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

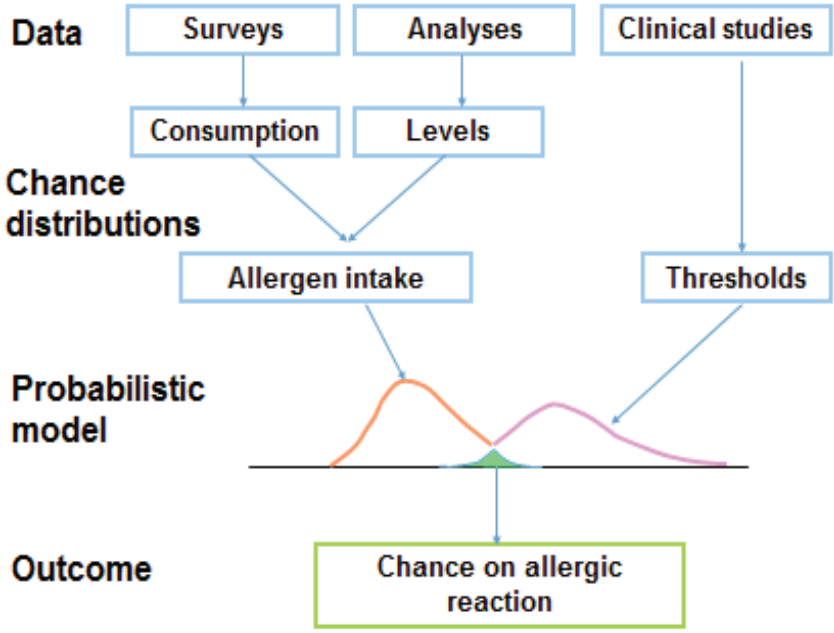

FIGURE 7-2 Figure prepresenting the concept of probabilistic risk assessment. The area in green represents those individuals who would react because their intake is above the Reference Dose.
SOURCE: Spanjersberg et al., 2007. Reprinted with permission from Elsevier.

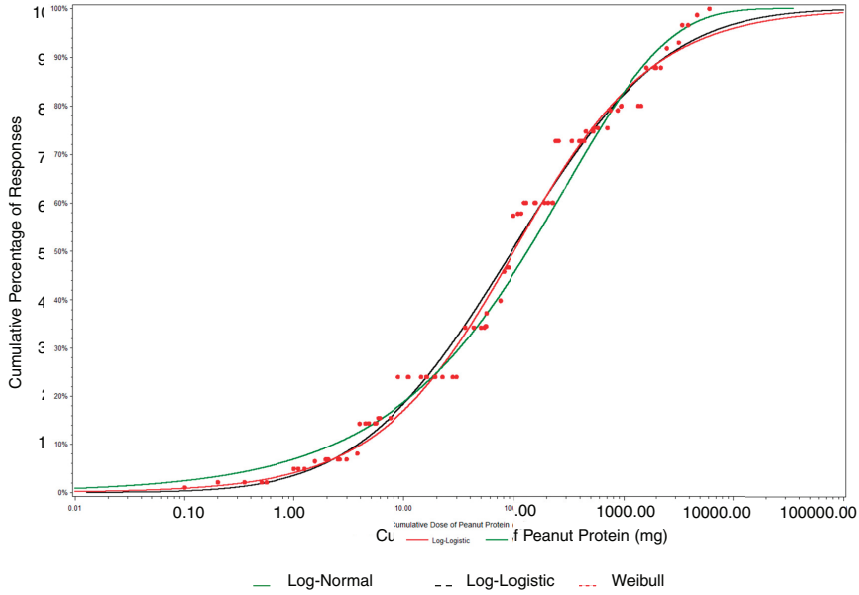

FIGURE 7-3 Dose distribution modeling of peanut protein minimum eliciting doses using log-normal, log-logistic, and Weibull probabilistic models.
SOURCE: Taylor et al., 2014. Reprinted with permission from Elsevier.

