SAP Report No. 2000-01A, June 29, 2000

REPORT:
FIFRA Scientific Advisory Panel Meeting,
February 29, 2000, held at the Sheraton Crystal City Hotel, Arlington, Virginia

Session I - A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding:

Food Allergenicity of Cry9C Endotoxin and Other Non-digestible Proteins

Mr. Paul Lewis	Ronald J. Kendall, Ph.D.,
Designated Federal Official	Chair
FIFRA Scientific Advisory Panel	FIFRA Scientific Advisory Panel
Date:________________________	Date:________________________

Federal Insecticide, Fungicide, and Rodenticide Act
Scientific Advisory Panel Meeting
February 29, 2000

SESSION I - Food Allergenicity of Cry9C Endotoxin and Other Non-digestible Proteins

PARTICIPANTS

Chair
Ronald J. Kendall, Ph.D., Director and Professor, The Institute of Environmental and Human Health, Texas Tech University/Texas Tech Health Sciences Center, Lubbock, TX

FIFRA Scientific Advisory Panel
Christopher Portier, Ph.D., National Institute of Environmental Health Sciences, Research Triangle Park, NC
Fumio Matsumura, Ph.D., Institute of Toxicology and Environmental Health
University of California, Davis, CA
Mary Anna Thrall, D.V.M., Professor, Department of Pathology, College of Veterinary Medicine & Biomedical Sciences, Colorado State University, Fort Collins, CO

FQPA Science Review Board Members
Martin Chapman, Ph.D., University of Virginia, Charlottesville, VA
Steven Gendel, Ph.D. National Center for Food Safety and Technology, Summit-Argo, IL
Rick Helm, Ph.D. Arkansas Childrens Hospital, Little Rock, AR
T. P. King, Ph.D. Rockefeller University, New York, NY 10023
Hugh A. Sampson, M.D.; Mount Sinai School of Medicine, New York, NY
Stephan Strobel, M.D., University College of London, Department of Immunobiology, London, United Kingdom

Designated Federal Official
Mr. Paul Lewis, FIFRA Scientific Advisory Panel, Office of Science Coordination and Policy, Office of Prevention, Pesticides and Toxic Substances, Environmental Protection Agency, Washington, DC

PUBLIC COMMENTERS

Oral statements were made by:
James D. Atwood, Ph.D., on behalf of Monsanto Company
Luca Bucchini, Ph.D., on behalf of the Environmental Defense
Andrew Cockburn, Ph.D., on behalf of Aventis Crop Science
Alan Hawkins, Ph.D., on behalf of Garst Seed Company
Mr. Chuck Ludlam, on behalf of the Biotechnology Industry Organization
Ms. Jackie Martins, on behalf of the National Corn Growers Association
A.H. Penninks, Ph.D., on behalf of TNO Nutrition and Food Research Institute
Leah Porter, Ph.D., on behalf of the American Crop Protection Association
Jane Rissler, Ph.D., on behalf of the Union of Concerned Scientists

Written statements were received from:
James D. Astwood, Ph.D., on behalf of Monsanto Company
Ms. Camilla Beech on behalf of Zeneca Plant Science
Luca Bucchini, Ph.D. on behalf of Environmental Defense
Anthony Cavalieri, Ph.D. on behalf of Pioneer HiBred International, Inc.
Andrew Cockburn, Ph.D. on behalf of Aventis Crop Science
Sue Hefle, Ph.D. and Steve Taylor, Ph.D. on behalf of the University of Nebraska
Mr. Chuck Ludlam, on behalf of the Biotechnology Industry Organization
A.H. Penninks, Ph.D. on behalf of TNO Nutrition and Food Research Institute
Leah Porter, Ph.D. on behalf of the American Crop Protection Association

INTRODUCTION

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), Scientific Advisory Panel (SAP) has completed its review of the set of scientific issues being considered by the Agency issues pertaining to food allergenicity of Cry9C endotoxin and other non-digestible proteins. Advance notice of the meeting was published in the *Federal Register* on February 4, 2000. The review was conducted in an open Panel meeting held in Arlington, Virginia, on February 29, 2000. The meeting was chaired by Ronald J. Kendall, Ph.D. Mr. Paul Lewis served as the Designated Federal Official.

