK = United Kingdom; US = United States.

[a] **Bold** indicates statistical significance at P<0.05. Results were reported as odds ratio (95% confidence interval) unless otherwise noted. Adjusted results were extracted in the summary table unless otherwise noted.

Food Allergy or Sensitization Outcome Definition	Exposure	Odds Ratio[a] (95% CI) of Food Allergy	Comments
Mother-reported food allergy in children (N=136): 37 had a medical diagnosis of cow milk allergy, 41 a medical diagnosis of food allergy, and 22 of both, while 36 children had no doctor's diagnosis	Farm animal contact (yes versus no)	8.9% versus 9.1%; P=0.88	Nonrespondents (N=1,496) were younger at the birth of the child, less educated, and more likely to smoke. These factors were considered as covariates in the paper. Unadjusted analysis results only.
IgE-mediated egg allergy: Allergic on formal egg challenge or previous history of clear reaction to egg occurring within 1 month of a positive SPT or RAST	(1) Dog outside only versus no dog (2) Dog allowed inside versus no dog (3) Cat outside only versus no cat (4) Cat allowed inside versus no cat	(1) 1.09 (0.75-1.57) (2) **0.72 (0.52-0.99)** (3) 0.93 (0.49-1.77) (4) 0.75 (0.52-1.09)	Same cohort as Peters et al., 2015 but different analyses and outcome definitions.

TABLE C-3a Allergen Avoidance Hypothesis (Randomized Controlled Trials)

Author Year	Study Design, Country	Population	N	Age When Outcome Was Ascertained
Breastfeeding				
Ivakhnenko and Nyankovskyy, 2013	Randomized controlled trial (formula feeding) + 1 BF group (nonrandomized), Ukraine	Healthy, term newborns	80 BF infants; 160 formula fed infants (80 formula enriched with the specific mixture of oligosaccharides; 80 standard formula)	18 months
Infant Formula				
Lowe et al., 2011	RCT, Australia	Infants with a family history of allergic disease	620	6, 12, and 24 months

NOTE: BF = breastfed; CI = confidence interval; GI = gastrointestinal; pHWF = partially hydrolyzed whey formula.

[a] **Bold** indicates statistical significance at P<0.05. Results were reported as odds ratio (95% confidence interval) unless otherwise noted. Adjusted results were extracted in the summary table unless otherwise noted.

Food Allergy or Sensitization Outcome Definition	Exposure	Odds Ratio[a] (95% CI) of Food Allergy	Comments
Allergic reactions to food (not defined) Allergic reactions to cow milk protein (not defined) GI symptoms of food allergy (not defined)	BF (group 1) versus formula enriched with oligosaccharides (scGOS/lcFOS; 9:1; 8 g/L) (group 2) versus standard formula (group 3)	Allergic reactions to food: **2/51 (3.92%)** versus **3/62 (4.84%)** versus **9/53 (16.98%); P<0.05** Allergic reactions to cow milk: **1/51 (1.96%)** versus **2/62 (3.23%)** versus **8/53 (15.09%); P<0.05** GI symptoms of food allergy: **1/51 (1.96%) versus 2/62 (3.23%) versus 7/53 (13.21%); P<0.05**	51 (63.7%), 62 (77.5%), and 53 (66.3%) infants in groups 1, 2, and 3, respectively, completed the study. Analysis was done in completers only. Duration and exclusivity of BF were not measured. Food allergy not confirmed by OFC.
Food reaction, SPT (milk, egg, peanut)	Soy-based formula, pHWF, or cow milk formula at cessation of breastfeeding	Positive SPT to cow milk within first 2 years: pHWF versus CMF: 0.79 (0.35-1.77) Soy formula versus CMF: 0.78 (0.32-1.92) Any food reaction: pHWF versus CMF: 0.95 (0.51-1.75) Soy formula versus CMF: 1.21 (0.67-2.19)	

TABLE C-3b Allergen Avoidance (Observational Studies)

Author, Year	Study Design, Country	Population	N	Age When Outcome Was Ascertained
Maternal Intake During Pregnancy and Lactation				
Bunyavanich et al., 2014	Prospective cohort, US	Mother-child pairs in the Project Viva prebirth cohort recruited from a large multidisciplinary practice	1,277 mother–child pairs	7.9 years (mean)

Food Allergy or Sensitization Outcome Definition	Exposure	Odds Ratio[a] (95% CI) of Food Allergy	Comments
Food allergy to peanut, milk, wheat, egg, and/or soy based on sIgE to the particular food and EpiPen prescribed. Food allergy to peanut was more specifically defined by parent report of convincing symptoms of a peanut allergic reaction (history of peanut allergy AND a cutaneous, respiratory, cardiovascular, gastrointestinal and/or anaphylactic symptom following peanut ingestion).	Maternal intake (total servings per day as measured by FFQ) during first and second trimester of: (1) peanut (2) milk (3) wheat (4) egg (5) soy Intake reported as z-scores	First trimester (1) **0.53 (0.30-0.94)** (2) 0.90 (0.50-1.62) (3) 1.26 (0.75-2.12) (4) 0.76 (0.28-2.08) (5) 0.61 (0.16-2.31) Second trimester (1) 0.88 (0.61-1.27) (2) 1.47 (0.91-2.37) (3) 1.07 (0.62-1.85) (4) 0.77 (0.28-2.15) (5) 1.18 (0.95-1.48)	All ORs are adjusted for child age, sex, breastfeeding history, parental atopy, and maternal education.

continued

TABLE C-3b Continued

Author, Year	Study Design, Country	Population	N	Age When Outcome Was Ascertained
Frazier et al., 2014	Prospective cohort, US	Boys and girls (born between 1990 and 1994) participating in the Growing Up Today Study 2 (GUTS2) and their mothers. (These are children of women in the Nurse's Health Study II.)	8,205 mother–child pairs	Unclear

Food Allergy or Sensitization Outcome Definition	Exposure	Odds Ratio[a] (95% CI) of Food Allergy	Comments
Peanut or tree nut (walnut, almond, pistachio, cashew, pecan, hazelnut, macadamia, and Brazil nut) allergy in offspring based on maternal confirmation of food allergy diagnosis, review of physical copies of laboratory results of testing (SPT, sIgE, OFC) by two board-certified pediatricians, and confirmation of food allergy in writing from the child's treating physician	Peripregnancy maternal consumption of peanuts or tree nuts: (1) <1 serving/ month (2) 1-3 servings/ month (3) 1-4 servings/ week (4) ≥5 servings/ week	Multivariable OR (1) reference group (2) 0.90 (0.55-1.48) (3) 0.65 (0.43-0.97) (4) 0.58 (0.34-0.99) P_{trend}=0.04	The dietary questionnaires were not specific for the actual dates of the pregnancy but were chosen as the one completed closest to the child's date of birth. Only 45% of the dietary questionnaires were completed during the pregnancy; 76% were within 1 year of the pregnancy. Multivariable models control for continuous maternal age, maternal history of non-nut food allergy, maternal allergic rhinitis, eczema, or asthma, and season at child's birth (spring or summer versus fall or winter).

continued

TABLE C-3b Continued

Author, Year	Study Design, Country	Population	N	Age When Outcome Was Ascertained
Pele et al., 2013	Prospective cohort, France	Respondents to the 2-year follow-up FFQ of the PELAGIE mother–child cohort study	1,500 mother–child pairs	2 years

Food Allergy or Sensitization Outcome Definition	Exposure	Odds Ratio[a] (95% CI) of Food Allergy	Comments
Mother-reported food allergy in children (N=136): 37 had a medical diagnosis of cow milk allergy, 41 a medical diagnosis of food allergy, and 22 of both, while 36 children had no doctor's diagnosis	(1) Maternal pre-pregnancy consumption of fish (<1 time/month versus 1-4 times/month)	(1) 1.27 (0.72-2.24)	Nonrespondent mothers (N=1,496) were younger at the birth of the child, less educated, and more likely to smoke than the participants (N=1,500). These factors were considered as covariates in the paper. ORs adjusted for: mother's age, maternal education, folic acid supplementation, familial history of asthma/allergy, child's sex, small-for-gestational age, infant's method of feeding, day care attendance, postnatal exposure to tobacco, and child's age at follow-up.
	(2) Maternal pre-pregnancy consumption of fish (<1 time/month versus ≥2 times/week)	(2) 1.48 (0.80-2.76)	
	(3) Maternal pre-pregnancy consumption of shellfish (<1 time/month versus ≥1 time/month) All exposures measured by FFQ	(3) **1.62 (1.11-2.37)**	

continued

TABLE C-3b Continued

Author, Year	Study Design, Country	Population	N	Age When Outcome Was Ascertained
Breastfeeding				
McGowan et al., 2015	Prospective cohort, Baltimore, Boston, New York City, St. Louis	Children from the Urban Environment and Childhood Asthma (URECA) study	516	1-5 years

Food Allergy or Sensitization Outcome Definition	Exposure	Odds Ratio[a] (95% CI) of Food Allergy	Comments
Food allergy (N=51) or sensitization (N=286): sIgE to milk, egg, peanut; clinical history	(1) Ever BF	(1) Food allergy versus no food allergy: **35/51 (68.8%) versus 193/377 (52.9%); P=0.05** Food sensitization versus no food sensitization: 161/286 (58.3%) versus 121/230 (53.8%); P=0.35	Of the 609 children initially enrolled, 516 (85%) were included. Unadjusted analysis.
	(2) BF at 3 months	(2) Food allergy versus no food allergy: 16/51 (32.7%) versus 76/377 (22.8%); P=0.18 Food sensitization versus no food sensitization: 64/286 (25.1%) versus 48/230 (23.4%); P=0.76	

continued

TABLE C-3b Continued

Author, Year	Study Design, Country	Population	N	Age When Outcome Was Ascertained
Peters et al., 2015	Prospective cohort, Australia	Infants from the HealthNuts study	5,276	1 year
Grimshaw et al., 2013	Prospective nested case-control study, UK	Cases: all infants with food allergy by age of 2 years from the Prevalence of Infant Food Allergy (PIFA) study Controls: age-matched controls from the PIFA study	123 (41 with food allergy; 82 controls)	1-2 years

Food Allergy or Sensitization Outcome Definition	Exposure	Odds Ratio[a] (95% CI) of Food Allergy	Comments
IgE-mediated food allergy = positive OFC in the presence of positive test of sensitization (SPT ≥2 mm or sIgE ≥0.35 kua/L). Separate analysis for single egg allergy (9% of the cohort), multiple food allergies predominantly peanut (3% of the cohort), and multiple food allergies predominantly egg (2% of the cohort), comparing to no allergic disease at baseline	Duration of BF (up to 12 months)	Single egg allergy: 1.02 (0.99-1.04) Multiple food allergy (predominantly peanut): 1.00 (0.96-1.05) Multiple food allergy (predominantly egg): **1.17 (1.09-1.24)**	5,142 infants underwent SPT to egg, peanut, or sesame and 1,089 infants were eligible for hospital assessment, of whom 908 participated in OFC. Multinomial logistic regression was used to determine risk factors for each class, also weighted for posterior probabilities of class membership. Three separate multivariable models were fitted for the three categories of risk factors (parental, infant, and environmental).
Food allergy determined by SPT, physical exam, clinical history, sIgE, DBPCOFC	(1) BF duration, median weeks (2) Exclusive BF, median weeks (3) % BF initiation	(1) Cases versus controls: 21.0 (3.0-30.5) versus 24.0 (7.0-31.0); P=0.295 (2) Cases versus controls: 5.0 (2.8-16.3) versus 8.5 (4.0-15.0); P=0.933 (3) Cases versus controls: 92.7% versus 96.3%; P=0.21	Only age adjusted (matching factor).

continued

TABLE C-3b Continued

Author, Year	Study Design, Country	Population	N	Age When Outcome Was Ascertained
Liao et al., 2014	Prospective cohort, Taiwan	Infants ≥37 weeks from the The Prediction of Allergy in Taiwanese Children (PATCH) cohort	258 (238, 226, 217, 210, and 198 completed 6, 12, 18, 24, and 36 months of follow-ups)	6, 12, 18, 24, and 36 months

Food Allergy or Sensitization Outcome Definition	Exposure	Odds Ratio[a] (95% CI) of Food Allergy	Comments
sIgE antibody included a mix of six common allergens: Dermatophagoides pteronyssinus (Dp), Dermatophagoides farinae (Df), egg white, cow milk, Cladosporium herbarum (Hormodendrum), and wheat. Participants were characterized as atopic or been sensitized if any of the sIgE level was greater than 0.35 IU/ml.	(1) Exclusive BF ≥4 versus <4 months	(1) Cow milk sensitization at 6, 12, 18, 24, 36 months: 1.0 (0.3, 3.3); **0.2 (0.07-0.5; 0.2 (0.07-0.5); 0.3 (0.1-0.7)**; 0.6 (0.2-1.7) Egg sensitization at 6, 12, 18, 24, 36 months: 1.3 (0.5-3.5); 1.4 (0.5-3.7); 1.6 (0.7-3.8); 1.6 (0.7-3.7); 0.7 (0.2-2.0)	Of the original 258 neonates, blood samples and questionnaires were available from 238 infants at the age of 6 months. 226, 217, 210, and 198 children completed 12, 18, 24 and 36 months of follow-ups, respectively. Unadjusted analysis only.
	(2) Partial BF	(2) Cow milk sensitization: There was a trend of reduced risk for cow milk protein sensitization as duration of partial breastfeeding was increased; the result was not statistically significant	

continued

TABLE C-3b Continued

Author, Year	Study Design, Country	Population	N	Age When Outcome Was Ascertained
Luccioli et al., 2014	Prospective cohort, US	Children who participated in the Infant Feeding Practices Study (IFPS) II	1,363 (823 high-risk group)	6 years
Mailhol et al. 2014	Cross-sectional study, France	Children (0 to 18 years of age) with atopic dermatitis seen consecutively at multi-disciplinary clinics from May 2002 to December 2008	386	0 to 18 years

Food Allergy or Sensitization Outcome Definition	Exposure	Odds Ratio[a] (95% CI) of Food Allergy	Comments
Total pFA (all children with a current physician diagnosis of food allergy at age 6 years). (N=89, 7%) New pFA (subset of children with physician diagnosis of food allergy at age 6 years but with no diagnosis before 1 year of age) (N=71, 5.2%) High-risk pFA (subset of children with pFA at age 6 years and report of any of the following atopic risk factors: family history of food allergy, family history of other atopy, or eczema before age 1 year)	Exclusive BF duration 1-3 months, ≥4 months versus 0 months (reference group)	Total pFA: Exclusive BF 1-3 month = 0.72 (0.42-1.23) Exclusive BF ≥4 months = 0.69 (0.36-1.29) New pFA: Exclusive BF 1-3 month = 0.78 (0.43-1.38) Exclusive BF ≥4 months = 0.51 (0.24-1.03) High risk pFA: Exclusive BF 1-3 month = 0.81 (0.42-1.51) Exclusive BF ≥4 months = 0.58 (0.26-1.25)	Adjusted for mother's education, race, income, child's gender, parity, type of delivery, family history of food allergy, family history of other atopy, reported eczema before age 1 year, maternal tobacco smoke, other tobacco smoke exposure in home, complementary food introduction by infant age.
SPT. Positive (histamine 10 mg/mL [Stallergenes, Antony, France]) and negative controls and fresh foods or commercial extracts in the case of food items with histamine-releasing properties were used	Exclusive BF yes versus no	1.8 (0.9-3.5)	Among the 386 evaluated children, food allergy was diagnosed in 69 children, of whom 26 children had a reaction to more than one food item. Duration of exclusive BF was not measured. Note: exclusive BF was dropped out in the final model.

continued

TABLE C-3b Continued

Author, Year	Study Design, Country	Population	N	Age When Outcome Was Ascertained
Stelmach et al., 2014	Prospective cohort, Poland	Children from the Polish Mother and Child Cohort Study (REPRO_PL cohort)	501	1-2 years

NOTE: BF = breastfed; CI = confidence interval; FFQ = food frequency questionnaire; IgE = immunoglobulin E; OFC = oral food challenge; OR = odds ratio; pFA = probable food allergy; RCT = randomized controlled trial; sIgE = food-specific serum IgE; SPT = skin prick test; UK = United Kingdom; US = United States.

