Clinical Commentary

Considerations About Pollen Used for the Production of Allergen Extracts

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Pollen is a biological product obtained to manufacture tree, weed, and grass allergen extracts, used to diagnose and treat allergies. Genetic and environmental factors affect the composition of pollen, e.g., the plant varieties from which pollen are obtained, weather, and levels of air pollution during plant growth. Therefore, appropriate guidelines and training of personnel to perform the activities associated with pollen are essential to produce appropriate allergen extracts. Various regulatory institutions, which vary in different countries, including the Food and Drug Administration (FDA) in the USA, control how such products should be produced. For example, the FDA regulates the manufacturing of pollen extracts but not the quality of the pollen used to prepare them, relying on each manufacturer to set its own standards to do so. To the contrary, European regulatory agencies, including the European Medicines Agency, control both the quality of the pollen and the manufacturing process to produce pollen extracts. Regulatory agencies, allergen manufacturers, scientific institutions, and pollen collection entities should collaborate to develop and implement guidelines appropriate for worldwide use for both the collection and processing of pollen raw materials. This article provides an overview of the subject of pollen for use in allergen extracts. **(J Allergy Clin Immunol Pract 2015;■:■-■)**

Key words: *Pollen raw materials; Allergen extracts; Allergen extracts manufacturers; Pollen collection; Regulations*

The factors responsible for the quality and composition of allergen extracts used to diagnose and treat allergic diseases include the raw materials used to produce these extracts.[1] Raw materials are diverse in origin and have different characteristics, including the particle size containing the allergenic components present in them.

For pollen, verifying their identity and purity and avoiding cross-contamination from other biological products are essential. In addition, phylogentically and nonphylogenetically related pollen taxons often have a high level of cross-reactivity, which should receive appropriate attention to assure that the materials contain clinically relevant, nonredundant allergens, and that pollen extracts are prepared from the appropriate genera and/or species.

A major challenge is associated with the fact that both genetic and environmental factors are responsible for the allergenic composition of pollen. These variables, difficult to control, include the characteristics of particular plant species and varieties[2-7] as well as the climatic and geographical locations where individual plants grow.[8-11] Likewise, pollen collection, purification, and storage conditions[12-15] can affect the purity and allergenic composition of pollen.[3,9,10,14] Although it is possible to address and monitor some of these variables, it is not possible to control all of them, in particular, the weather and soil composition where individual plants grow and the pollen is collected.

Molecular engineering techniques, including cloning-specific genes, can be used to increase plant nutrition and resistance to pesticides.[16-18] Such techniques can also be used to produce plants with reduced allergenicity.[19] Theoretically, a similar approach could be used to obtain pollen with ideal allergenic characteristics for the production of allergen extracts. However, there are safety concerns regarding potential human exposure to such modified pollen because molecular engineering techniques involve the use of microbial genomes, which could perhaps expose humans to them and potentially impact health.[20]

Recombinant allergens to diagnose and treat allergic diseases are also practical alternatives to circumvent the caveats of using natural pollen allergens.[21-23] Although this science continues to evolve, natural products most likely will continue to be used for many years to come because of the varying limitations regarding the production and use of recombinant allergens. For example, it is currently not possible to obtain recombinant forms of all clinically relevant allergens. In addition, the safety and efficacy of

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CBER- Center for Biologics Evaluations and Research
FDA- Food and Drug Administration

such allergens need to be properly documented through appropriate clinical trials, which takes time and is extremely expensive.

The purpose of this article is to provide health care professionals and other interested individuals with insight into the topic of natural pollen utilized to prepare allergen extracts. This article also integrates some information about the regulations associated with natural pollen used to manufacture allergen extracts in both the USA and Europe and provides possible recommendations as to how to address some of the caveats associated with the use of these materials.

GENETIC AND ENVIRONMENTAL FACTORS RESPONSIBLE FOR THE ALLERGENIC COMPOSITION OF POLLEN

Genetic factors

A number of genetic varieties of botanical species exist because of agricultural practices and natural hybridization. Different plant varieties of the same species often produce pollen with distinctive allergenic characteristics. For example, a study that investigated the allergenicity of pollen derived from 6 different varieties of olive (*Olea europaea*) identified large differences in allergenicity, as determined by various chemical and immunochemical tests.[10]

The application of molecular engineering techniques since 1996 has steadily increased to obtain crops with certain desirable characteristics.[16-18] Today, more than 50% of crops in the USA are transgenic.[18] In some cases, allergen extracts are prepared from pollen derived from transgenic plants because of the difficulty of obtaining sufficient quantities of pollen derived from wild-type plants. These plants include many grass and some tree species, for example, corn (*Zea mays*) and olive (*Olea europaea*), respectively.