John Kough, Ph.D (EPA, Office of Pesticide Programs) highlighted issues concerning the Cry9C insecticidal protein derived from *Bacillus thuringiensis* and expressed in field corn. This included presentations on the use of amino acid homology, the brown Norway rat model for food allergenicity and other subjects with regards to the assessment for potential allergenicity.

CHARGE

1. a. Does the Panel agree with EPA that the Brown Norway rat study an as animal model of food allergy is not recognized as valid and useful by the scientific community? Are there any other animal models of food allergy that might be useful?

b. Does the Panel know of cases where the model has been validated for recognizing known food allergens while not recognizing other dietary proteins? Is the use of an adjuvant such as carrageenan appropriate to examine a normally functioning immune system?

2. Does the bioavailability study provide useful information about allergic potential? Can a protein be a food allergen without being able to cross the GI mucosa? Is gut permeability too variable with the population to be used as a screening tool?

3. In the case of the Cry9C protein, does the apparent degradation of the 68kDa protein to a 55-kDa protein suggest anything regarding the digestibility/allergenicity of this protein?

4. Does the additional data provided by AgrEvo either reduce or alleviate concern of Cry9C as a potential allergen or further implicate Cry9C as a potential allergen?

5. Are the characteristics of heat stability and resistance to enzyme digestive enzymes useful criteria to screen for food allergenicity? Are there known examples of dietary proteins that have these characteristics yet are not allergenic?

6. Does the lack of amino acid homology offer predictive function to examine the allergenicity of a new dietary protein, alternatively, does it simply indicate which allergenic population should be examined to look for possible reactivity?

7. There is anecdotal evidence that total dietary exposure to a food correlates to food allergy (i.e., prevalence of rice allergy in eastern Asia, fish allergy in Scandinavia, wheat allergy in Europe and the Americas). Does level of exposure in the diet affect the sensitization phase of food allergy? Would exposure to a protein as a minor component of direct dietary consumption lessen the likelihood a protein would either be or become a food allergen? Is there evidence that feed exposure (i.e., soybean meal as an animal feed) can affect the allergenicity of the resulting meat, milk or eggs? For example, does the use of soybean meal as animal feed make the resulting meat, milk or eggs an allergenic risk for a soybean sensitive individual?

8. Is it feasible to monitor changes in the incidence of human food allergy to stable proteins? How quickly are newly introduced food allergens typically identified after they first become part of the human diet?

DETAILED RESPONSE TO THE CHARGE

The specific issues to be addressed by the Panel are keyed to the Agency's background document "Cry9C Food Allergenicity Assessment", dated January 18, 2000, and are presented as follows:

1. a. Does the Panel agree with the Agency that the Brown Norway rat study, as an animal model of food allergy, is not recognized as valid and useful by the scientific community? Are there any other animal models of food allergy that might be useful?

b. Does the Panel know of cases where the model has been validated for recognizing known food allergens while not recognizing other dietary proteins? Is the use of an adjuvant such as carrageenan appropriate to examine a normally functioning immune system?

A consensus was reached that the Brown Norway rat model could be useful but could not be regarded to be a valid animal food allergy model by the scientific community. Validation of this, or any animal model, takes on several different levels of response depending upon the intended use and questions addressed in the model. At the highest level, the model should be: 1) sensitive (can accurately identify proteins as allergens when they exist); 2) specific (can accurately exclude proteins as nonallergens) and; 3) address the mechanism(s) for IgE-mediated disease. An animal model that addresses these issues will be useful as a screening instrument for identifying potential proteins as allergens for humans. It will be difficult to accurately address an animal food allergy model without evidence of clinical responses. It is unlikely an animal model will provide the equivalent of human clinical responses.