[a] **Bold** indicates statistical significance at P<0.05. Results were reported as odds ratio (95% confidence interval) unless otherwise noted. Adjusted results were extracted in the summary table unless otherwise noted.

Food Allergy or Sensitization Outcome Definition	Exposure	Odds Ratio[a] (95% CI) of Food Allergy	Comments
Food allergy ever diagnosed by doctor according to international guidelines	Duration of BF (up to 12 months)	**0.88 (0.82-0.95)**	A stepwise forward procedure was then used to select variables.

TABLE C-4a Dual Antigen Hypothesis (Randomized Controlled Trials)

Author, Year	Study Design, Country	Population	N	Age When Outcome Was Ascertained
Timing of Introduction of Solid Foods and Infant Feeding				
DuToit et al., 2016	RCT, UK (follow-up to primary trial [DuToit et al., 2015])	Children, median age 61.3 months, who had completed the primary trial. Half were in the peanut-avoidance group; the other half were in the peanut-consumption group.	628	72 months
Perkin et al., 2016	RCT, UK	Exclusively breastfed infants age 3 months in the general population	1,303	3 years

Food Allergy or Sensitization Outcome Definition	Exposure	Odds Ratio[a] (95% CI) of Food Allergy	Comments
DBPCOFC to peanut	12 months of peanut avoidance (peanut-avoidance versus peanut-consumption group based on primary trial)	Prevalence of peanut allergy at 72 months: Peanut-avoidance group: **18.6%** Peanut-consumption group: **4.8%** **P<0.001**	
DBPCOFC (peanut, cooked egg, cow milk, sesame, whitefish, and wheat)	Early Introduction Group (EIG): early introduction of 6 allergenic foods Or Standard Introduction Group (SIG): exclusive BF to ~6 months of age. After 6 months, the consumption of allergenic foods was allowed according to parental discretion.	Intention to Treat Analysis • Food allergy to ≥1 allergen (EIG versus SIG); RR=0.80 (0.51-1.25) • Food allergy to individual allergens: all nonsignificant Per Protocol analysis • Food allergy to ≥1 allergen (EIG versus SIG): **RR=0.33 (0.13-0.83)** • Food allergy to peanut (EIG versus SIG): **RR=0** • Food allergy to egg (EIG versus SIG): **RR=0.25 (0.08-0.82)** No significant effects with respect to milk, sesame, fish, or wheat	Low adherence to the protocol in the EIG (42.8%).

continued

TABLE C-4a Continued

Author, Year	Study Design, Country	Population	N	Age When Outcome Was Ascertained
DuToit et al., 2015	RCT, UK	Infants, age least 4 months and less than 11 months at enrollment with severe eczema, egg allergy, or both	640	60 months

Food Allergy or Sensitization Outcome Definition	Exposure	Odds Ratio[a] (95% CI) of Food Allergy	Comments
Clinical history, SPT, OFC, DBPCOFC, sIgE (peanut) 530 had negative SPT at baseline 98 had positive SPT at baseline	Peanut intake (avoidance versus consumption)	Prevalence of peanut allergy at 60 months: *SPT Negative Group* **13.7% avoidance group** **1.9% consumption group** **(P<0.001)** (86.1% relative reduction in the prevalence of peanut allergy) *SPT Positive Group* **35.3% avoidance group** **10.6% consumption group** **(P=0.004)** (70.0% relative reduction in the prevalence of peanut allergy) No significant between-group difference in the incidence of serious adverse events	

continued

TABLE C-4a Continued

Author, Year	Study Design, Country	Population	N	Age When Outcome Was Ascertained
Palmer et al., 2013	RCT, Australia	Singleton term infants with symptoms of moderate-to-severe eczema. Infants who had begun solids before 4 months of age or who had any previous known direct ingestion of egg were excluded	86 49 egg group 37 rice group (control)	12 months

NOTE: CI = confidence interval; EIG = Early Introduction Group; IgE = immunoglobulin E; OFC = oral food challenge; SIG = Standard Introduction Group; sIgE = food-specific serum IgE; SPT = skin prick test; UK = United Kingdom; US = United States.

[a] **Bold** indicates statistical significance at P<0.05. Results were reported as odds ratio (95% confidence interval) unless otherwise noted. Adjusted results were extracted in the summary table unless otherwise noted.

Food Allergy or Sensitization Outcome Definition	Exposure	Odds Ratio[a] (95% CI) of Food Allergy	Comments
IgE-mediated egg allergy, as defined based on the results of an observed pasteurized raw egg challenge and SPT	1 teaspoon of pasteurized raw whole egg powder versus rice powder (control) daily from 4 to 8 months of age Cooked egg was introduced to both groups after an observed feed at 8 months	RR: 0.65 (0.38-1.11)	At 4 months of age, before any known egg ingestion, 36% (24/67) of infants already had egg-specific IgE levels of greater than 0.35 kilounits of antibody (kUA)/L. Egg-specific IgG4 levels were significantly (P<0.001) greater in the egg group at both 8 and 12 months.

TABLE C-4b Antigen Exposure Hypothesis (Observational Studies)

Author, Year	Study Design, Country	Population	N	Age When Outcome Was Ascertained
Diet Diversity				
Grimshaw et al., 2014	Nested case control, UK	Infants from the PIFA Study who had been diagnosed as having a food allergy and their 2 age-matched controls	41 cases 82 controls	2 years
Roduit et al., 2014	Prospective cohort, Europe	Children from rural areas in five European countries	856	Up to age 6 years

NOTE: CI = confidence interval; DBPCOFC = double-blind, placebo-controlled oral food challenge; sIgE = food-specific serum IgE; SPT = skin prick testing; UK = United Kingdom.

[a] **Bold** indicates statistical significance at P<0.05. Results were reported as odds ratio (95% confidence interval) unless otherwise noted. Adjusted results were extracted in the summary table unless otherwise noted.

Food Allergy or Sensitization Outcome Definition	Exposure	Odds Ratio[a] (95% CI) of Food Allergy	Comments
Parent report, physical exam, SPT, sIgE, exclusion diet, DBPCOFC	Dietary patterns during first year of life	Scores were significantly different between the food allergic and control infants (P=0.002) for component 1 (diet high in fruits and vegetables)	Early infant feeding patterns did not have an association with the later development of food allergy. Children who did not have a food allergy by the age of 2 years had a dietary pattern in later infancy characterized by higher intake of fruits, vegetables, and home-prepared foods as compared to children who had a food allergy. Unadjusted analysis only.
Parent report of doctor diagnosis; sIgE (hen egg, cow milk, peanut, hazelnut, carrot, and wheat flour)	Food diversity during first year of life (1) 0-3 items (2) 4-5 items (3) 6 items (ref) (4) diversity score, continuous	(1) **4.43 1.62-12.10** (2) **1.85 1.02-3.35** (3) 1 (4) **0.70 (0.57-0.86)**	Adjusted for center, farmer, parents with allergy, sex, breast-feeding, siblings, and maternal education.

TABLE C-5 Nutritional Immunomodulation Hypothesis (Observational Studies)

Author, Year	Study Design, Country	Population	N	Age When Outcome Was Ascertained
Lipids/Omega-3 Fatty Acids (see systematic reviews below)				
Vitamin D				
Koplin et al., 2016	Prospective cohort, Australia	Infants participating in the HealthNuts study	5,276	1 year
Baek et al., 2014	Cross-sectional, Korea	Children with atopic dermatitis or suspected food allergy, who had not been on vitamin supplementation for at least 1 month before the study	226	3-24 months

Food Allergy or Sensitization Outcome Definition	Exposure	Odds Ratio[a] (95% CI) of Food Allergy	Comments
SPT, sIgE, OFC	Serum $25(OH)D_3$ ≤50 nmol/L = vitamin D insufficiency 51-74 nmol/L = intermediate vitamin D ≥75 nmol/L = high vitamin D	Infants with GG genotype (insufficient versus intermediate): 6.0 (0.9-38.9) Infants with GT/TT phenotypes (insufficient versus intermediate): 0.7 (0.2-2.0) Infants with GG genotype (high versus intermediate): 4.0 (1.3-12.9)	Adjusted for infants' consumption of egg and formula use and parents' country of birth and used a seasonally adjusted measure of serum $25(OH)D_3$.
History of acute reaction + sIgE ≥0.35 kU/L or >95% predictive decision points	Serum $25(OH)D_3$ Deficiency: <20ng/mL Insufficiency: 20-29ng/mL Sufficiency: ≥30ng/mL	Deficient versus sufficient Food allergens: 5.0 (1.8-14.1) Milk: 10.4 (3.3-32.7) Wheat: 4.2 (1.1-15.8)	Vitamin D deficiency increased the risk of sensitization to food allergens, especially to milk and wheat. The Scoring Atopic Dermatitis index was independently related to 25(OH)D levels after adjusting for the level of sensitization.

continued

TABLE C-5 Continued

Author, Year	Study Design, Country	Population	N	Age When Outcome Was Ascertained
Norizoe et al., 2014	Longitudinal Study, Japan	Infants with facial eczema and their mothers	164	3-24 months
Wawro et al., 2014	Cross-sectional, Germany	Samples from two German birth cohort studies	2,815	10 years
Allen et al., 2013	Cross-sectional, Australia	Infants from HealthNuts population-based cohort	5,276	1 year

Food Allergy or Sensitization Outcome Definition	Exposure	Odds Ratio[a] (95% CI) of Food Allergy	Comments
Doctor-diagnosed allergic incidents, including atopic dermatitis, food allergy with or without being positive for IgE food allergens, or wheeze or asthma with or without being positive for IgE inhaled allergens	Maternal vitamin D (800 IU/day) supplement	RR=**3.42 (1.02-11.77)**	Vitamin D supplementation may not decrease the severity of infantile eczema at 3 months of age, but may rather increase the risk of later food allergy up to 2 years of age. Unadjusted analysis only.
sIgE >0.35 kU/l	Serum 25(OH)D Q1: <57.9 (nmol/L) Q2: 57.9- <71.5 Q3: 71.5- <87.8 Q4: ≥87.8 Continuous variable	 1 0.91 (0.67-1.25) 1.25 (0.93-1.69) 1.30 (0.97-1.75) **1.07 (1.02-1.11)**	Lifetime prevalence also was significantly related to vitamin D status.
OFCs + SPT/ sIgE ≥0.35 kU/L	Vitamin D ≥50 nmol/L (insufficiency) (1) All infants (2) Infants with one or both parents born overseas (3) Infants with both parents born in Australia	Any food allergy versus none: (1) 1.29 (0.51-3.25) (2) 0.39 (0.08-1.76) **(3) 3.08 (1.10-8.59)** Peanut allergy versus none (infants with both parents born in Australia): **11.51 (2.01-65.79)** Egg allergy versus none (infants with both parents born in Australia): **3.79 (1.19-12.08)**	

continued

TABLE C-5 Continued

Author, Year	Study Design, Country	Population	N	Age When Outcome Was Ascertained
Liu et al., 2013	Prospective longitudinal cohort study, US	Children in the Boston Birth cohort	460	0-3 years
Weisse et al., 2013	Prospective longitudinal cohort study, Germany	Mother–child pairs from the Lifestyle and environmental factors and their Influence on Newborns Allergy risk (LINA) cohort study	378	First 2 years

Food Allergy or Sensitization Outcome Definition	Exposure	Odds Ratio[a] (95% CI) of Food Allergy	Comments
sIgE >0.35 kU/l	Vitamin D (ng/ml) cord blood/ postnatal	All children:	There was no association between low vitamin D status and food sensitization at any single time point alone.
	≥11 / ≥30 (reference)	1	
	≥11 / <30	0.73 (0.42-1.29)	
	<11 / ≥30	0.90 (0.54-1.51)	
	<11 / <30	**2.03 (1.02-4.04)**	
		Children with C allele of rs2243250:	Adjusted for a child's sex and ancestry proportion, breastfeeding, postnatal maternal smoking, household income, and maternal age.
		1	
		0.52 (0.23–1.18)	
		1.26 (0.65–2.43)	
		3.23 (1.37-7.60)	
Parental report of a doctor diagnosis. tIgE levels >0.7 kU/l in cord blood and >3.8 kU/l at age of 1 or 2 yrs, or sIgE >0.35 kU/l	Maternal vitamin D Median = 22.2 ng/ml (55.41 nmol/ml)	1st year of life: 1.27 (0.67–2.40)	Adjusted for sex, number of siblings, increased cord blood tIgE levels, family atopy history, cotinine levels during pregnancy, breastfeeding, UV intensity at birth and vitamin D supplementation within the first year of life.
		2nd year of life: **3.66 (1.36–9.87)**	
		2-year lifetime period: **1.91 (1.09–3.37)**	
	Cord blood vitamin D Median = 10.95 ng/ml (27.33 nmol/ml)	1st year of life: 0.92 (0.45–1.85)	
		2nd year of life: **4.65 (1.50–14.48)**	
		2-year lifetime period: 1.70 (0.92-3.14)	

continued

TABLE C-5 Continued

Author, Year	Study Design, Country	Population	N	Age When Outcome Was Ascertained
Jones et al., 2012	Prospective longitudinal cohort study, Australia	High-risk infants	231	12 months
Liu et al., 2011	Prospective longitudinal birth cohort, US	Mother-infant pairs in the Boston Birth Cohort	649 children	Around 2 years
Lipids/Omega-3 Fatty Acids (see systematic reviews below)				
Folate				
Okupa et al., 2013	Cohort study, US	Children at high risk of developing asthma and allergic disease	138	2, 4, 6, and 8 years

