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How Allergen Extracts Are Made—From Source Materials to Allergen Extracts

Food allergen extracts to diagnose food-induced allergic diseases
How they are made

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ABSTRACT

Objective: To review the manufacturing procedures of food allergen extracts and applicable regulatory requirements from government agencies, potential approaches to standardization, and clinical application of these products. The effects of thermal processing on allergenicity of common food allergens are also considered.

Data Sources: A broad literature review was conducted on the natural history of food allergy, the manufacture of allergen extracts, and the allergenicity of heated food. Regulations, guidance documents, and pharmacopoeias related to food allergen extracts from the United States and Europe were also reviewed.

Study Selections: Authoritative and peer-reviewed research articles relevant to the topic were chosen for review. Selected regulations and guidance documents are current and relevant to food allergen extracts.

Results: Preparation of a food allergen extract may require careful selection and identification of source materials, grinding, defatting, extraction, clarification, sterilization, and product testing. Although extractions for all products licensed in the United States are performed using raw source materials, many foods are not consumed in their raw form. Heating foods may change their allergenicity, and doing so before extraction may change their allergenicity and the composition of the final product.

Conclusion: The manufacture of food allergen extracts requires many considerations to achieve the maximal quality of the final product. Allergen extracts for a select number of foods may be inconsistent between manufacturers or unreliable in a clinical setting, indicating a potential area for future improvement.

Introduction

Humans consume a wide variety of foods in their daily diet, and virtually any of these foods can cause an allergic reaction. Food allergy is a nonprotective immune response induced by exposure to certain foods or food additives.[1] In the United States, the most common allergenic foods are milk, eggs, fish, crustacean shellfish, tree nuts, peanuts, wheat, and soybeans (Table 1).[2–6] Worldwide, differences in food allergies exist based on factors that include, but are not limited to, geographic location, age, genetic variation, and dietary habits. For example, sesame is a common food allergy in Israel, whereas buckwheat and the edible nest of swiftlets, called bird's nest, are common allergens in Japan and Singapore, respectively.[7–9] In addition, some studies have found that the incidence of food allergy is higher in infants and toddlers when compared with adults and adolescents, indicating that the prevalence of food allergy slightly decreases with age.[2,10] Despite this general trend, allergies to certain foods, fish and shellfish in particular, become more common during adolescence and adulthood.[11] Age may also predict the allergen(s) to which an individual might become sensitized. For example, although allergy to cow's milk, egg, soy, and wheat is more prevalent in infants and children, peanut, tree nut, fish, and shellfish allergies typically persist in adolescents and adults.[2,12,13]

Although treatments are available for food-induced allergic reactions, the only way to prevent adverse reactions is to avoid the problematic food(s). The offending food(s) can be identified using skin prick tests (SPTs) with allergen extracts, specific IgE testing, or double-blind, placebo-controlled food challenges (DBPCFCs). Allergen extracts have been used since the early 20th century for the diagnosis and treatment of allergic diseases. Unlike with some allergies, subcutaneous immunotherapy using allergen extracts is not licensed for the treatment of food allergy.[2,14] We describe the selection of source materials, manufacturing procedures, relevant

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Table 1
Estimated Prevalence of Select Food Allergies

Food	Estimated Prevalence, %
Big 8	
Milk	0.2–2.5
Egg	0.5–5
Fish	0.4
Crustacean shellfish	2.0
Peanut	1.4
Tree nut	1.4
Wheat	<1
Soybean	<1
Other allergens	
Fruit	0.1–4.3
Vegetable	0.1–1.4
Any food allergy	3.5–4.0

regulations, and standardization efforts for food allergen extracts and challenges associated with developing allergen extracts for particular foods.

Methods of Collecting, Identifying, and Processing Food Source Materials

The appropriate selection of the starting source material and all subsequent manufacturing steps contribute to the final quality of an allergen extract. Once the optimal conditions are established, deviations in any of these procedures may result in increased heterogeneity of allergen extracts between manufacturers or even between production lots of a single manufacturer.