As noted by the Panel, food allergy is a complex disease. Considerations that must be addressed include the host, the allergen, and environmental/adjuvant effects. A comparison between animal and human responses is useful but it does not necessarily indicate that a particular protein will be a food allergen in humans. There is an apparent inherent capacity of allergens and a genetic predisposition in both animals and humans for sensitization to allergenic food proteins. In addition, immune response genes in the human population and in the test animals are different.

Based on the available literature, animal food allergy models need to be further investigated with respect to non-food allergen sensitization and IgE responses. A known food allergen should be used as a standard by which potential allergenic proteins could be compared. Duration of exposure, time of introduction into the diet, dietary mixture concerns versus single protein (food complexity) and additional non-allergen proteins need to be validated. Current allergenicity models will address an IgE-mediated reaction; however, they do not address sensitization patterns nor do they necessarily correlate with clinical reactivity. There is strain specificity with respect to high and low IgE responders to proteins and known food allergens as

well as differences in sensitization with respect to age and maturity of the food allergen. The usefulness of the current animal models is that the mouse, rat and human IgE recognize similar IgE-binding epitopes. In the human, a single antibody, IgE, has been clearly identified as the antibody responsible for allergic responses. However, in animal models, non-IgE antibodies also have been shown to be responsible for antigen-induced anaphylaxis. In the rat model, IgG2a and IgE, and in the guinea pig and mouse models, IgG1 and IgE can also be responsible for antigen-induced anaphylaxis. Therefore, care must be taken to differentiate which immunoglobulin class(es) is responsible for the immunopathologic/mechanistic studies of IgE-mediated allergic reaction if comparisons are to be made between these animal models and the human.

It is possible that a protein is an allergen, not because of its unique sequence, structure or epitope but because of other factors in the allergen source. As an example, allergenicity of an egg protein may be due to some component(s) in the egg or other food ingredients that function as adjuvants to promote the egg protein-specific IgE response. The age of an individual exposed to a food allergen plays an important role to the individual's subsequent immune response. The response varies for different foods and is likely to affect different age groups [i.e. neonates, infants...adults] in different ways. It also appears that exposure at the time of weaning may be significant. Cholera toxin and other adjuvants, e.g., carageenan, have been used successfully because they create a Th2 environment (Th2 T lymphocytes secrete cytokines [IL-4, IL-5, IL-13] that promote the development of an allergic response; i.e., favor cells that will produce IgE antibodies to a given protein) that is believed necessary for good IgE responses to proteins.

2. Does the bioavailability study provide useful information about allergic potential? Can a protein be a food allergen without being able to cross the GI mucosa? Is gut permeability too variable with the population to be used as a screening tool?

Bioavailability measurements are not particularly useful for Cry9C allergic potential since the precise mechanism by which any protein (allergen) induces an IgE response is poorly understood. Thus, there is no known detection system that will differentiate between non-food and food allergens in animal models or humans.

When considering characteristics of food allergen proteins, the best available criteria presently known are: 1) heat stability and 2) resistance to digestion. However, as reported by public commenter Dr. Cockburn on behalf of Aventis Crop Sciences, there are certainly exceptions to both these criteria. Unfortunately, sufficient information is lacking to predict what characteristics contribute to a protein being an allergen. Other factors that need to be considered include the level of accumulation in the product and host, consumption patterns by the public, and duration and age of exposure. There also is the characteristic of IgE-binding epitopes, conformational versus linear. In peanuts, we know they are predominantly linear with minimal conformational epitopes. In egg (i.e. ovomucoid), the linear epitopes are consistent with a persistent allergic response, whereas, with conformational epitopes, the allergy may be outgrown.

Similarly, with casein, persistence with disease is associated with linear IgE-binding epitopes.

GI permeability of proteins may not be a useful means for allergenicity screening. Because of the intricate network of interactions between the gastrointestinal epithelium and the immune cells of the GI tract, the development of an immune response to food proteins is extremely difficult to predict. Co-administration of other foods and local environmental factors (e.g., normal or pathogenic bacterial flora) may provide adjuvant effects that contribute to immunogenicity/allergenicity of individual food proteins, limiting GI permeability for allergenicity screening.