Food Allergy or Sensitization Outcome Definition	Exposure	Odds Ratio[a] (95% CI) of Food Allergy	Comments
SPT History of immediate symptoms + SPT	Cord blood vitamin D <50 nmol/L versus ≥75 nmol/L (reference)	Risk of allergen sensitization: 1.0 (0.9-1.01) Risk of developing IgE-mediated food allergy: 1.00 (0.99-1.02)	Adjusted for season of birth, pets in the home, infant sex, maternal age, maternal education, and ethnicity.
sIgE (milk, egg white, peanut, soy, shrimp, walnut, cod fish, and wheat)	Cord blood plasma total 25(OH)D concentrations (<11 ng/ml = deficiency)	Vitamin D deficient versus not deficient (reference) Any food sensitization: 1.16 (0.83-1.63) Egg sensitization: 0.84 (0.56-1.27) Milk sensitization: 1.15 (0.76-1.73) Peanut sensitization: 1.06 (0.64-1.75)	
Allergic sensitization (sIgE to milk/ egg/ peanut for years 1 to 3 and egg/peanut for years 5+)	Plasma folate levels	High versus low folate levels at or before age 6 years): 8% versus 26% (P=0.02)	Unadjusted analysis only.

continued

TABLE C-5 Continued

Author, Year	Study Design, Country	Population	N	Age When Outcome Was Ascertained
Dunstan et al., 2012	Prospective cohort, Australia	Pregnant women (healthy nonsmokers with uncomplicated term pregnancies)	628 women 484 infants	12 months
Magdelijns et al., 2011	Prospective birth cohort, the Netherlands	Children in the KOALA birth cohort	2,834	2 years

Food Allergy or Sensitization Outcome Definition	Exposure	Odds Ratio[a] (95% CI) of Food Allergy	Comments
IgE-mediated food allergy was defined as a history of immediate symptoms following contact and/or ingestion and a positive SPT to the implicated food Allergic sensitization (milk, peanut, whole egg) was assessed by SPT at 1 year of age	Tertiles of maternal folate intake from supplements (FFQ during 3rd trimester) (1) <200 mg/day (2) 200-499 mg/day (3) >500 mg/day Tertiles of cord blood folate at delivery (1) <50.3 nmol/l (2) 50.3-75.1 nmol/l (3) >75.1 nmol/l	Folate intake: IgE-mediated food allergy (1) reference group (2) 1.4 (0.7-3.0) (3) 1.1 (0.5-2.4) Sensitized to food allergens (1) reference group (2) 1.3 (0.7-2.3) (3) 1.1 (0.6-2.0) Cord blood folate: IgE-mediated food allergy (1) 1.7 (0.5-5.6) (2) reference group (3) 2.6 (0.9-8.1) Sensitized to food allergens (1) 2.2 (0.9-5.6) (2) reference group (3) 1.1 (0.5-2.4) All ORs adjusted for maternal allergy and infant postnatal diet	Also looked at maternal intake of folate from food, but found no differences in the maternal dietary folate intakes of infants with any allergic outcomes. Because of the focus on allergy in the primary study, sensitized allergic mothers were over represented (70.6%). All ORs adjusted for maternal allergy and infant postnatal diet.
sIgE (hen egg, cow milk, peanut, and aeroallergens)	Folic acid supplement use during pregnancy (measured as quintiles of intracellular folate status during 3rd trimester)	Folic acid supplement use versus no use (reference) Increased sIgE: 1.06 (0.67-1.68)	Allergic sensitization was to both food allergens and aeroallergens.

continued

TABLE C-5 Continued

Author, Year	Study Design, Country	Population	N	Age When Outcome Was Ascertained
Other Nutrient Intakes				
West et al., 2012	Prospective cohort, Australia	Pregnancy cohort with a family history of allergic rhinitis, asthma, eczema, food or other allergy	300 mother–infant pairs	12 months

NOTE: CI = confidence interval; FFQ = food frequency questionnaire; IgE = immunoglobulin E; OFC = oral food challenge; OR = odds ratio; RCT = randomized controlled trial; RR = relative risk; sIgE = food-specific serum IgE; SPT = skin prick test; tIgE = total IgE; UK = United Kingdom; US = United States; UV = ultraviolet.

[a] **Bold** indicates statistical significance at P<0.05. Results were reported as odds ratio (95% confidence interval) unless otherwise noted. Adjusted results were extracted in the summary table unless otherwise noted.

Food Allergy or Sensitization Outcome Definition	Exposure	Odds Ratio[a] (95% CI) of Food Allergy	Comments
IgE-mediated food allergy was defined as a history of immediate symptoms after contact with and/or ingestion and a positive SPT at 12 months (milk, egg, peanut)	Quartiles of daily maternal dietary and total intakes during pregnancy (1) β-carotene (2) vitamin C (3) vitamin E (4) copper (5) zinc Quartiles Q1 lowest (reference) Q2 Q3 Q4 highest Measured by semiquantitative FFQ administered after 28 weels gestation	(1) β-carotene 0.40 (0.12-1.32) 1.16 (0.43-3.11) 0.38 (0.11-1.27) P_{trend}=0.2 (2) Vitamin C **0.22 (0.06-0.78)** 0.75 (0.27-2.06) 0.46 (0.16-1.36) P_{trend}=0.1 (3) Vitamin E 0.96 (0.32-2.84) 0.86 (0.29-2.54) 0.57 (0.19-1.72) P_{trend}=0.8 (4) copper 0.60 (0.22-1.60) 0.40 (0.13-1.22) **0.38 (0.11-0.95)** P_{trend}=0.2 (5) zinc 0.67 (0.22-2.03) 1.28 (0.46-3.53) 0.52 (0.16-1.73) P_{trend}=0.4	Adjusted for maternal education, paternal history of allergic disease, birth weight, and exposure to furred pets at home; all were included in the multiple logistic regression model.

TABLE C-6 Systematic Review Summaries

Author, year	Best et al., 2016
Aims/Key questions	To develop a clearer understanding of the effect to the developing fetus, before commencement of the progression of atopy ("atopic march") and establishment of allergic disease symptoms.
Study eligibility criteria	Inclusion criteria: • Study design: prospective studies, including longitudinal observational studies and RCTs and quasi-randomized trial. • Exposure: maternal fish or n-3 LCPUFA intake during pregnancy. • Intervention and comparator: intervention modifying maternal n-3 LCPUFA intake during pregnancy with a parallel control group or placebo. • Outcome measures: Incidence of atopic disease (i.e., IgE-mediated allergic disease) or sensitization in the offspring during infancy, childhood, or adolescence. The presence of IgE-mediated allergic disease is defined as a clinician diagnosis, parent report of symptoms of allergic disease, or parent report of a physician's diagnosis. Sensitization is defined as a positive SPT or IgE serology indicating sensitization. Exclusion criteria: • Animal studies, cross-sectional studies, and retrospective and case-control studies. • Studies of maternal n-3 LCPUFA consumption or supplementation in the postnatal period only (breastfeeding or direct supplementation of the infant). • Studies that reported immune biomarkers by laboratory assessment in the absence of evaluation of symptoms or clinical diagnosis of allergic disease in the offspring.
Literature search dates or year range	Inception to July 30, 2015
Number of food allergy studies included	3 RCTs (based on SPT)
Synthesis methods	Summary tables and meta-analysis

TABLE C-6 Continued

Key findings	Three RCTs with sensitization outcomes at age 12 months were combined in meta-analysis. Definitions of sensitization were inconsistent. Overall risk of bias of the three RCTs was low to moderate. One RCT was rated high risk of bias for incomplete outcome data reporting and one was rated high risk of bias for selective reporting. • Fixed effect meta-analysis showed a significant reduction in "sensitization to egg" at 0-12 months (pooled RR: 0.55; 95% CI: 0.39-0.76; P=0.0004) • Fixed effect meta-analysis showed a significant reduction in "sensitization to any food" at 12 months (pooled RR: 0.59; 95% CI: 0.46-0.76; P<0.0001)
Limitations	• This systematic review did not focus on food allergy. • Fixed effect meta-analysis ignores clinical heterogeneity (e.g., different doses of n-3 fatty acids) and produced more significant results. Note: Discordant results with Klemens et al. (2011) meta-analysis. Overlaps in two RCTs. Best et al. (2016) did not include one study that was included in Klemens et al. (2011). Klemens et al. (2011) performed random-effects meta-analysis while Best et al. (2016) performed fixed-effects meta-analysis.

AMSTAR rating	
An a priori design?	Y
Duplicate study selection and data extraction?	N
Comprehensive literature search?	Y
Status of the publication as an inclusion criterion?	Y
List of studies (included and excluded) provided?	Y
Characteristics of included provided?	Y
Scientific quality of the included studies assessed and reported?	Y
Scientific quality used in formulating conclusions?	Y
Methods used to combine the findings appropriate?	N
Likelihood of publication bias assessed?	Y (the authors noted that the risk of publication bias cannot be excluded because only published studies were included in meta-analysis)
Conflict of interest (COI) stated?	Y/N (COI of the systematic review authors was provided but not provided for included studies)

continued

TABLE C-6 Continued

Author, year	Boyle et al., 2016
Aims/Key questions	To determine whether feeding infants with hydrolyzed formula reduces their risk of allergic or autoimmune disease.
Study eligibility criteria	Interventions and comparators: • Inclusions: Any hydrolyzed formula of cow milk origin compared with any nonhydrolyzed cow milk formula, human milk, or another type of hydrolyzed cow milk formula. Also included were studies in which hydrolyzed formula was given as part of a multifaceted intervention, which the authors defined as an intervention with at least two other components in addition to the hydrolyzed formula—for example, exclusion of allergenic food from the mother's diet, promotion of breastfeeding, delayed introduction of solid food, or measures to avoid exposure to house dust mite. Studies in which other interventions were applied to both intervention and control groups, such as exclusion of cows' milk from the mother's diet during lactation also were included. • Exclusions: Studies of hydrolyzed formula of milk other than cow milk, such as hydrolyzed rice, goat milk, or soy formula. Study designs of interest: All intervention trials. Populations of interest: • Inclusions: Studies of infant feeding between birth and age 12 months. • Exclusions: Studies in which infants or their mothers were defined by the presence of a pre-existing disease state, including very low birth weight or premature infants. Outcomes of interest: • Atopic outcomes included were asthma (categorized as wheeze, recurrent wheeze, atopic wheeze, bronchial hyper-reactivity, forced vital capacity, peak expiratory flow rate, forced expiratory volume in 1 second), eczema, allergic rhinitis and/or conjunctivitis, food allergy, allergic sensitization (that is, SPT or sIgE assessment, or tIgE level). • Autoimmune outcomes included were type 1 diabetes mellitus (defined serologically and/or clinically), celiac disease (defined serologically and/or clinically), inflammatory bowel disease, autoimmune thyroid disease, juvenile rheumatoid arthritis, vitiligo, or psoriasis.
Literature search dates or year range	The Cochrane Library (2013, issue 7), EMBASE (1947 to July 2013), LILACS (1982 to July 2013), Medline (1946 to July 2013), and Web of Science (1970 to July 2013). Searches run on July 25, 2013, and rerun on April 17, 2015.

TABLE C-6 Continued

Number of food allergy studies included	13
Synthesis methods	Narrative text and meta-analysis
Key findings	There was no significant difference in risk of "any food allergy" with partially (pooled RR: 1.73; 95% CI: 0.79-; I^2=42%) or extensively (pooled RR 0.86; 95% CI: 0.26-2.82; I^2=42%) hydrolyzed formula compared with standard formula at age 0-4 years, nor for extensively hydrolyzed formula at age 5-14 years. [Note that number of studies included in each meta-analysis was not reported in text.] No difference was found in food allergy to cow milk, egg, or (partially hydrolyzed formula only) peanut. Direct comparison of the two formulas (egg allergy) and casein versus whey dominant extensively hydrolyzed formula showed no significant difference in risk of food allergy. [Note: no other details reported in text.] There was no significant difference in risk of allergic sensitization to cow milk with partially (pooled RR: 1.30; 95% CI: 0.65-2.60; I^2=0%; seven studies) or extensively (pooled RR: 0.77; 95% CI: 0.09-6.73; I^2=77%; three studies) hydrolyzed formula, and no significant difference between groups for risk of allergic sensitization to "any allergen" or raised total IgE level. The strength of evidence was graded as moderate for partially hydrolyzed formula, and as very low for exclusively hydrolyzed formula.
Limitations	Many studies of allergic outcomes included in this review had unclear or high risk of bias and evidence of conflict of interest, often because of inadequate methods of randomization and treatment allocation (selection bias) and support of the study or investigators from manufacturers of hydrolyzed formula. In many cases study participants were infants with early full formula feeding, so findings might not be applicable to populations with more typical feeding patterns.
AMSTAR rating	
An a priori design?	Y
Duplicate study selection and data extraction?	Y
Comprehensive literature search?	Y – Appendix 1
Status of the publication as an inclusion criterion?	Y
List of studies (included and excluded) provided?	Partially – List of excluded studies was not reported
Characteristics of included provided?	Y – Characteristics of included studies are summarized in tables A and B in appendix 3.

continued

TABLE C-6 Continued

Scientific quality of the included studies assessed and reported?	Y
Scientific quality used in formulating conclusions?	Y – GRADE approach
Methods used to combine the findings appropriate?	Y
Likelihood of publication bias assessed?	Y
Conflict of interest stated?	Y

Author, year	Cuello-Carcia et al., 2016
Aims/Key questions	To provide evidence-based recommendations about the use of prebiotic supplements for the primary prevention of allergies.
Study eligibility criteria	According to the evidence profiles table, the study eligibility criteria can be assumed to be: • Population: healthy infants • Intervention: prebiotic supplementation • Comparison: no prebiotic supplementation • Main outcomes: development of allergy, nutritional status, adverse effects • Setting: outpatient
Literature search dates or year range	Up to January 2015, with an update on July 29, 2015
Number of food allergy studies included	1
Synthesis methods	GRADE approach

Key findings	Outcome	Without prebiotics (per 1,000)	With prebiotics (per 1,000)	Difference (95% CI) (per 1,000)	Relative effect (95% CI)	Certainty of the evidence (GRADE)
	Food allergy	170	48 (14 to 170)	122 fewer (0 to 156 fewer)	RR 0.28 (0.08 to 1.00)	VERY LOW

TABLE C-6 Continued

Conclusions and research needs	The guideline panel determined that there is a low certainty of a net benefit from using prebiotics in infants. Based on the body of available evidence, it is likely that prebiotic supplementation in infants reduces the risk of developing recurrent wheezing and possibly also the development of food allergy. There is very low certainty prebiotics have an effect on other outcomes. However, because of low certainty of evidence or no published information about other outcomes, the fact that the authors did not find evidence of an effect on these outcomes does not imply that such an effect does not exist.
Limitations	This publication is a guideline paper. Although the guideline appears to be based on a systematic review, the methods of systematic review were not fully reported in this publication. No other source or citation to the systematic review was found.