Some allergen extract manufacturers purchase source materials from source material suppliers who have already processed foods from vendors into a form ready to use in manufacturing, whereas others maintain divisions dedicated to acquiring source materials directly from food vendors and processing the materials themselves.[15–17] Food source material may be obtained in powdered, liquid, or freeze-dried forms, but processing should be minimal. Ideally, food sources should be fresh or frozen and should be of a quality suitable for human consumption.[18,19] Careful consideration of the origin of source materials may be important to preserve lot-to-lot consistency of the final product.[20] Controlled collection, storage, and processing of the raw materials also enhances consistency.[21] Changes in cultivars, climate, timing of source material collection, geography, or environmental conditions may produce inconsistent levels of specific allergens in source materials.[15,22] Manufacturers may align their production schedules with the harvest season of a particular food or may freeze or freeze-dry it for storage on receipt of the fresh food.[23]

Special attention should also be paid to identification and purity of source materials to minimize heterogeneity.[20] For food allergies, misidentification of source material may result in the production of an improperly labeled allergen extract and incorrect diagnoses for patients. Inaccurate diagnosis of food allergy, based on skin testing alone, may cause patients to avoid foods they are able to tolerate while inadvertently failing to avoid truly problematic foods. Surveys have found that certain foods, particularly fish, may be mislabeled by US wholesalers, restaurants, and grocery stores; a 2016 review of studies published since 2014 revealed a normalized mean rate of seafood fraud of 28% in the United States.[24] In a 2014 study conducted by the Center for Food Safety and Applied Nutrition at the US Food and Drug Administration (FDA), 15% of tested fish samples ($n = 174$) across 14 states were not labeled in accordance with the FDA Seafood List.[25]

Considering these findings, it is important that source materials be properly identified. Although definitive chemical or biochemical procedures are not used at this time in the United States,[15,26] most foods can be identified definitively by gross appearance. In particular, fish and other seafood may be identified with reasonable certainty by visual appearance alone if the whole organism is purchased rather than fillets or fragments. When whole organisms are unavailable, manufacturers can consult the FDA's Regulatory Fish Encyclopedia, which includes high-resolution photographs of fish fillets and isoelectric focusing electrophoresis tissue protein patterns and mitochondrial DNA sequencing information. By sequencing a 600-base pair segment of the highly polymorphic mitochondrial gene cytochrome oxidase I, an organism can be taxonomically identified, an approach called DNA barcoding.[27] In addition, databases such as the Fish Barcode of Life initiative, Catalog of Fishes, and FishBase may assist in seafood identification.

Regulatory Considerations for Source Materials

Regulation of source materials is the responsibility of FDA in the United States and the European Medicines Agency (EMA) and European Pharmacopoeia (EP) in Europe. Requirements for source materials used in the production of allergen extracts licensed in the United States are specifically addressed in 21 CFR §680. The FDA requires that licensed extract manufacturers provide a listing of the manufacturer's source material suppliers.[28] Manufacturers are responsible for ensuring that suppliers of source materials are qualified and that procedures for collection and identification of source materials are appropriate. In addition, animals used as food source materials must have been in good health,[29] and source materials must be used fresh or appropriately stored.[30]

The 1999 FDA guidance document for allergenic product manufacturers provides additional information recommended for products licensed in the United States.[18] Manufacturers should identify source materials by genus, species, common name, and microscopic and macroscopic characteristics.[18,26] For foods, the guidance specifies that canned and processed foods are not to be used as source materials. In addition, the batch production record includes the packaging label from the store where the food is purchased. If no packaging label is available, the location and identity of the supplying store are identified.

Regulation of source materials in Europe is similar: control methods, acceptance criteria for identity and purity, and controlled storage conditions are particularly important. In addition, information detailing source materials suppliers, specifications, quality control methods, storage conditions, and identification are provided. The origin of food source materials is maintained constant to provide uniformity of the licensed product.[31] The procedure for any source materials that have been pretreated (eg, flour, spices) is described. For meat, fish, and seafood, any veterinary and microbiological controls to which the animal or source material was subjected are indicated. If certain part(s) of the animal are used, the procedure for its isolation and treatment is included.[32]

Manufacturing Allergen Extracts

Although the scale and available technologies for extract preparation have changed markedly since the process was first described, many of the manufacturing steps remain unchanged.[33,34] In general, the following procedures apply to the preparation of food extracts: grinding, defatting, extraction, clarification, sterilization, and product testing (Table 2).[23,33] After careful selection and preservation of the allergen source material, foods may undergo preliminary processing, such as grinding or blending, which increases the surface area of the material before extraction. Defatting, the removal of fats, oils, and or waxes using solvents, may be performed. Manufacturers remove these substances to improve exposure of allergenic proteins and extraction efficiency and to remove components insoluble in water.[23] Foods with high water content (such as fruits and vegetables) are usually not defatted; meats, fish, and nuts are often defatted.[34]