All foods and food proteins are subject to different digestive processes and to different degrees of digestion. Intestinal permeability, although a likely route of allergic sensitization, is but one mechanism by which proteins can gain access to the immune system. Food proteins, both with and without allergenic activity potential, are subject to intralumenal (i.e., gastric and intestinal digestion) that precedes intracellular (i.e., antigen-processing) digestion by antigen processing cells in the GI tract. Intact food particles (e.g., peanuts) and soluble proteins are handled differently. In addition, antigen presenting cells (macrophages and dendritic cells), T and B cells, and other cells of the immune system are all located at or near the surface of mucosal surfaces and are important factors to be considered in immune recognition of potential allergenic proteins. Although intestinal permeability can be used as a guideline for protein access to the immune cells of the intestine, it is certainly not indicative of potential allergenicity.

In the study of inhalant allergens, many more proteins have been identified and characterized compared to food allergens. Known biochemical properties include hydrolytic enzymes, enzyme inhibitors, transport proteins, and regulatory proteins. In the hundreds of allergens characterized, there does not appear to be a biochemical property or amino acid sequence motif in these proteins that will prove helpful in determining the potential allergenicity of a novel protein. As a result, there is no common function (e.g., enzymatic), structure or amino acid sequence motif that has been identified that will be useful in the prediction of a protein demonstrating potential allergenicity, either as an inhalant or a food.

3. In the case of the Cry9C protein, does the apparent degradation of the 68kDa protein to a 55kDa protein suggest anything regarding the digestibility/allergenicity of this protein?

Food proteins (allergens) are generally subject to intralumenal and intracellular digestion. However, this is true for proteins with and without known allergenic potential. There is no evidence that active degradation contributes to the allergenicity of proteins. Proteins (e.g., in milk and in a hen's egg), are digested in different ways resulting in differently sized breakdown products (e.g., peptides) without allowing prediction of the allergenic potential of the allergen. A major allergen of egg (ovomucoid) for example is less susceptible to enzymatic hydrolysis than major allergens of cow's milk (beta lactoglobulin, casein, and bovine serum albumin), although

both foods have clearly grossly comparable allergenic potential. In the Cry9C case, the reduction of the 68kDa protein to a 55kDa fragment, as with other proteins, may be caused by degradation of the resident intestinal flora. Absorption of proteins from the lower intestine is well described and the 55kDa fragment could theoretically affect the immune system in a sensitizing (or tolerizing) way.

4. Does the additional data provided by AgrEvo either reduce or alleviate concern of Cry9C as a potential allergen or further implicate Cry9C as a potential allergen?

The Panel agreed that based on the available data, there is no evidence to indicate that Cry9C is or is not a potential food allergen. In the event novel proteins cannot be measured for their allergenic potential, the question remains how should the allergenicity of these novel proteins in the exposed population be assessed. The Panel concluded that there is a need for continued exposure monitoring. Thus, a cooperative effort should develop between the registrant, Federal agencies such as EPA and the medical community (especially trained allergists), to identify significant allergic problems arising in the exposed population. This should include the sharing of information and resources among all interested parties on the allergenic potential of food allergens.

In the case of Cry9C not being a potential food allergen, animal exposure to Cry9C seed corn only suggests that the ingestant route may not be a problem. In animal feed studies, there does not appear to any reported adverse reactions to Cry9C seed corn. However, the Panel acknowledges that corn pollen allergy or corn food allergy is not considered a significant allergy problem in the allergic population. Thus, it is difficult to predict if the introduction of Cry9C into the diet will be a potential allergenic source. The failure to identify amino acid sequence homology of Cry9C with other known allergens could provide evidence for the lack of an allergenic potential of Cry9C. However, neither the structure nor the amino acid sequences are reliable in determining the potential allergenicity of a protein as there is no common structure or amino acid motif that has been established as a criteria for allergenicity.