AMSTAR rating	
An a priori design?	Yes
Duplicate study selection and data extraction?	Not reported
Comprehensive literature search?	Yes
Status of the publication as an inclusion criterion?	Not reported
List of studies (included and excluded) provided?	Partially – Excluded studies were not reported
Characteristics of included provided?	Yes
Scientific quality of the included studies assessed and reported?	Yes
Scientific quality used in formulating conclusions?	Yes
Methods used to combine the findings appropriate?	Yes
Likelihood of publication bias assessed?	No
Conflict of interest stated?	Yes

continued

TABLE C-6 Continued

Author, year	Newberry et al., 2016
Aims/Key questions	To update a prior systematic review on the effects of omega-3 fatty acids (n-3 fatty acids) on maternal and child health and to assess the evidence for their effects on, and associations with, additional outcomes. Key Question 2: Fetal/childhood exposures – What is the influence of maternal intakes of n-3 fatty acids or the n-3 fatty acid content of maternal breast milk (with or without knowledge of maternal intake of n-3 fatty acids) or n-3 fatty acid-supplemented infant formula or intakes of n-3 fatty acids from sources other than maternal breast milk or supplemented infant formula on the following outcomes in term or preterm human infants? • Growth patterns • Neurological development • Visual function • Cognitive development • Autism • Learning disorders • ADHD • Atopic dermatitis • Allergies (Note: including food allergies) • Respiratory illness
Study eligibility criteria	Populations of interest: • Healthy preterm or term infants of healthy women/mothers whose n-3 fatty acid exposures were monitored during pregnancy. • Breastfed infants of healthy mothers whose n-3 fatty acid exposure was monitored and/or who participated in an n-3 fatty acid intervention during breastfeeding beginning at birth. • Healthy preterm or term infants with and without family history of respiratory conditions (for outcomes related to atopic dermatitis, allergy, respiratory conditions) of mothers whose n-3 exposures were monitored during pregnancy and/or breastfeeding. • Healthy children or children with a family history of a respiratory disorder, a cognitive or visual development disorder, autism spectrum disorder, ADHD, or learning disabilities, age 0 to 18 years who participated in an n-3 fatty acid-supplemented infant formula intervention or an n-3 supplementation trial during infancy.

TABLE C-6 Continued

	Interventions of interest: • N-3 fatty acid supplements (e.g., EPA, DHA, ALA, singly or in combination); • N-3 fatty acid supplemented foods (e.g., eggs) with quantified n-3 fatty acid content • High-dose pharmaceutical grade n-3 fatty acids, e.g., Omacor®, Ropufa®, MaxEPA®, Efamed, Res-Q®, Epagis, Almarin, Coromega, Lovaza®, Vascepa® (icosapent ethyl) o Exclude doses of more than 6g/d, except for trials that report adverse events • N-3 fatty acid fortified infant formulae o E.g., Enfamil® Lipil®; Gerber® Good Start DHA & ARA®; Similac® Advance® o N-3 fatty acid fortified follow-up formula o Exclude parenterally administered sources • Marine oils, including fish oil, cod liver oil, menhaden oil, and algal with quantified n-3 fatty acid content • Algal or other marine sources (e.g., phytoplankton) of omega-3 fatty acids with quantified n-3 content Exposures of interest: • Dietary n-3 fatty acids from foods if concentrations are quantified in food frequency questionnaires • Breast milk n-3 fatty acids (KQ2) • Biomarkers (EPA, DHA, ALA, DPA, SDA), including but not limited to the following: o Plasma fatty acids o Erythrocyte fatty acids o Adipocyte fatty acids Comparators of interest: • Inactive comparators: o Placebo o Nonfortified infant formula • Active comparators: o Different n-3 sources o Different n-3 concentrations o Alternative n-3 fortified infant formula o Soy-based infant formula o Diet with different level of Vitamin E exposure Outcomes of interest: • Risk for allergies. Validated allergy assessment procedures, preferably challenge (SPT or validated blood tests accepted) Timing of interest: • Interventions implemented within 1 month of birth or exposures measured within 1 month of birth • Follow-up duration is 0 to 18 years
Literature search dates or year range	Update searches were from the year 2000. For the newly added topics (e.g., allergies), the authors "reference mined" articles that they identified to determine whether any studies conducted and published before 2000 should be obtained and included.

continued

TABLE C-6 Continued

Number of food allergy studies included	3 RCTs
Synthesis methods	Narrative text and meta-analysis
Key findings	All three RCTs recruited pregnant women whose infants were at high risk of atopy (e.g., parent diagnosis of allergy, or sibling has diagnosed or suspected allergy). • Among the three prenatal n-3 interventions and two follow-up studies, three found associations between maternal n-3 fatty acid supplementation (DHA + EPA, varying doses ranging from 0.8 to 3.09 g/d) and lower risk of allergies (denoted by sensitization to egg allergen and positive skin prick test). However, in all but one study, these relationships were no longer observed or became marginal after adjusting for potential confounders or after long-term follow-up. • Meta-analysis of three RCTs (N=949) with 12-month food allergy outcomes yielded an insignificant summary effect size for DHA+EPA supplementation and risk of food allergy (OR: 0.54; 95% CI 0.05-6.2; I^2=42.3%). • Note that the strength of evidence was graded as low for the conclusion of no significant effect of DHA or DHA+EPA supplementation during pregnancy on food allergies.
Limitations	• The risk for allergies is an additional outcome of interest that was not included in the original review. • The search strategy was not designed specifically for food allergies outcomes.

AMSTAR rating	
An a priori design?	Y
Duplicate study selection and data extraction?	Y
Comprehensive literature search?	Y/N (The search strategy was not designed to specifically for food allergies outcomes because "food allergies" were not one of the pre-specified outcomes of interest)
Status of the publication as an inclusion criterion?	Y
List of studies (included and excluded) provided?	Y
Characteristics of included provided?	Y
Scientific quality of the included studies assessed and reported?	Y
Scientific quality used in formulating conclusions?	Y

TABLE C-6 Continued

Methods used to combine the findings appropriate?	Y
Likelihood of publication bias assessed?	N (only published studies were included)
Conflict of interest stated?	Y

Author, year	Cuello-Carcia et al., 2015
Aims/Key questions	To synthesize the evidence supporting use of probiotics to prevent allergies and inform World Allergy Organization guidelines on probiotic use. Three key questions of this systematic review are: 1. Should supplementation of probiotics versus no such supplementation be used in pregnant women to prevent development of allergy in their children? 2. Should supplementation of probiotics versus no such supplementation be used in breastfeeding mothers to prevent development of allergy in their children? 3. Should supplementation of probiotics versus no such supplementation be used in infants to prevent development of allergy?
Study eligibility criteria	• Types of studies: RCTs with a minimum follow-up of 4 weeks that compared any type of probiotic with placebo, irrespective of their language or publication status. • Types of participants: Pregnant women, breastfeeding mothers, and infants and children (up to age 9 years). • Types of interventions: Any probiotic supplementation, irrespective of formulation (capsules, oil droplets, suspension, and supplements in infant formulas or cereals), microorganism, supplement composition (single versus multiple strains), or dose. • Types of outcome measures: The World Allergy Organization guideline panel members in a formal process determined the outcomes of interest. The following outcomes were deemed critical to the decision whether to use probiotics to prevent allergies: eczema, asthma and/or wheezing, food allergy, allergic rhinitis, any adverse effects, and severe adverse effects.
Literature search dates or year range	From inception to December 2014
Number of food allergy studies included	6 RCTs [Note: some RCTs contributed data for more than one meta-analysis.]
Synthesis methods	Narrative text, meta-analysis, and GRADE

continued

TABLE C-6 Continued

Key findings

- No RCTs for the comparison of probiotics versus no probiotics in pregnant women for prevention of allergy in their children (direct evidence).
- No RCTs for the comparison of probiotics versus no probiotics in breastfeeding women for prevention of allergy in their children (direct evidence)

				Anticipated absolute effects	
Outcomes	**No. of participants (studies)**	**Strength of evidence (GRADE)**	**Relative effect, RR (95% CI)**	**Risk with no probiotics**	**Risk difference with probiotics**
Probiotics versus no probiotics in pregnant women for prevention of allergy in their children (indirect evidence)					
Food allergy, follow-up: range, 12-24 months	355 (3 RCTs)	●○○○ Very low	1.08 (0.73-1.59)	Study population	
			Note: 1.49 (0.58, 3.81) in the forest plot	39 per 1,000	3 more per 1,000 (11 fewer to 23 more)
Probiotics compared with no probiotics in breastfeeding women to prevent allergies in their children (indirect)					
Food allergy, follow-up: range, 12-24 months	167 (2 RCTs)	●○○○ Very low	1.7 (0.58-4.96)	Study population	
				59 per 1,000	41 more per 1,000 (25 fewer to 233 more)
Probiotics compared with no probiotics in infants to prevent allergies (direct)					
Food allergy, follow-up: range, 6-24 months	349 (3 RCTs)	●○○○ Very low	0.88 (0.55-1.43)	Study population	
				167 per 1,000	20 fewer per 1,000 (75 fewer to 72 more)

TABLE C-6 Continued

Outcomes	No. of participants (studies)	Strength of evidence (GRADE)	Relative effect, RR (95% CI)	Anticipated absolute effects: Risk with no probiotics	Anticipated absolute effects: Risk difference with probiotics
Probiotics compared with no probiotics in infants to prevent allergies (indirect)					
Food allergy, follow-up: range, 6-24 months	295 (2 RCTs)	●○○○ Very low	1 (0.25-3.91)	Study population	
				27 per 1,000	0 fewer per 1,000 (20 fewer to 79 more)

Limitations

- There were moderate-to-serious concerns about the risk of bias in most studies.
- Some inconsistency in reporting of the meta-analysis results.
- Confidence that one would observe effects in real life is low to very low (low to very low certainty in the evidence). This is a result of the relative paucity of direct evidence in any of the three groups in whom probiotics could be used, the high likelihood of bias in primary studies, and the serious imprecision of the estimated pooled effects.

AMSTAR rating	
An a priori design?	Y
Duplicate study selection and data extraction?	Y
Comprehensive literature search?	Y
Status of the publication as an inclusion criterion?	Y
List of studies (included and excluded) provided?	Y
Characteristics of included provided?	Y – Table E3 and online repository
Scientific quality of the included studies assessed and reported?	Y
Scientific quality used in formulating conclusions?	Y
Methods used to combine the findings appropriate?	Y
Likelihood of publication bias assessed?	N
Conflict of interest stated?	Y

continued

TABLE C-6 Continued

Author, year	Gunaratne et al., 2015
Aims/Key questions	To assess the effect of n-3 LCPUFA supplementation in pregnant and/or breastfeeding women on allergy outcomes (food allergy, atopic dermatitis [eczema], allergic rhinitis [hay fever] and asthma/wheeze) in their children.
Study eligibility criteria	Inclusion criteria: • Types of studies: RCTs focusing on n-3 LCPUFA supplementation of pregnant and/or breasfeeding women (compared with placebo or no treatment) and assessed allergy outcomes of the infants or children. Quasi-RCTs and RCTs using a cluster-randomized design were eligible for inclusion but none were identified. • Types of participants: Women and their children, with either a normal or high risk of developing allergic disease, were included. A fetus or a child with a first degree relative with medically diagnosed allergies, or a positive SPT, or a positive RAST was defined as being at high risk of allergies. Infants were also considered at high risk of allergies if their cord blood IgE level was above 0.70 IU/mL. • Types of interventions: All randomized comparisons of n-3 LCPUFA supplementation given to pregnant or lactating women (either with or without arachidonic acid), with placebo or no supplementation as a control, regardless of dose regimens and duration of intervention. Trials in which fish was the intervention were included if appropriately controlled, for example, if the diet was appropriately adjusted to match the protein contribution of fish. • Primary outcomes: o Medically diagnosed any allergy with sensitization, i.e., IgE-mediated allergies where both the signs and symptoms of the allergic disease and a positive SPT and/or RAST test are present. o Medical diagnosis or parental report (using validated questionnaire) of any allergy, +/– IgE sensitization. • Secondary outcomes: Children with specific forms of allergy, including food allergy, atopic dermatitis (eczema), asthma/wheeze, allergic rhinitis (hay fever) with IgE sensitization and +/– IgE sensitization, SPT results, and parent-reported allergies using non-validated questionnaires. Exclusion criteria: • Types of studies: Trials published in abstract form only, trials using a crossover design, and trials examining biochemical outcomes only.

TABLE C-6 Continued

Literature search dates or year range	Inception to August 2014
Number of food allergy studies included	Five
Synthesis methods	Narrative text and meta-analysis
Key findings	Three of the five trials had high risk of bias for incomplete outcome data (attrition bias) and/or selective reporting bias. • N-3 LCPUFA supplementation reduced the incidence of IgE-mediated food allergies in children up to 12 months of age (117 infants, RR: 0.13; 95% CI: 0.02-0.95), but there were no clear differences found between the intervention and control groups at any other age (12 to 36 months, 825 children, average RR: 0.58; 95% CI: 0.18-1.88; >36 months, 706 children, RR: 1.43; 95% CI: 0.63-3.26). • When food allergies +/– IgE sensitivity were considered, results showed few differences from those for IgE-mediated allergies with no differences in the direction of findings from those for IgE-mediated allergies: o Up to 12 months of age, 117 infants, RR: 0.13; 95% CI: 0.02-0.95. o Between 12 and 36 months, random-effects meta-analysis of four trials (973 children) showed pooled RR: 0.72; 95% CI: 0.40-1.30. o >36 months of age, 706 children, RR: 1.43; 95% CI: 0.63-3.26.
Limitations	• Review authors MM and CTC were investigators on two trials included in the review. • Studies included in this review used differing doses, DHA to EPA ratios, and duration of n-3 LCPUFA supplementation, and did not take into account the baseline n-3 LCPUFA status of the women.

AMSTAR rating	
An a priori design?	Y
Duplicate study selection and data extraction?	Y
Comprehensive literature search?	Y
Status of the publication as an inclusion criterion?	Y
List of studies (included and excluded) provided?	Y
Characteristics of included provided?	Y
Scientific quality of the included studies assessed and reported?	Y
Scientific quality used in formulating conclusions?	Y
Methods used to combine the findings appropriate?	Y
Likelihood of publication bias assessed?	Y
Conflict of interest stated?	Y

continued

TABLE C-6 Continued

Author, year	de Silva et al., 2014
Aims/Key questions	This systematic review is one of the series of systematic reviews for developing EAACI *Guidelines for Food Allergy and Anaphylaxis*. This systematic review examined ways to prevent the development of food allergy in children and adults.
Study eligibility criteria	• This review focused solely on studies that were primarily concerned with preventing sensitization to food(s) and/or the development of food allergy. Studies seeking to prevent potential manifestations of food allergy, such as atopic dermatitis (eczema) or asthma, but not including an explicit diagnosis of sensitization to food or food allergy, were not included. • Systematic reviews and meta-analyses, RCTs, quasi-RCTs, controlled clinical trials, controlled before-and-after studies, interrupted time series studies, and prospective cohort studies were eligible. • No language restrictions were applied and, where possible, relevant studies in languages other than English were translated.
Literature search dates or year range	The following databases were searched: Cochrane Library, MEDLINE, Embase, CINAHL, ISI Web of Science, TRIP Database, and Clinicaltrials.gov from inception to September 30, 2012
Number of food allergy studies included	74
Synthesis methods	Narrative synthesis and summary tables

TABLE C-6 Continued

Key findings	Table 1 summarized key evidence about prevention strategies: • Overall, the evidence is not strong enough to recommend changing the diet or supplements of pregnant or breastfeeding women at normal or high risk. Although breastfeeding may have many other benefits, the evidence in relation to the prevention of food allergy is not strong. This, to a large extent, reflects the ethical challenges of randomizing infants to a nonbreastfeeding arm. • There is more evidence about the benefits of alternatives to cow milk formula for babies at high risk. Extensively hydrolyzed whey or casein formula and partially hydrolyzed formula may have a protective effect, but it appears that soy formula does not protect against food allergies. • Probiotics do not seem to be protective in infants at high or normal risk, and neither does delaying the introduction of solid foods until later than the recommended minimum weaning age. Combining dietary with environmental modifications during infancy may be the best way forward for infants at high risk.
Limitations	• The studies included were heterogeneous, and as a result, it was not appropriate to quantitatively synthesize this evidence. • There are also limitations with the studies themselves. To date, the focus of research has largely been on preventing IgE-mediated food allergy rather than on non-IgE-mediated food allergy. Many studies are small, short term, and focus on the surrogate measure of food sensitization rather than food allergy. Sensitization may be a normal, harmless, and transitory phenomenon, which does not necessarily correlate with allergic disease.