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

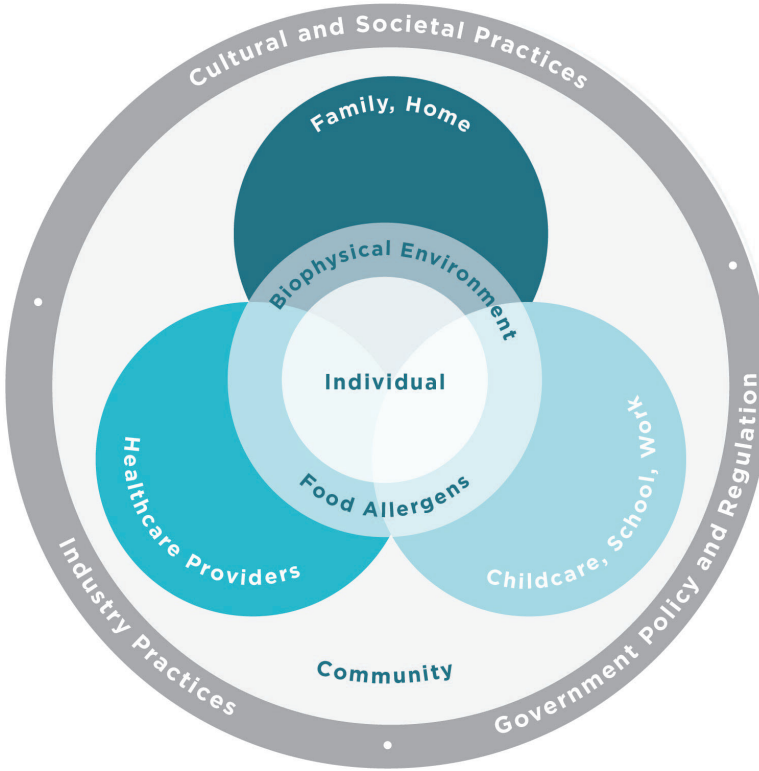

FIGURE 10-1 Ecological-developmental model for food allergies. Different systems that an individual interacts with are depicted as proximal (e.g., food, biophysical environment) and distal (e.g., industry, government).
NOTES: **Industry practices** refers to all the manufacturing processes and allergen 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

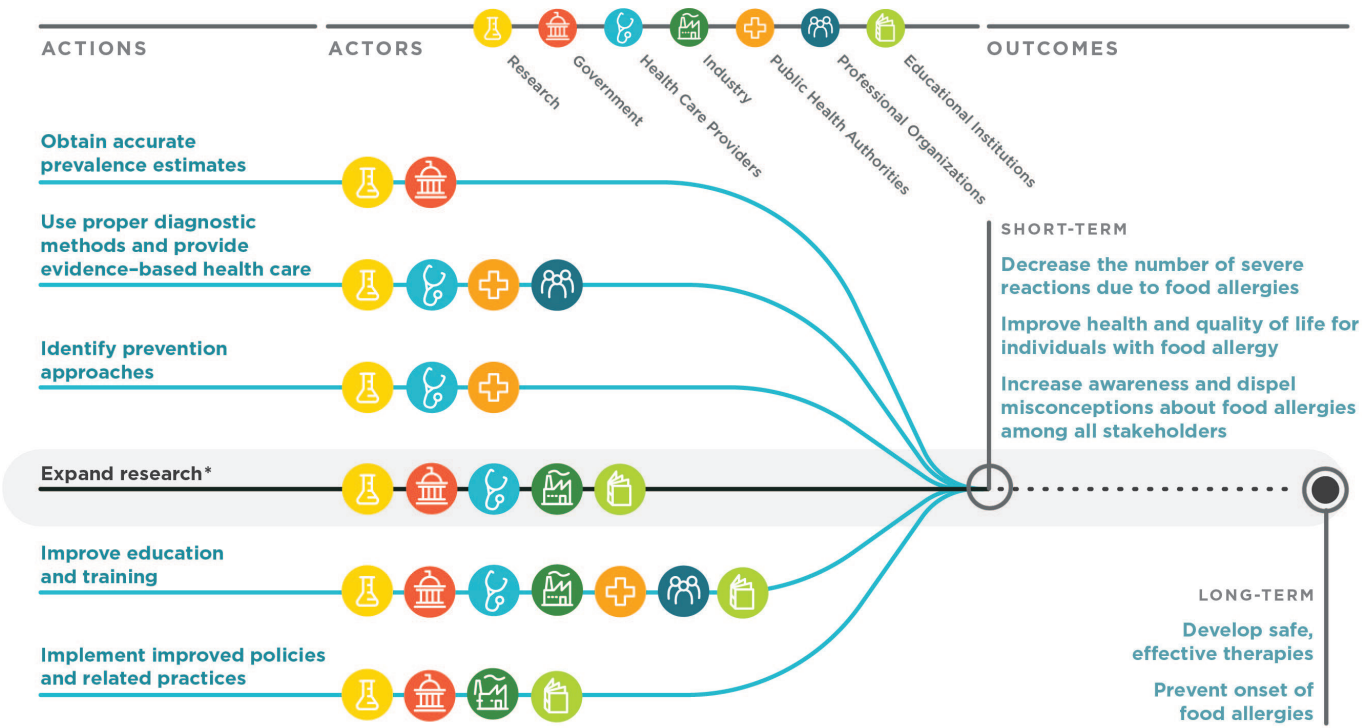

FIGURE 10-2 Roadmap to food allergy safety in six actions.
*Research is needed to achieve all other actions and to reach the short- and long-term goals (see Chapter 9 for all specific areas of research). The actors represent the primary stakeholders that will be involved in implementing the actions.

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