Assessment of Allergenic Potential of Genetically Modified Foods: An Agenda for Future Research

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Speakers and participants in the workshop "Assessment of the Allergenic Potential of Genetically Modified Foods" met in breakout groups to discuss a number of issues including needs for future research. These groups agreeed that research should progress quickly in the area of hazard identification and that a need exists for more basic research to understand the mechanisms underlying food allergy. A list of research needs was developed. *Key words:* **biotechnology, food allergy, genetically modified food, hazard identification, research needs.** *Environ Health Perspect* **111:1140–1141 (2003). doi:10.1289/ehp.5815 available via** *http://dx.doi.org/* **[Online 19 December 2002]**

Potential benefits that may be derived from biotechnologies involving genetically modified organisms could be enormous. Potential risks of allergenicity possibly associated with their use will likely be manageable, provided appropriate information is available to decision makers. At the end of the workshop "Assessment of the Allergenic Potential of Genetically Modified Foods," speakers and participants met in small groups to discuss information needs. Five groups considered the following key issues: *a*) use of human clinical data, *b*) animal models to assess food allergy, *c*) biomarkers of exposure and effect, *d*) sensitive populations, *e*) dose–response assessment, and *f*) postmarket surveillance. The groups were asked to consider two general questions: On the basis of current information, what can we do to assess the potential allergenicity of genetically modified food, and what do we need to know to improve this process, i.e., what are the most critical research needs? The first question is the topic discussed in another article in this mini-monograph (Germolec et al. 2003). The research needs are the topic of this article. Just as research provided the tools to generate genetically modified food, it can also provide the tools needed for effective safety evaluation and risk assessment/management.

Regulatory problems are rarely stated in scientific terms. The problem in this case is we wish to avoid inadvertently introducing an allergenic protein into the food supply. One task for this workshop was to translate this problem into research needs. Because there is a sense of urgency to develop tools for hazard identification, much of the conversation revolved around the short-term research required to develop test methods for this purpose. This discussion focused largely on the potential allergens and how to distinguish these from other proteins. However, it was recognized also that more long-term (basic) research is needed on the characteristics of food allergens, allergic disease, and the mechanisms underlying susceptibility to food allergy. This discussion considered more broadly the factors leading to allergic sensitization, including the nature of the allergen, and how genetics, life stage, and other environmental influences might affect susceptibility.

Hazard Identification: Immediate Needs

Research needed to improve hazard identification fell into three categories: development of animal models, identification and characterization of food allergens, and establishment of well-defined clinical serum banks. All were deemed important to improve the Food and Agriculture Organization of the United Nations/World Health Organization (FAO/WHO) decision tree (FAO/WHO 2001) or to replace it with a better approach. Also discussed was the need to improve human skin test technology for incorporation in a decision tree. Animal models are needed that could be used not only for hazard identification purposes but also to determine relative potency, to derive sensitization and elicitation thresholds, and to define the conditions under which tolerance (failure to develop an allergic response to potential food allergens) is induced. Identification, characterization, purification, and banking of food allergens (and nonallergens) are needed for two reasons: to provide positive (and negative) controls for animal and serum bank tests and for use in defining the characteristics that confer on food proteins the ability to induce allergic sensitization, that is, to establish structure–activity relationships. Serum from clinically well-defined allergic individuals needs to be banked for use in screening proteins of unknown allergenicity. Development of proteomic approaches to screen potential allergens (specific IgE on a chip) was also suggested as a research need. Characterization of allergens and development of serum banks require a systematic process for recording adverse events and obtaining informed consent for use of serum obtained in epidemiologic and experimental studies. Once developed, all tests for hazard identification will require standardization and validation—no small task. These research needs are summarized in Table 1.

Basic Mechanistic Research

Appropriate animal models (not necessarily the same as those used for hazard identification) and human clinical and epidemiologic studies are needed to assess the correlation between antigen-specific IgE and clinical disease and to investigate the influence of the route, duration, and nature of exposure on the development of sensitization. An important research need is to investigate the mechanisms underlying food allergy, including the development of and failure to develop oral tolerance, and identification of possible windows of vulnerability during immune development (including *in utero* and during lactation) or unique exposure conditions that might place children at greater risk. The mechanisms underlying the development of tolerance to ingested antigens, whether by passive (anergy) or active (suppressor cells) processes, are poorly understood and may be crucial to understanding what makes a protein allergenic and what makes an individual susceptible. The contributions of *in utero* exposure, gut immaturity, and exposure via breast milk to children's risk of sensitization

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Table 1. Summary of research needs.

Hazard identification
Development, evaluation, and validation of animal models
Establishment of clinically well-defined banks of human serum containing antibodies to allergens
Improved human skin test technology
Identification, purification, and banking of both known protein allergens and proteins believed not to be allergenic
A systemic approach to recording adverse events (case studies)
Definition of relative potency and thresholds for sensitization and the elicitation of allergic reactions
Development, refinement, standardization, and validation of test protocols
Basic mechanistic
Development of animal models of allergic disease
Studies of the qualitative and quantitative relationships between antigen-specific IgE and overt disease
Investigation of the influence of route, duration, timing, and nature of exposure on the development of sensitization
Studies of the factors that contribute to susceptibility to food allergy
Investigation of the mechanisms underlying food allergy
Investigation of potential windows of vulnerability during development
Identification of unique situations that cause children or other individuals to be at greater risk
Epidemiology to establish the incidence of food allergy and whether it is changing
Studies of the potential role of non–IgE-mediated reactions in food allergy

also need to be determined. Studies (possibly using transgenic mice) are needed to assess the heritable factors that contribute to susceptibility to food allergy. Epidemiology is needed to determine whether the incidence of food allergy in the industrialized world, like the incidence of other types of allergic disease, is increasing.

The natural history of non–IgE-mediated food allergies (although somewhat beyond the scope of this current workshop) was also considered an important long-term research need. Questions were raised as to whether certain foods were associated with this type of allergy and whether IgE is a reasonable surrogate marker in this instance or if other biomarkers would be more appropriate. The context in which food is presented, including the matrix, concomitant infections, and other sources of gut inflammation, also deserves further attention with respect to both IgE- and non–IgE-mediated food allergies. Basic mechanistic research needs are summarized in Table 1.

Recommendations

In summary, there was consensus that research should progress quickly in the area of hazard identification to improve or replace the FAO/WHO decision tree. Support was particularly strong for the development, standardization, and validation of appropriate animal model(s) for this purpose. It was also generally agreed that there is much we do not know about the development of food allergies, and that more basic research in this area would help us to control the risks more effectively and efficiently. More work is needed than any one funding organization is likely to be able to support. Therefore, it is recommended that there be significant coordination between these organizations and an integrated approach to tackling this problem. Open and free exchange of information as it becomes available is needed to facilitate these research endeavors.

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