AMSTAR rating	
An a priori design?	Y
Duplicate study selection and data extraction?	Y
Comprehensive literature search?	Y (protocol published elsewhere)
Status of the publication as an inclusion criterion?	Y (protocol published elsewhere)
List of studies (included and excluded) provided?	Y
Characteristics of included provided?	Y
Scientific quality of the included studies assessed and reported?	Y
Scientific quality used in formulating conclusions?	Y
Methods used to combine the findings appropriate?	Y
Likelihood of publication bias assessed?	N
Conflict of interest stated?	Y

continued

TABLE C-6 Continued

Author, year	Kong et al., 2014
Aims/Key questions	To investigate the preventive effect of probiotics on pediatric food allergy.
Study eligibility criteria	• Study design of interest: RCTs with any sample size. • Population of interest: Infants and their mothers whose first-degree relatives have a history of allergic disease (asthma, allergic nose inflammation, allergic conjunctivitis, allergic eczema, food allergies, etc.). • Interventions of interest: Probiotics may be of single or multiple mixed bacteria type with any treatment course and dose. • Outcome of interest: Incidence of food allergy diseases.
Literature search dates or year range	Last search conducted September 30, 2013
Number of food allergy studies included	10
Synthesis methods	Meta-analysis
Key findings	• Total 1,349 subjects in the probiotics groups and 1,352 subjects in the control groups. Individual study sample size ranged from 60 to 888. • Fixed-effects meta-analysis of 10 RCTs showed no significant difference in the incidence of food allergies (pooled RR: 0.88; 95% CI: 0.76-1.03) with moderate heterogeneity (I^2=33%) comparing prenatal and postnatal probiotics supplementation with placebo or control.
Limitations	• Major sources of heterogeneity include: follow-up durations (ranging from 1 to 7 years); flora types of probiotic bacteria; dose and concentration of probiotics. • Individual study characteristics were not reported, overall risk of bias (or quality) for the included 10 RCTs was moderate, and some methodological concerns regarding the systematic review (see AMSTAR rating below). • Food allergy outcome definitions were not reported.
AMSTAR rating	
An a priori design?	Y
Duplicate study selection and data extraction?	Y
Comprehensive literature search?	N – Only one database used
Status of the publication as an inclusion criterion?	N

TABLE C-6 Continued

List of studies (included and excluded) provided?	N – Excluded studies not provided
Characteristics of included provided?	N
Scientific quality of the included studies assessed and reported?	Y
Scientific quality used in formulating conclusions?	Y
Methods used to combine the findings appropriate?	Y
Likelihood of publication bias assessed?	Y
Conflict of interest stated?	N – COI not provided for either the review of the included studies

Author, year	Marrs et al., 2013
Aims/Key Questions	To systematically review the evidence on the associations between microbial exposure and food allergies.
Study eligibility criteria	Inclusion criteria: • Food allergy outcomes included food challenge data, physician-diagnosed food allergy, reported doctor diagnosis of food allergy or food sensitization diagnosed by either SPT or elevated sIgE levels. • Using a study design appropriate to assess impact of microbial exposure. [Note: not explicitly defined.] Exclusion criteria: • Management guidance documents, reviews and studies investigating celiac disease, food intolerance and animal models were excluded.
Literature search dates or year range	Medline from inception to July 2012
Number of food allergy studies included	46
Synthesis methods	• Summary tables. • Qualitative synthesis using a pragmatic score (quality grading/rating scores) developed for this study. Publications were awarded greater weight of evidence if they used food challenge data rather than reported doctor diagnosis or only sensitization data (challenge-proven food allergy +2; [reported] physician-diagnosis +1, SPT or IgE measurement sensitization +0).

continued

TABLE C-6 Continued

Key findings	• Mode of delivery: All 13 studies reported that being born by caesarean was associated with an increased risk of developing food allergy or food sensitization, except the study of lowest quality. Six of these associations were significant. However, only two pertained to clinical food allergy diagnoses. The overall quality of these 13 studies was moderate (2 studies received a quality score of 4, 4 received a score of 3, 5 received a score of 2, and 2 received a score of 1). • Farming lifestyle and animal exposure: Of four studies investigating farm and animal exposure on food allergy, the Healthnuts Study found significantly less challenge-proven egg, sesame and peanut allergy among infants living with a dog during the first year of life (aOR: 0.6 [0.5-0.8]). However the quality of this study was poor (score of 2). • Endotoxin exposure: Two studies were included but the quality was very poor (score of 0 and 1). • Childhood infections: No studies investigated the association between viral and bacterial infections and challenge-proven food allergy. • Childhood vaccinations: No association was found for any of the recommended childhood vaccinations. • Antibiotic use: Some evidence suggests that antibiotic exposure increases the risk of eczema, but no such relationship has been found for food allergy. • Gut microbiota: Five studies investigated gut microbiota characteristics, two of which compared data with respect to food challenge outcomes and the other three used food sensitization parameters. The two studies ranking highest in quality originated from the same Spanish infants who were diagnosed with IgE-mediated cow milk allergy by milk challenge at a tertiary referral center. [Note that studies were not summarized in the summary tables. Summary of individual study findings was provided in text.] • Pro- and prebiotics: Eleven probiotic RCTs (quality score ranged from 0 to 3) have assessed whether microbial supplementation may be used in the prevention or treatment of food allergy or sensitization, but results have been disappointing overall.

TABLE C-6 Continued

Limitations	• Some methodological concerns regarding the search and study selection process. The authors seem to "up-play" some positive results, not taking into account the quality scores in their synthesis. Most of the studies were rated poor quality. • With exception of probiotics, all studies for other microbial exposures were observational studies. • The studies selected were highly heterogeneous in design and quality. • Most studies were primarily designed to investigate respiratory allergies or eczema, and hence lacked objective characterization of clinical food allergy and statistical power to detect significant risk estimates.

AMSTAR rating	
An a priori design?	Y
Duplicate study selection and data extraction?	Not reported
Comprehensive literature search?	N (Medline only)
Status of the publication as an inclusion criterion?	Y
List of studies (included and excluded) provided?	No but available on request
Characteristics of included provided?	Y
Scientific quality of the included studies assessed and reported?	Y
Scientific quality used in formulating conclusions?	Y
Methods used to combine the findings appropriate?	Y
Likelihood of publication bias assessed?	N
Conflict of interest stated?	Y/N – COI of the systematic review authors were reported but COI not provided for the included studies

Author, year	Kramer and Kakuma, 2012
Aims/Key questions	To assess the effects of prescribing an antigen avoidance diet during pregnancy or lactation, or both, on maternal and infant nutrition and on the prevention or treatment of atopic disease in the child; positive SPTs to dietary antigens; and cord blood levels of IgE (a predictor of subsequent atopic disease).

continued

TABLE C-6 Continued

Study eligibility criteria	Inclusion criteria: • Study design: All acceptably controlled (randomized or quasi-randomized) comparisons of maternal dietary antigen avoidance prescribed to pregnant (at any time during pregnancy) or lactating women at high risk, regardless of degree (number of foods eliminated from the diet) or duration. • Population: Pregnant or lactating women at high risk of giving birth to an atopic child, based on a history of atopic disease (eczema, asthma, or hay fever) in the mother, father, or a previous child. Lactating mothers of infants with established atopic eczema. • Intervention: Prescription of diet with exclusion (or reduced quantity) of potentially antigenic foods such as cow milk, egg, peanut, fish, and chocolate. • Outcome measures: o Primary outcomes: Occurrence and severity of atopic disease in the child. o Secondary outcomes: Nutritional status of mother (gestational weight gain) and fetus (birth weight); other pregnancy outcomes (e.g., preterm birth); positive SPT to ingested antigen (especially egg and milk); and cord blood IgE levels. Exclusion criteria: • Trials of multimodal interventions that include, in addition to maternal dietary antigen avoidance, manipulation of the infant's diet other than breast milk or of other non-dietary aspects of the infant's environment (i.e., exposure to inhaled allergens).
Literature search dates or year range	Unspecified; search conducted on July 6, 2012
Number of food allergy studies included	Three (based on SPT results)
Synthesis methods	Summary tables and meta-analysis

TABLE C-6 Continued

Key findings	• Antigen avoidance during pregnancy: Results from two trials involving 334 pregnant women at high risk of atopic offspring suggest a lower incidence of positive SPT to egg antigen at 6 months of age, but the effect was no longer evident at 18 months, nor was any benefit apparent at either age for SPT to milk antigen (random-effects meta-analysis pooled RR: 0.95; 95% CI: 0.52-1.74). The risk of bias of the two trials is mixed (one was low risk and one was high risk of bias). • Antigen avoidance during lactation: A larger included trial (N=497) did not report on atopic eczema or other allergic disease outcomes, but found no evidence of sensitization to milk, egg, or peanut antigen on SPT at 1, 2, or 7 years of age. The risk of bias of this trial was unclear because the information available is based solely on a published abstract.
Limitations	• This Cochrane systematic review did not focus on food allergies or sensitization. Out of 12 trials, only 3 reported SPT results. • Food sensitization outcomes were based on SPT results only. • Included trials had small sample sizes.

AMSTAR rating	
An a priori design?	Y
Duplicate study selection and data extraction?	Y
Comprehensive literature search?	Y
Status of the publication as an inclusion criterion?	Y
List of studies (included and excluded) provided?	Y
Characteristics of included provided?	Y
Scientific quality of the included studies assessed and reported?	Y
Scientific quality used in formulating conclusions?	Y
Methods used to combine the findings appropriate?	Y
Likelihood of publication bias assessed?	Y
Conflict of interest stated?	Y/N (funding sources of included studies were not reported but the systematic review authors reported no conflict of interest)

Author, year	Fisher et al., 2011
Aims/Key questions	To determine whether specific oral tolerance induction is more effective than avoidance in inducing tolerance in children ages 0 to 18 years who have IgE-mediated food allergy.

continued

TABLE C-6 Continued

Study eligibility criteria	Inclusion criteria: • Population: Children ages 0 to 18 years with IgE-mediated food allergy proven by DBPCOFC at the start of the study. • Outcome measures: The success of specific oral tolerance induction was objectively assessed using oral food challenge or DBPCOFC for tolerance but DBPCOFC for allergy. • Quality of trial: Scored ≥1+ using the National Institute for Health and Clinical Excellence (NIHCE) criteria for quality assessment. • Other: English language publications.
Literature search dates or year range	1950 to July 2009
Number of food allergy studies included	Three
Synthesis methods	Summary tables and meta-analysis
Key findings	• All three RCTs examined the effect of oral tolerance induction to cow milk protein, with one study enrolling children who were exquisitely sensitive, reacting at <1 ml of whole cow milk at the start of the study. Age ranges of children included in each RCT were wide (0.6-12.9; 5-17; 6-17 years). • One RCT also performed oral tolerance induction to hen egg, although each child was desensitized to only one food (cow milk or hen egg) during the study. In two RCTs, children who were not randomized to receive specific oral tolerance induction practiced avoidance of the relevant allergen. Children in the third RCT consumed a placebo, although no details of the substance used for the placebo were provided. • Meta-analysis: Total of 127 children were included in the meta-analysis. Although a reduction in allergy after treatment is highlighted, this fails to meet statistical significance (pooled RR: 0.61; 95% CI: 0.32-1.12; P=0.1302). Cochran Q (8.87; P=0.0118) and I^2 (77.5%; 95% CI: 0%-91%) found high heterogeneity between studies, which further reduces the significance of findings.
Limitations	• One author reviewed the studies using the NIHCE quality framework, but no details about quality assessment were reported. It is unclear how many studies were excluded based on quality score. • Included studies performed specific oral tolerance induction only to cow milk or hen egg, and although these are the most common childhood food allergens trials had small sample size.

TABLE C-6 Continued

AMSTAR rating	
An a priori design?	Y
Duplicate study selection and data extraction?	N (only one author conducted the search and one author reviewed the studies)
Comprehensive literature search?	Y
Status of the publication as an inclusion criterion?	N
List of studies (included and excluded) provided?	Y
Characteristics of included provided?	Y
Scientific quality of the included studies assessed and reported?	Y
Scientific quality used in formulating conclusions?	Y
Methods used to combine the findings appropriate?	Y
Likelihood of publication bias assessed?	N
Conflict of interest stated?	Y/N (COI of the systematic review authors was provided but not provided for included studies)

Author, year	Klemens et al., 2011
Aims/Key questions	To determine if n-3 PUFA supplementation during pregnancy and lactation reduces risk for childhood allergic disease.
Study eligibility criteria	Inclusion criteria: • RCTs comparing supplementation in pregnancy and lactation with n-3 PUFA or placebo for primary prevention of allergic disease in neonates, infants, and children. • Study participants were pregnant or lactating women and their offspring. • Studies had to report on one of the following clinical or immunological outcomes in neonates, infants, or children: asthma, atopy, and food allergy as a clinical diagnosis or as response to the egg SPT at any time during the first 12 months of life. Diagnoses must be verified by medical or nursing clinicians.
Literature search dates or year range	1950 to October 2010
Number of food allergy studies included	Three
Synthesis methods	Summary tables, meta-analysis and narrative synthesis

continued

TABLE C-6 Continued

Key findings	• Three RCTs (N=264) reported on clinical diagnoses of food allergy in children. All RCTs were rated high quality. • Random-effects meta-analysis showed no significant difference in food allergy between children of mothers who received n-3 PUFA supplementation and children of mothers receiving placebo (6/128 versus 16/136, pooled OR: 0.46; 95% CI: 0.156-1.38). There was no significant between-study heterogeneity (P=0.226, I^2=32.777) nor was there evidence of publication bias (Egger's regression intercept P=0.998). o When only RCTs in which supplementation was started during pregnancy were considered, fewer children with food allergies were born to n-3 PUFA-supplemented mothers than to placebo-supplemented mothers, but this difference was not significant (4/92 versus 15/108, pooled OR: 0.34; 95% CI: 0.10-1.15). • Two of the included studies (N=187) reported on the period prevalence of positive response to the egg SPT in children up to age 12 months after maternal n-3 PUFA supplementation during pregnancy. Supplementation significantly reduced a positive SPT response to egg (12/87 versus 32/100, pooled OR: 0.33; 95% CI: 0.16-0.70). There was no significant between-study heterogeneity (P=0.957, I^2=0.000).
Limitations	• The different doses of supplementation in the combined studies also may represent a weakness of this meta-analysis, given that n-3 PUFA supplementation may have an inverted U-shaped dose–response curve, with moderate doses conferring more benefit than high doses in some models. • Although a positive SPT indicates the presence of food-specific IgE antibodies, a positive response may be seen in tolerant individuals and does not necessarily represent food allergy.