Because of a general fear about genetically modified crops plants, particularly in Europe, European regulatory agencies restrict the use of pollen derived from transgenic plants, and, if utilized, require that their use be appropriately justified.[24] However, scientific evidence, obtained from risk-analysis evaluations, is lacking to preclude the use of such pollen for pharmaceutical use due to potential health concerns.[25-27]

Environmental factors

Geographical location, local weather, and soil composition are responsible for plant growth and nutrition, one of the main factors that affect the qualitative and quantitative allergenic composition of pollen. For example, a study that investigated the Amb a 1 content of short ragweed (*Ambrosia artemissifolia*) pollen collected from the same location during different years indicates that the concentration of this allergen can vary by 10-fold, as assessed by quantitative immunochemical tests.[1]

Environmental contaminants can potentially affect pollen before and during collection, and include those naturally present in the environment and those generated by humans. Naturally occurring biologic contaminants are fungal spores and associated structures, bacteria, pollen grains derived from other species, plant debris, algae, and insect debris.

Human activities, such as the use of fossil fuels and fertilizers, cause the release of chemical products into the environment. The potential effects of these activities and agents on pollen are largely unknown. There is some evidence that increasing levels of carbon dioxide in the atmosphere could augment the allergenicity of ragweed and other pollen species.[28] In addition, several observations suggest that pollen collected from areas with high levels of air pollution have greater pro-inflammatory properties than pollen obtained from nonpolluted locations.[29]

POLLEN SPECIES COLLECTED FOR THE PRODUCTION OF ALLERGEN EXTRACTS

In 2004, the Food and Drug Administration (FDA) Center for Biologics Evaluations and Research (CBER), which regulates allergenic products, created a committee to review scientific data about the safety and efficacy of nonstandardized allergen extracts. Such extracts were classified into various categories according to the level of scientific information available and safety considerations to justify their use.[30]

CBER proposed to remove all products with potential safety concerns or lack of therapeutic value (Docket #FDA-2011-N-599). Although this activity is taking place slowly, the number of pollen extracts currently available on the market will likely be reduced from 708 to 451 species in the near future. Allergen cross-reactivity should be considered to help determine which pollen genera and/or species are clinically relevant.

A reduction in the number of pollen extracts available on the market should be the first step to select additional allergens for standardization. These decisions should be based on their clinical importance and feasibility of obtaining the necessary reagents for standardization. The high level of effort and cost associated with allergen standardization requires a thorough evaluation of the potential benefits of this process.

Because of the increasing regulatory requirements regarding allergenic raw materials used in Europe, Lorenz et al[31] in 2009 proposed the concept of "homologous groups" to classify allergen sources. This concept is based on similar biochemical composition and homology/cross-reactivity of allergens or allergen sources. European regulatory agencies adopted this concept,[24] and now require that allergen manufacturing companies obtain quality data for representative allergen sources classified in each homologous group, 7 of which represent pollen species.

European regulatory agencies also have proposed norms to reduce the number of allergenic preparations available on the market. These approximations are analogous in concept to that proposed by CBER in the USA, but are generally more rigorous, and the number of allergen extracts permitted are fewer than those currently available in the USA.[32]

GENERAL REGULATIONS REGARDING POLLEN IN THE USA AND EUROPE

Allergen manufacturing companies in the USA must comply with CBER regulations for pollen allergen extracts, particularly with mandated limits for relative potency or major allergen concentrations of standardized pollen allergen extracts.[33] However, regulations or guidelines for nonstandardized extracts are lacking. In addition, the organization has not proposed regulations for pollen raw materials because it is assumed that the manufacturing process will assure that the final extracts are appropriate for human use.

In Europe, regulatory agencies control the quality of both the pollen used to manufacture allergen extracts and the derived extracts. Therefore, European allergen manufacturing companies