AMSTAR rating

An a priori design?	Y
Duplicate study selection and data extraction?	Y
Comprehensive literature search?	Y
Status of the publication as an inclusion criterion?	N
List of studies (included and excluded) provided?	Y
Characteristics of included provided?	Y
Scientific quality of the included studies assessed and reported?	Y
Scientific quality used in formulating conclusions?	Y
Methods used to combine the findings appropriate?	Y
Likelihood of publication bias assessed?	Y

TABLE C-6 Continued

Conflict of interest stated?	Y/N (COI of the systematic review authors was provided but not provided for included studies)
Author, year	Osborn and Sinn, 2006
Aims/Key questions	• To determine the effect of feeding hydrolyzed formulas on allergy and food intolerance in infants and children compared to adapted cow milk or human breast milk. If hydrolyzed formulas are effective, to determine what type of hydrolyzed formula is most effective, including extensively and partially hydrolyzed formulas. • To determine which infants benefit, including infants at low or high risk of allergy and infants receiving early, short-term, or prolonged formula feeding.
Study eligibility criteria	Inclusion criteria: • Types of studies: RCTs and quasi-RCTs that compare the use of a hydrolyzed infant formula to human milk or an adapted cow milk formula. Random and quasi-random (e.g., using alternation) trials with ≥80% follow-up of participants were eligible for inclusion. • Types of participants: Infants in the first 6 months of life without clinical evidence of allergy. • Types of interventions: Hydrolyzed cow milk and soy formulas, and extensively and partially hydrolyzed formulas. Hydrolyzed formulas may be used for either o early, short-term supplementary or sole formula feeding in infants unable to be exclusively breastfed in the first days of life; o prolonged supplementation of breastfed infants or sole formula feeding in infants in the first months of life; or o weaning from the breast using infant formula. • Type of controls: The control group may include infants who receive exclusive human milk (either breast fed or expressed) or an adapted cow milk formula. • Primary outcomes: o All allergy including asthma, atopic dermatitis, allergic rhinitis or food allergy. o Food intolerance.
Literature search dates or year range	Inception to March 2006
Number of food allergy studies included	Five

continued

TABLE C-6 Continued

Synthesis methods	Meta-analysis, summary table, narrative text
Key findings	For Comparison 01 Early short-term feeding: Hydrolyzed formula versus human milk feeding among low-risk infants: • (90 infants) no significant difference in any allergy (RR: 1.43; 95% CI: 0.38-5.37), food allergy (RR: 1.43; 95% CI: 0.38-5.37), and cow milk allergy (RR: 7.11; 95% CI: 0.35-143.84) at age 3 years. • (3,559 infants) no significant difference in cow milk allergy up to mean age of 27 months (RR: 0.87; 95% CI: 0.52-1.46). For Comparison 03 Early short-term feeding: Hydrolyzed formula versus cow milk formula: • (77 infants) no significant difference in childhood allergy incidence (RR: 1.37; 95% CI: 0.33-5.71), childhood food allergy (RR: 1.37; 95% CI: 0.33-5.71), and childhood cow milk allergy (RR: 5.13; 95% CI: 0.25-103.43). • (3,478 infants) a reduction in infant cow milk allergy of borderline significance (RR: 0.62; 95% CI: 0.38-1.00). For Comparison 04 Prolonged feeding: Hydrolyzed formula versus cow milk formula: • (141 infants) no significant difference in infant food allergy (RR: 1.82; 95% CI: 0.64-5.16). • (67 infants) a significant reduction in infant cow milk allergy (RR: 0.36; 95% CI: 0.15-0.89). For Comparison 07 Prolonged feeding: Extensively hydrolyzed formula versus cow milk formula: • (96 infants) no significant difference in food allergy (RR: 1.15; 95% CI: 0.33-4.02). For Comparison 08 Prolonged feeding: Partially hydrolyzed formula versus cow milk formula: • (91 infants) no significant difference in infant food allergy (RR: 2.56; 95% CI: 0.86-7.56). • a significant reduction in cow milk allergy in infancy (RR: 0.36; 95% CI: 0.15-0.89). For Comparison 09 Prolonged feeding: Extensively hydrolyzed formula versus partially hydrolyzed formula: • Meta-analysis of two studies (N=341) found a significant reduction in infant food allergy (typical RR: 0.43; 95% CI: 0.19-0.99). • (246 infants) no significant difference in infant cow milk allergy (RR: 0.13; 95% CI: 0.01-1.16).

TABLE C-6 Continued

Key findings (continued)	For Comparison 11 Prolonged feeding: Hydrolyzed formula versus cow milk formula: Allergy/intolerance confirmed by test: • (141 infants) no significant difference in infant food allergy confirmed by specific IgE (RR: 1.82; 95% CI: 0.64-5.16). • significant reduction in infant cow milk allergy confirmed by specific IgE (RR: 0.36; 95% CI: 0.15-0.89). • no significant difference in infant food intolerance confirmed by DBPCOFC (RR: 0.48; 95% CI: 0.07-3.33). For Comparison 14 Prolonged feeding: Partially hydrolyzed whey formula versus cow milk formula: • significant reduction in infant cow milk allergy (RR: 0.36; 95% CI: 0.15-0.89). For Comparison 15 Prolonged feeding: Partially hydrolyzed casein containing formula versus cow milk formula: • (91 infants) no significant difference in infant food allergy (RR: 2.56; 95% CI: 0.86-7.56). For Comparison 17 Prolonged feeding: Extensively hydrolyzed casein containing formula versus cow milk formula: • (96 infants) no significant difference in infant food allergy (RR: 1.15; 95% CI: 0.33-4.02).
Limitations	• Many "meta-analyses" of small number of studies. • Infant and childhood allergy had different definitions, timing of measurement and methods for measurement from study to study. Most studies were small or had methodological limitations, with benefits not persisting when analysis was restricted to trials with blinding of measurement to study formula or to studies of adequate methodology.

AMSTAR rating	
An a priori design?	Y
Duplicate study selection and data extraction?	Y
Comprehensive literature search?	Y
Status of the publication as an inclusion criterion?	N
List of studies (included and excluded) provided?	Y
Characteristics of included provided?	Y
Scientific quality of the included studies assessed and reported?	Y
Scientific quality used in formulating conclusions?	Y
Methods used to combine the findings appropriate?	N (many "meta-analysis" had one study)
Likelihood of publication bias assessed?	N
Conflict of interest stated?	Y

continued

TABLE C-6 Continued

Author, year	Kramer and Kakuma, 2004
Aims/Key questions	To assess the effects on child health, growth, and development, and on maternal health, of exclusive breastfeeding for 6 months versus exclusive breastfeeding for 3 to 4 months with mixed breastfeeding (introduction of complementary liquid or solid foods with continued breastfeeding) thereafter through 6 months.
Study eligibility criteria	Inclusion criteria: • Study design: Controlled clinical trials and observational studies, published in all languages, examining whether or not exclusive breastfeeding until age 6 months has an impact on growth, development, morbidity, and survival of healthy, term infants and their mothers. • Comparison: The comparisons must have been based on one group of infants who received exclusive breastfeeding for at least 3 but less than 7 months and mixed breastfeeding until 6 months or later (i.e., infants were introduced to liquid or solid foods between 3 and 6 months of age), and another group of infants who were exclusively breastfed for at least 6 months. Studies comparing infants receiving prolonged exclusive breastfeeding (more than 6 months) to those exclusively breastfed for 6 months and continued mixed breastfeeding after 6 months also were included. Among infants exclusive breastfeeding for at least 3 months, the interventions/exposures compared were continued exclusive breastfeeding versus mixed breastfeeding. The "complementary" foods used in mixed breastfeeding included juices, formula, other milks, other liquids, or solid foods. Although the WHO defines exclusive breastfeeding as breastfeeding with no supplemental liquids or solid foods other than medications or vitamins, few studies strictly adhered to the WHO's definition. • Population: Lactating mothers and their healthy, term, singleton infants.

TABLE C-6 Continued

Study eligibility criteria (continued)	• Outcome measures: Any infant or maternal health outcomes. The infant outcomes specifically sought (but not necessarily found) included growth (weight, length, and head circumference and z-scores (based on the WHO/CDC reference) for weight-for-age, length-for-age, and weight-for-length), infections, morbidity, mortality, micronutrient status, neuromotor and cognitive development, asthma, atopic eczema, other allergic diseases, type 1 diabetes, blood pressure, and subsequent adult chronic diseases such as coronary heart disease, hypertension, type 2 diabetes, and inflammatory and autoimmune diseases. Maternal outcomes sought included postpartum weight loss, duration of lactational amenorrhea, and such chronic diseases as breast and ovarian cancer and osteoporosis. Exclusion criteria: • Studies of (or including) low birthweight (less than 2,500 g) infants were not excluded, provided that such infants were born at term (at least 37 completed weeks). Only those studies with an internal comparison group were included in the review, i.e., the authors excluded studies based on external comparisons (with reference data). • Studies comparing exclusive breastfeeding and mixed breastfeeding from birth were excluded, as were those that investigated the effects of age at introduction of nonbreast milk liquid or solid foods but did not ensure exclusive breastfeeding at least 3 months before their introduction.
Literature search dates or year range	Inception to June 15, 2011
Number of food allergy studies included	One cohort study
Synthesis methods	Narrative synthesis; meta-analysis (N/A for food allergy outcome because only one study was included)
Key findings	• 1 cohort study enrolled 135 healthy Finnish infants of atopic parents reported food allergy outcome. This study was rated unclear overall risk of bias. • For the comparison of exclusive breastfeeding for 6-7 months versus 3-4 months, this study also reported a reduced risk of a history of food allergy at 1 year but double food challenges showed no significant risk reduction (RR: 0.77; 95% CI: 0.25-2.41).
Limitations	• This systematic review did not focus on food allergy. Only 1 cohort study reported food allergy outcomes.

continued

TABLE C-6 Continued

AMSTAR rating	
An a priori design?	Y
Duplicate study selection and data extraction?	Y
Comprehensive literature search?	Y
Status of the publication as an inclusion criterion?	Y
List of studies (included and excluded) provided?	Y
Characteristics of included provided?	Y
Scientific quality of the included studies assessed and reported?	Y
Scientific quality used in formulating conclusions?	N
Methods used to combine the findings appropriate?	N (many "meta-analysis" only has 1 study)
Likelihood of publication bias assessed?	N
Conflict of interest stated?	N

NOTE: ALA = alpha-linolenic acid; CDC = Centers for Disease Control and Prevention; CI = confidence interval; DBPCOFC = double-blind, placebo-controlled oral food challenge; DHA = docosahexaenoic acid; DPA = docosapentaenoic acid; EAACI = European Academy of Allergy & Clinical Immunology; EPA = eicosapentaenoic acid; IgE = immunoglobulin E; IU = international units; LCPUFA, long-chain polyunsaturated fatty acid; N/A = not available; OR = odds ratio; PUFA = polyunsaturated fatty acid; RAST = radioallergosorbent; RCT = randomized controlled trial; RR = relative risk; SDA = stearidonic acid; SPT = skin prick test; tIgE = total IgE; WHO = World Health Organization.

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Appendix D

Acronyms and Abbreviations

AAAAI	American Academy of Allergy, Asthma & Immunology
AAFA	Asthma and Allergy Foundation of America
AAP	American Academy of Pediatrics
ACAA	Air Carrier Access Act
ACAAI	American College of Allergy, Asthma & Immunology
ACD	allergic contact dermatitis
ACP	allergen control plan
AD	atopic dermatitis
ADA	American Diabetes Association
ADA	Americans with Disabilities Act
aOR	adjusted odds ratio
AP	allergenic proctocolitis
APC	antigen-presenting cell
APT	atopy patch test
ASCIA	Australasian Society of Clinical Immunology and Allergy
BAT	basophil activation test
BEAT	Beating Egg Allergy Trial
CAC	Codex Alimentarius Commission
CCP	critical control point
CD14	cluster of differentiation 14
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CPSC	Consumer Product Safety Commission

CRD	component resolved diagnostics
DBPCOFC	double-blind, placebo-controlled oral food challenge
DC	dendritic cell
DMP	differentially methylated probe
DOJ	U.S. Department of Justice
DOT	U.S. Department of Transportation
EAACI	European Academy of Allergy & Clinical Immunology
EAT	Enquiring About Tolerance
ECHO	Environmental Influences on Child Health Outcomes
ED	eliciting dose
EFSA	European Food Safety Authority
EG	eosinophilic gastroenteritis
EHF	extensively hydrolyzed cow's milk formula
ELISA	enzyme-linked immunosorbent assay
EoE	eosinophilic esophagitis
EPIT	epicutaneous immunotherapy
ESPGHAN	European Society for Pediatric Gastroenterology, Hepatology, and Nutrition
EU	European Union
EWAS	epigenome-wide association study
FAA	Federal Aviation Administration
FALCPA	Food Allergen Labeling and Consumer Protection Act
FAMPP	Food Allergy Management and Prevention Plans
FAO	Food and Agriculture Organization of the United Nations
FDA	Food and Drug Administration
FDEIA	food-dependent, exercise-induced allergy
FNS	U.S. Food and Nutrition Service
FPIES	food protein–induced enterocolitis syndrome
FSIS	Food Safety and Inspection Service
FSMA	Food Safety Modernization Act
GI	gastrointestinal
GINI	German Infant Nutritional Intervention
GWAS	genome-wide association study
GxE	genome–environment
HACCP	hazard analysis and critical control point
HEAP	Hen's Egg Allergy Prevention

HHS	U.S. Department of Health and Human Services
HLA	human leucocyte antigen
HRQL	health-related quality of life
ICD	*International Classification of Diseases*
ICN	Institute of Child Nutrition
ICSA	interval censoring survival analysis
IDEA	Individuals with Disabilities Education Act
IEP	individualized education program
IFN	interferon
IgE	immunoglobulin E
ILSI-EU	International Life Sciences Institute-Europe
IOM	Institute of Medicine
ITP	Interstate Travel Program
JCAAI	Joint Council of Allergy, Asthma & Immunology
LEAP	Learning Early About Peanut Allergy
LOAEL	lowest-observed-adverse-effect level
MAPK	mitogen-activated protein kinase
MED	minimal eliciting done
Mis-BAIR	Melbourne Infant Study-BCG for Allergy and Infection Reduction
MMR	measles, mumps, rubella
NAS	National Academy of Sciences
NCHS	National Center for Health Statistics
NEISS	National Electronic Injury Surveillance System
NHAMCS	National Hospital Ambulatory Medical Care Survey
NHANES	National Health and Nutrition Examination Survey
NHDS	National Hospital Discharge Survey
NHMRC	National Health and Medical Research Council
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NOAEL	no-observed-adverse-effect level
NRC	National Research Council
NSAID	nonsteroidal anti-inflammatory drug
OFC	oral food challenge
OIT	oral immunotherapy
OR	odds ratio

PAL	precautionary allergen labeling
PASTURE	Protection against Allergy Study in Rural Environments
PCR	polymerase chain reaction
PFAS	pollen-associated food allergy syndrome
PHF	partially hydrolyzed formula
PIFA	Prevalence of Infant Food Allergy; Pertussis Immunisation and Food Allergy
PreventADALL	Preventing Atopic Dermatitis and Allergies in Children
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
RAST	radioallergosorbent test
RCT	randomized controlled trial
RFR	Reportable Food Registry
RR	relative risk
sIgE	allergen-specific IgE (or food-specific IgE)
SLIT	sublingual immunotherapy
SNP	single nucleotide polymorphism
SOP	standard operating procedure
SPT	skin prick test
STEP	Starting Time for Egg Protein
SyMBIOTA	Synergy in Microbiota
TNO	Netherlands Organization for Applied Scientific Research
TTB	U.S. Tax and Trade Bureau
TWG	Threshold Working Group
USDA	U.S. Department of Agriculture
VDR	vitamin D receptor
VITAL®	Voluntary Incidental Trace Allergen Labeling
WAO	World Allergy Organization
WHO	World Health Organization

Appendix E

Definitions

Acceptable level of risk: A risk management decision regarding the degree of risk that would be acceptable within the affected population.

Allergen-specific IgE (sIgE): An IgE that recognizes a specific allergen and that is formed by the immune systems of some individuals after they have been exposed to that allergen in food. Also referred to in the text as food-specific IgE.

Allergy/allergic disease: A disease caused by immunologic dysfunction that falls under one of two key classifications: immunoglobin E (IgE)-mediated or non-IgE-mediated.

Anaphylaxis: An acute, potentially life-threatening syndrome with multi-systemic manifestations due to the rapid release of inflammatory mediators.

Atopic disorder: Disorder characterized by exaggerated or hypersensitive immune reactions to foreign antigens.

Atopic march: Refers to the idea that atopic disorders progress over time from eczema (i.e., atopic dermatitis) to asthma.

Atopy patch test (APT): A test performed in a manner similar to patch testing that is routinely used for evaluation of allergic contact dermatitis, except that foods are used. The food, presented as a fresh extract or powder, is generally placed under an aluminum disc on the skin for 48

hours then removed. The final test result is determined at 72 hours after application. Current guidelines do not recommend the APT for the routine diagnosis of food allergies.

Auto-injector of epinephrine: A device used in first-aid management to self-inject epinephrine.

Basophil activation test (BAT): A test conducted by exposing the basophils in a test tube to various concentrations of the allergen to be tested, either an extract or individual component proteins in the test tube. The readout is the number of cells responding, or the concentration of allergen at which 50 percent of the cells respond. About 10 percent of people are BAT non-responders, even though they are allergic and have positive skin tests. The test is a functional assay akin to a provocation test, such as a skin prick test.

Basophils (basophilic granulocytes): The least abundant of the granulocytes (the others being neutrophils and eosinophils). Basophils can release histamine, lipid mediators, and cytokines in response to the aggregation of their cells surface FcεRI, which is induced when IgE bound to these FcεRI recognizes specific allergens, including those from foods. Unlike mast cells, basophils mature in the bone marrow and circulate in the blood, but can enter tissues at sites of allergic inflammation.

Component resolved diagnostics: A test sometimes referred to as molecular testing. This test involves measuring sIgE against individual allergenic food proteins.

Cross-contact: A situation in which an unintended allergen may be present in an otherwise allergen-free food because of contact between the unsafe and safe foods.

Cytokines: Small proteins produced by various immune cells and other cell types that carry signals to facilitate communication and interaction between cells.

Desensitization: A state of clinical and immunological nonresponsiveness to an allergen, including food allergens, that can be induced by the careful, physician-guided administration of gradually increasing amounts of the offending allergen over a relatively short period of time (hours to days). The maintenance of such desensitization typically requires continued regular exposure to the offending allergen (also see **Tolerance**).

Epinephrine: Also known as adrenaline, first-line therapy for food-induced anaphylaxis. Recommended to be injected intramuscularly.

Epitopes: Specific fragments of food allergens (antigens) that the immune system recognizes; if recognized by IgE bound to FcεRI on the surface of mast cells and basophils, epitopes can trigger an allergic reaction that may include anaphylaxis.

Exposure assessment: An action that plays an essential role in determining whether the hazardous properties of a substance will translate to adverse health effects. For foods, the exposure assessment estimates the amounts (or range of amounts) of the hazard that are likely to be consumed. If these amounts exceed a Reference Dose or the established maximum level in foods (established using a hazard assessment), then a risk of adverse health consequences to the exposed (sub)population is predicted. In contrast, an exposure at or below the Reference Dose or maximum level in foods is assumed to be safe for the vast majority of individuals. In the case of food allergens, the Reference Dose could also be used as an action level to determine when precautionary allergen labeling should be applied to a product package. (Also see **Hazard identification and hazard characterization** and **Reference Dose**.)

FcεRI: The high-affinity receptor for IgE that binds IgE and thereby permits cells bearing FcεRI on their surface (e.g., mast cells, basophils, some dendritic cells, and macrophages) to become "sensitized" so that they can be activated to release inflammatory mediators by allergens recognized by the bound IgE. For the FcεRI to initiate the cell signaling that results in activation of mast cells and basophils to release their mediators requires that the receptors are aggregated when their bound IgE reacts with allergens that are at least bivalent (e.g., have two epitopes that can bind IgE). This permits such allergens to bridge adjacent IgE molecules and to aggregate the FcεRI receptors that bind such IgE.

Food: Any substance—whether processed, semiprocessed, or raw—that is intended for human consumption. Food includes drinks, chewing gum, food additives, and dietary supplements.

Food allergens: The components within foods that trigger adverse immunologic reactions; these are most often specific glycoproteins that can interact with the body's immune cells in a way that initiates the development of a food allergy.

Food allergy: An adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food, and that can be either IgE-mediated or non-IgE-mediated.

Food intolerance: An adverse reaction to foods or food components that lacks an identified immunologic pathophysiology.

Food protein-induced enterocolitis syndrome and food protein-induced allergic proctocolitis: Non-IgE-mediated disorders that lack current means of simple laboratory testing to identify causal foods or to confirm the diagnosis. Guidelines suggest using the medical history, resolution of signs and symptoms during dietary elimination, and recurrence of signs and symptoms upon exposure, for example during an oral food challenge, as a means of diagnosis.

Hazard: An inherent property of an agent or situation having the potential to cause adverse effects when an organism, system, or given population is exposed to that agent.

Hazard identification and hazard characterization: The two components of the hazard assessment process. Hazard identification includes a determination that the substance with the hazardous properties is present, but also more generally refers to the identification of the type and nature of the adverse effects that an agent can cause in an organism, system, or given population. In the hazard identification of an allergenic food, the prevalence and severity of the specific food allergy would be considered. Hazard characterization involves a qualitative and, wherever possible, quantitative description of the inherent property of an agent or situation having the potential to cause adverse effects. Hazard characterization encompasses the dose–response relationship. A hazard assessment (involving both hazard identification and hazard characterization) can be used to derive safe levels of exposure, for instance through the elaboration of a Reference Dose.

Immunoglobulin E (IgE): An antibody that can trigger intense inflammatory reactions. IgE causes the IgE-mediated allergic response by binding strongly to IgE receptors (FcεRI) found on the surface of mast cells and basophils, and triggering these cells to release powerful inflammatory mediators once the cell-bound IgE recognizes the offending food allergen.

Lowest-observed-adverse-effect level (LOAEL): The lowest dose of a hazard (e.g., allergen, expressed as milligrams (mg) of total protein from the allergenic food) that can provoke an observable reaction in an individual or population. Also known as the minimal eliciting dose.

Mast cells: Cells derived from hematopoietic precursors that mature after migrating into essentially all vascularized tissues, where they can reside for long periods of time. Mast cells are present within the mucosal tissues of the entire gastroinstestinal tract (and many other anatomical sites, including the skin and airways) and contain cytoplasmic granules rich in histamine, proteoglycans (depending on the mast cell population, these consist of heparin and/or chondroitin sulfates), serine proteases (depending on the mast cell population, these can consist of carboxypeptidase A3, tryptases and/or chymase). Upon activation by IgE and specific antigens (including food allergens), mast cells can release such granule-associated inflammatory mediators and also secrete newly synthesized lipid mediators and cytokines. Mast cells also can be activated by diverse agents that act independently of IgE, which can result in the release of the same products produced by mast cells activated through IgE.

No-observed-adverse-effect level (NOAEL) or threshold: The highest dose of a hazard (e.g., allergen, expressed as mg of total protein from the allergenic food) that will not provoke an observable reaction in an individual or population.

Objective response: A reaction that can be independently verified by a clinically trained observer (e.g., urticaria [hives], vomiting, flushing, angioedema).

Oral food challenge (OFC): A feeding test that typically involves a gradual, medically supervised ingestion of increasingly larger doses of the food being tested as a possible food allergen. Guidelines recommend using the OFC to diagnose food allergy, particularly in individuals whose clinical history and other test results do not definitively establish the diagnosis of food allergy. There are three types of OFCs depending on the protocol. An open OFC is one where the food is in its natural form; a single-blind OFC is one where the food is masked from the patient's perspective so less patient bias occurs because of anxiety; a double-blind, placebo-controlled oral food challenge (DBPCOFC) involves masking the tested allergen and feeding it or indistinguishable placebo randomly without the patient or observer knowing if the allergen or placebo is being tested. A DBPCOFC is considered the "gold standard" for diagnosis of food allergy.

Pollen-associated food allergy syndrome (oral allergy syndrome): A type of food allergy with signs and symptoms that include itching or swelling of the lips, mouth, or throat in response to eating certain raw fruits and vegetables that typically develops in adults with hay fever. The specific IgE antibodies formed exhibit reactivity with both proteins found in pollens and similar proteins found in certain fruits and vegetables.

Reference Dose: The lowest dose of a hazard (e.g., allergen, expressed in mg of total protein from the allergenic source) that is predicted to elicit symptoms of a reaction when ingested by a defined, small percentage of the population of individuals who are known to experience adverse reactions to that hazard.

Risk: The probability of an adverse effect in an organism, system, or (sub) population caused under specified circumstances by exposure to an agent.

Risk characterization: A process that can be used to assess the likelihood of risk even in cases where a Reference Dose or maximum level has not been established. The risk characterization is the determination of quantitative probability, including attendant uncertainties, that adverse health effects will occur in a given individual or (sub)population, under defined conditions of exposure.

Safety: The control of recognized hazards to achieve an acceptable level of risk.

Sensitization: A condition in which an individual produces detectable IgE to a particular allergen or allergens. It precedes and is required for the cell manifestations of a food allergy, but not all individuals with detectable IgE will experience a food allergy reaction to the allergen recognized by that IgE.

Skin prick test: An allergy detection test performed by puncturing the surface of the skin to introduce an allergen and evaluating the area of the induced wheal (small swelling) and flare (redness) responses that can be measured.

Subjective response: A mild transitory reaction that cannot be independently confirmed by a clinically trained observer (e.g., palatal itching or stomach cramping).

T cells: Lymphocytes produced by the thymus that guide many aspects of the immune system, particularly its adaptability and ability to recognize threats.

Tolerance: A state of relatively unresponsiveness of the immune system to substances or tissue that have the capacity to elicit an immune response. It can be natural (e.g., to the body's own proteins) or acquired (e.g., to

external proteins). It also is said that some persons can "grow out" of an allergy; this can be envisioned as a form of acquired tolerance to the offending allergen(s). In some instances, the state of tolerance may be transient (also see **Desensitization**); in others it can be durable.

Appendix F

Committee Members Biographical Sketches

Virginia A. Stallings, M.D. (*Chair*) is the Jean A. Cortner Endowed Chair in Gastroenterology, and Director of the Nutrition Center at The Children's Hospital of Philadelphia, and Professor of Pediatrics at the Perelman School of Medicine, University of Pennsylvania. Her research interests include pediatric nutrition, evaluation of dietary intake and energy expenditure, and nutrition-related chronic disease. Dr. Stallings has been a member of the National Academy of Medicine since 2005 and has served on several National Academies of Sciences, Engineering, and Medicine committees: Committee on Nutrition Standards for National School Lunch and Breakfast Programs, Committee on Nutrition Services for Medicare Beneficiaries, Committee on the Scientific Basis for Dietary Risk Eligibility Criteria for WIC (Women, Infants, and Children) Programs, the Committee to Review the WIC Food Packages, and the Committee to Review Child and Adult Care Food Program Meal Requirements. She is a former member (1997-2000) and co-vice chair (2000-2002) of the Food and Nutrition Board. Dr. Stallings is board certified in pediatrics and clinical nutrition. She received the Fomon Nutrition Award from the American Academy of Pediatrics and is a Fellow of the American Society of Nutrition. Dr. Stallings earned a B.S. in Nutrition and Foods from Auburn University, an M.S. in Human Nutrition and Biochemistry from Cornell University, and an M.D. from the University of Alabama at Birmingham School of Medicine.

Katrina (Katie) Allen, Ph.D., is Director of the Population Health Research Theme, Murdoch Childrens Research Institute, Professor of Paediatrics at the University of Melbourne, Australia, and holds a Chair in Food

Allergy at the University of Manchester, United Kingdom. She is an active pediatric allergist and gastroenterologist at the Royal Children's Hospital, Melbourne. Her research focuses on the evolving field of food allergy and her vision is to prevent food allergy in children. She is a National Health and Medical Research Council (NHMRC) Practitioner Fellow and Chief Investigator on five NHMRC-funded studies, which seek to answer questions about population health and evolution of the allergy epidemic, including gene-environment and epigenetic associations with food allergy. Dr. Allen also is Director of the NHMRC-funded Australian Centre of Food & Allergy Research, which aims to translate research findings into clinical practice and public health policy to ensure the best outcomes for children with food allergy.

A. Wesley Burks, M.D., is Executive Dean for the University of North Carolina (UNC) School of Medicine. In this role he provides overall academic leadership for the School of Medicine and the UNC Health Care System. He also is the Curnen Distinguished Professor in Pediatrics. Dr. Burks joined the UNC system in November 2011. His research interests are in the allergic diseases, particularly adverse reactions to foods. Dr. Burks heads a research team whose work centers on identifying the allergens in specific foods at a molecular level, improving understanding of the mechanism of adverse food reactions, and developing treatments for food allergy in animal models and in clinical studies. Dr. Burks and his colleagues are currently conducting clinical studies with different types of mucosal immunotherapy. His laboratory funding comes from many sources, including the National Institutes of Health (NIH) and private foundations. He is a past Chair and member of the NIH Hypersensitivity, Autoimmune, and Immune-mediated Diseases study section and is Past President of the American Academy of Allergy, Asthma & Immunology. He received an M.D. from the University of Arkansas for Medical Sciences and completed a fellowship in Allergy and Immunology at Duke University Medical Center.

Nancy R. Cook, Sc.D., is a Professor in the Department of Medicine at the Brigham & Women's Hospital and Harvard Medical School, and Professor of Epidemiology at the Harvard School of Public Health. Dr. Cook is a biostatistician involved in the design, conduct, and analysis of several large randomized trials, including the Women's Health Study, the Physicians' Health Study, and the VITamin D and OmegA-3 TriaL (VITAL). She leads the Trials of Hypertension Prevention (TOHP) Follow-up Study, an observational follow-up of participants in Phases I and II of TOHP. Dr. Cook's methodologic efforts focus on the predictive modeling of observational data and developing risk prediction scores using clinical biomarkers. She was a member of the National Academy of Sciences, Engineering, and Medicine's

Committee on the Consequences of Sodium Reduction in Populations. She received her M.S. and Sc.D. from the Harvard School of Public Health.

Sharon M. Donovan, Ph.D., R.D., is Professor and Melissa M. Noel Endowed Chair in the Department of Food Science and Human Nutrition at the University of Illinois at Urbana-Champaign. Her research focuses on pediatric nutrition, with an emphasis on optimization of neonatal intestinal development. She compares the biological effects of human milk and infant formulas on intestinal function in human infants and neonatal piglets and in various models of intestinal disease. Dr. Donovan is actively involved in several professional societies and served as the President of the American Society for Nutrition (2011-2012). She is the recipient of several awards in recognition of her research, including the Mead Johnson Award and the Norman A. Kretchmer Award from the American Society for Nutrition. She is currently a member of the National Academies of Sciences, Engineering, and Medicine's Food and Nutrition Board. Dr. Donovan received her B.S. and Ph.D. in Nutrition from the University of California, Davis, and completed a post-doctoral fellowship in Pediatric Endocrinology at the Stanford University School of Medicine.

Stephen J. Galli, M.D., was chair of the Department of Pathology (1999-2016), and since 1999 has been the Mary Hewitt Loveless, M.D. Professor, and Professor of Pathology and of Microbiology and Immunology at the Stanford University School of Medicine. He also was the Co-Director of the Stanford Center for Genomics and Personalized Medicine from 2009-2016. He served on the faculty of Harvard Medical School from 1979 to his arrival at Stanford. Dr. Galli's research has focused on the development and function of mast cells and basophils and the development of new animal models for studying the roles of these cells in health and disease, with particular interests in the roles of these cells in asthma, anaphylaxis, and food allergies, and the roles of mast cells and IgE in innate and acquired host defense against venoms. He is currently principal investigator of a National Institute of Allergy and Immune Diseases (NIAID) Asthma and Allergic Diseases Cooperative Research Center (AADCRC) at Stanford (2013-2018), for a project entitled "Integrated Genomic and Functional Studies of Tolerance Therapy for Peanut Allergy." Dr. Galli served as one of two Co-Chairs of an NIAID Food Allergy Research Expert Panel (2006) and is a member of the National Allergy and Infectious Diseases Council of the NIH (2014-2018). Dr. Galli was a member of the National Research Council committee that wrote the report *Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease*. Dr. Galli was elected to the Collegium Internationale Allergologicum (serving as president from 2010-2014) and the National Academy of Medicine. He

also is a foreign member of the *Accademia Nazionale dei Lincei* (National Academy of the Lynxes) in Rome. Dr. Galli received a MERIT Award from the NIAID/NIH (1995), Scientific Achievement Awards from the International Association of Allergy & Clinical Immunology (1997) and the World Allergy Organization (2011), the Rous-Whipple Award of the American Society for Investigative Pathology (2014), and the Karl Landsteiner Medal of the Austrian Society of Allergology and Immunology (2014). Dr. Galli received an M.D. from Harvard Medical School, and completed a residency in Anatomic Pathology at Massachusetts General Hospital.

Bernard Guyer, M.D., M.P.H., is the Zanvyl Krieger Professor of Children's Health, Emeritus, at the Johns Hopkins Bloomberg School of Public Health in Baltimore. A physician trained in both pediatrics and preventive medicine, Dr. Guyer's 40-year career in public health has been devoted to advancing the health of mothers, children, and families worldwide. Retired in 2011, he continues to be actively involved in the Women's and Children's Health Policy Center at the Bloomberg School of Public Health, where he lectures, teaches, and advises students and faculty. He is a member of the National Academy of Medicine and chaired the National Academy of Sciences, Engineering, and Medicine's Board on Children, Youth, and Families (2007-2013). Dr. Guyer received his B.S. from Antioch College, his M.D. from the University of Rochester School of Medicine, and his M.P.H. from the Harvard School of Public Health.

Gideon Lack, M.B.B.Ch., is Head of the Children's Allergy Service at Guy's and St. Thomas' National Health Service Foundation Trust, Professor of Paediatric Allergy and Head of Department of Paediatric Allergy at King's College London. His research has focused on severe childhood asthma, peanut allergy, and new strategies to prevent and treat food allergies, eczema, asthma, and hay fever in children and adults. His clinical expertise includes allergic asthma, anaphylaxis, and desensitizing vaccines to treat hay fever and other allergies. Dr. Lack is principal investigator of a current randomized controlled clinical trial designed to determine the best strategy to prevent peanut allergy in young children, the LEAP-On (Learning Early About Peanut Allergy) study and principal investigator of the EAT (Enquiring About Tolerance) study. He is a member of the British Medical Association, the British Society of Allergy and Clinical Immunology, the European Academy of Allergy & Clinical Immunology, the Medical Research Council Asthma UK Centre in Allergic Mechanisms of Asthma, and the Collegium Internationale Allergolicum. He also is a Fellow of the Royal College of Paediatrics and Child Health. Dr. Lack obtained his medical degree from the University of Oxford Medical School and his specialization in Allergy

and Immunology from the National Jewish Centre for Immunology and Respiratory Medicine in Denver, Colorado.

Ann S. Masten, Ph.D., LP, is Regents Professor and Irving B. Harris Professor of Child Development in the Institute of Child Development at the University of Minnesota. Dr. Masten's research focuses on understanding processes that promote competence and prevent problems in human development, with a focus on adaptive processes and pathways, developmental tasks and cascades, and resilience in the context of high cumulative risk, adversity, and trauma. She directs the Project Competence studies of risk and resilience, including studies of normative populations and high-risk young people exposed to war, natural disasters, poverty, homelessness, and migration. Dr. Masten co-chairs the Forum on Investing in Young Children Globally and serves on the Board of Children, Youth, and Families for the National Academies of Sciences, Engineering, and Medicine. She is a member of the U.S. National Committee of Psychology, a past-president of the Society for Research in Child Development, and recipient of the Bronfenbrenner Award for Lifetime Contributions to Developmental Psychology in the Service of Science and Society from the American Psychological Association. Her publications include the 2014 book *Ordinary Magic: Resilience in Development* and numerous empirical articles. She completed her Ph.D. in psychology at the University of Minnesota and her clinical psychology internship at the University of California, Los Angeles.

Jose M. Ordovas, Ph.D., is Professor of Nutrition at the Friedman School of Nutrition Science and Policy, Professor of Genetics at the Sackler School of Graduate Biomedical Sciences at Tufts University and Senior Scientist at the U.S. Department of Agriculture (USDA) Human Nutrition Research Center on Aging at Tufts University in Boston, Massachusetts, where he also is the Director of the Nutrition and Genomics Laboratory. He is a Senior Collaborating Scientist at the Centro Nacional de Investigaciones Cardiovasculares and Instituto Madrileño de Estudios Avanzados en Alimentación (IMDEA), both in Madrid, Spain. Dr. Ordovas's major research interests focus on the genetic factors predisposing to cardiovascular disease and obesity and their interaction with the environment and behavioral factors, with special emphasis on diet. Throughout his career, Dr. Ordovas has received multiple honors for his scientific achievements, including the USDA Secretary's Award, the Centrum American Nutrition Society Award, the Mary Swartz Award from the Dietetic Association, the Garry-Labbe Award from the American Association for Clinical Chemistry, the Francisco Grande Memorial Lecture for Excellence in Nutrition Research, The Rafael del Pino Foundation Lecture, the Turkish Genetics Society Award, the Jaén Paraíso Interior and Asociación Española de Municipalidades del

Olivo (AEMO) awards for his contributions to the diffusion of the Mediterranean diet and the olive oil, the Good Cholesterol award from Aviles and the Danone Foundation Award for achievements in Nutrition Research, the Gold Medal of the Spanish Society of Cardiology, and the Francisco Grande Award from the Fundacion Dieta Mediterranea. He has been awarded an honorary degree in Medicine from the University of Cordoba in Spain and the title of Member of the Royal Academies of Sciences, Medicine, Nutrition and Pharmacy, all of them in Spain. Dr. Ordovas serves on multiple editorial boards and is active with multiple international peer review and steering committees. He served on the National Academy of Sciences, Engineering, and Medicine's Food and Nutrition Board (2005-2011). Dr. Ordovas was educated in Spain at the University of Zaragoza where he completed his undergraduate work in chemistry and received his doctorate in human lipoprotein metabolism. He did postdoctoral work at the Massachusetts Institute of Technology, Harvard, and Tufts.

Hugh A. Sampson, M.D., is the Kurt Hirschhorn, M.D. and Children's Center Foundation Professor of Pediatrics and the Director of the Jaffe Food Allergy Institute at Mount Sinai's Icahn School of Medicine. Dr. Sampson's research interests have focused on food allergic disorders, and now include work on the pathogenesis of food-induced anaphylaxis, characterization of allergenic food proteins and their processing by the immune system, genetics of food allergy, development of novel diagnostic tests, and mechanisms of immunotherapeutic strategies for treating food allergies, including basic studies and clinical trials in oral, sublingual, and epicutaneous immunotherapy and the potential use of biologics, such as anti-IgE and anti-cytokine monoclonal antibodies. Dr. Sampson is past chair of the Section on Allergy & Immunology of the American Academy of Pediatrics and the past-president of the American Academy of Allergy, Asthma & Immunology. He has served on several editorial boards, including 20 years on the *Journal of Allergy and Clinical Immunology,* and as Chair of the Medical Advisory Board for *Food Allergy & Anaphylaxis Network/Food Allergy Research and Education* for 25 years. He also has served as a Director of the American Board of Allergy and Immunology. Dr. Sampson is a member of the National Academy of Medicine. He received his M.D. from the University at Buffalo, the State University of New York.

Scott H. Sicherer, M.D., is the Elliot and Roslyn Jaffe Professor of Allergy, Immunology and Pediatrics at the Icahn School of Medicine at Mount Sinai, Chief of the Division of Pediatric Allergy and Immunology, and Medical Director of Mount Sinai's Clinical Research Unit. His research interests include the following aspects of food allergy: natural history, gastrointestinal manifestations, epidemiology, psychosocial and quality of life issues,

modalities to educate physicians and parents, and treatment modalities (including novel therapies). He is a co-author of three Practice Parameters (two on food allergy and one on diagnostic testing), and participated as a member of the Coordinating Committee for the NIAID/NIH-supported food allergy Guidelines. He is also a co-author of four American Academy of Pediatrics (AAP) Clinical Reports covering allergy prevention, diagnostics, use of epinephrine for anaphylaxis, and school issues for management of food allergy. Dr. Sicherer was the AAP representative for drafting the Centers for Disease Control and Prevention's guidelines for managing food allergies in schools. He is past chair of the Adverse Reactions to Foods Committee of the American Academy of Allergy, Asthma & Immunology, the board of directors of the American Board of Allergy and Immunology, and the Section on Allergy and Immunology of the AAP. He is associate editor of *The Journal of Allergy and Immunology, In Practice*. Dr. Sicherer received his M.D. from the Johns Hopkins University School of Medicine and his pediatric training, including a chief residency, at Mount Sinai in New York City. He completed a fellowship in allergy and immunology at Johns Hopkins.

Anna Maria Siega-Riz, Ph.D., was the Associate Dean for Academic Affairs and Professor in the Departments of Epidemiology and Nutrition at the Gillings School of Global Public Health, the University of North Carolina (UNC) at Chapel Hill at the start of this report. She is now a Professor in the Departments of Public Health Sciences and Obstetrics and Gynecology at the University of Virginia School of Medicine. She has focused her research on maternal nutritional status, including maternal obesity and gestational weight gain and their effect on the short- and long-term outcomes of the mother and child. She studies dietary patterns among Hispanic adults and children. She was a member of the 2015 Dietary Guidelines Advisory Committee and has served on multiple committees for the National Academy of Sciences, Engineering, and Medicine, examining topics from the WIC (Special Supplemental Nutrition Program for Women, Infants, and Children) food packages to standards for systematic reviews in health care. She currently serves on the advisory council of the National Heart, Lung, and Blood Institute and on the USDA working group preparing for the Dietary Guidance during pregnancy for the 2020 report. Dr. Siega-Riz earned a B.S. in Public Health in Nutrition from the UNC Gillings School of Global Public Health, an M.S. in Food, Nutrition, and Food Service Management from UNC–Greensboro, and a Ph.D. in Nutrition (Minor in Epidemiology) from the UNC Gillings School of Global Public Health.

Stephen L. Taylor, Ph.D., is Co-Founder and Co-Director of the Food Allergy Research and Resource Program, and Professor in the Department

of Food Science and Technology at the University of Nebraska–Lincoln. His research interests involve food allergies and allergy-like illnesses, including the development, evaluation, and improvement of immunochemical methods for the detection of allergens and allergenic foods; the determination of threshold doses for allergenic foods and implementation of risk assessment approaches for allergenic foods; and the effect of food processing on food allergens. Dr. Taylor has served on several committees and was a member of the National Academy of Sciences, Engineering, and Medicine's Food and Nutrition Board (1999-2004). He received his B.S. and M.S. in Food Science and Technology from Oregon State University and his Ph.D. in Biochemistry from the University of California, Davis.

Xiaobin Wang, M.D., M.P.H., Sc.D., is Zanvyl Krieger Professor in Child Health, Director of the Center on the Early Life Origins of Disease, and Professor of Pediatrics at the Johns Hopkins Bloomberg School of Public Health and School of Medicine. In the past 16 years, Dr. Wang has served as the principal investigator in a number of large scale molecular epidemiological studies funded by NIH. She has led a multi-institution, multidisciplinary team to investigate environmental, nutritional, genetic and epigenetic factors during critical developmental windows (preconception, in utero, infancy, and childhood) aiming to elucidate the root causes of high-impact pediatric and adult diseases, including adverse reproductive and pregnancy outcomes, obesity/diabetes/metabolic syndrome, and food allergies. In particular, her team has conducted a series of innovative studies on food allergies and related traits or conditions in three unique study cohorts (the Boston Birth Cohort, Chicago Family Cohort, and Chinese Twin Cohort) and contributed to an improved understanding of the role of genetics, gene–environment interactions, and epigenetics in the development of food allergies. Dr. Wang previously served as a member of the Institute of Medicine Committee on Understanding Premature Birth and Assuring Healthy Outcomes. Dr. Wang received her M.D. from Peking University (formerly, Beijing Medical University) in Beijing, China, and M.P.H. from the School of Public Health and Tropical Medicine at Tulane University in New Orleans. She also received an Sc.D. degree from the Department of Maternal and Child Health at the Johns Hopkins Bloomberg School of Public Health in Baltimore. She completed a 3-year research fellowship in Environmental Epidemiology at the Harvard School of Public Health and a residency in pediatrics at the Boston University Medical Center.