The question that must be addressed is what additional data should be collected to assess if Cry9C or any other protein plant-pesticides is a potential food allergen. The level of the allergen in the environment would be useful for its potential as an inhalant or ingestant allergen. Exposure levels are important; both dust/pollen and antigen/allergen levels should be considered. For example, it is known that nanogram levels of house dust mites are capable of causing dust mite allergy symptoms. With peanut allergies, ingestion of nanogram quantities can cause anaphylaxis. However, the caveat here is that sensitization levels are not as well characterized in either inhalant or food allergies. Animal sera in both exposed humans and animals exposed to Cry9C would be helpful. For example, there has been an exposure to Bt in both humans and animals for 5 – 50 years; however, estimates of the level of exposure and data/evidence of antigenicity/allergenicity are not readily available. Serum from animal (toxicological and

carcinogenicity studies) and/or human (food source exposed populations; e.g., in the case of Cry9C, corn pollen and food-sensitive individuals) sources for detecting antigens/allergens to known proteins would certainly be helpful in determining immunogenicity of the protein by *in vitro* analysis (e.g. RAST or ELISA testing). The exposure and/or monitoring of Cry9C as an inhalant or potential food allergen source in the population has not taken into consideration the exposed population demographics, the exposure concentrations or the exposure time in hours, days, or subsequent seasonal exposures. In essence, well designed scientific studies are not available to critically assess Cry9C as a potential food allergen.

The Panel provided considerable discussion on the public comment data presented by Alan Hawkins, on behalf of Garst Seed Company. Garst Seed Company monitored the incidence of allergic responses by workers handling corn hybrids expressing the Cry9C endotoxin. The data indicated that field workers exposed to the pollen of Cry9C treated corn did not incur any significant allergenic responses. The surveillance and results presented appear to be casual observations without evidence of disparate responses by the workers. The Panel questioned the reliability of the analysis. Specifically, if 20 – 30% of the population believes they have a food allergy, the Panel was uncertain how 2000 workers would have reported no incidence of any allergy related health symptom(s). Thus, these data have limited structural or scientific basis for determining allergic potential.

If a worker monitoring program, such at that described by Garst Seed Company, is to be pursued, a more scientifically based experimental monitoring design is needed. Levels of exposure (concentration of Cry9C in the air), duration of exposure (time in hours/days exposed and succeeding seasonal exposures), clinical histories and the worker questionnaire should be made available. Furthermore, the Garst Seed Company data represents a population of individuals exposed solely by the inhalant route to corn pollen without evidence of potential corn pollen or other allergies in the reported population (age, ethnic background etc were not considered). Thus, although the data presented by Garst Seed Company provides the beginning of experimental design for an epidemiological assessment of Cry9C as an inhalant allergy, it does not assess the ingestion route, an important aspect of studying the epidemiology of Cry9C as a food allergen.

5. Are the characteristics of heat stability and resistance to enzyme digestive enzymes useful criteria to screen for food allergenicity? Are there known examples of dietary proteins that have these characteristics yet are not allergenic?

The heat stability and digestibility of a particular protein do not correlate exactly with allergenicity of that protein. Major allergenic proteins are typically more stable to heat and enzymatic digestion than less allergenic proteins, but there is not a one-to-one correlation. Consequently, these properties can be used as screening tools, but they do not absolutely predict that a protein will or will not be an allergen.

This is similar to the practice of using skin tests or RASTs in the diagnosis of IgE-mediated food allergy. A positive skin test or RAST indicates that a patient may experience an allergic reaction to a given food [40% - 50% chance], and a negative test does not absolutely rule-out that a patient will react to a given food [~2% - 3% chance]. However, virtually all patients that do react will have a positive skin test or RAST. Similarly, virtually all major food allergens that cause systemic reactions will be more stable to heat and enzyme digestion.

6. Does the lack of amino acid homology offer predictive function to examine the allergenicity of a new dietary protein, or alternatively, does it simply indicate which allergenic population should be examined to look for possible reactivity?

The lack of homology is useful in excluding potential allergens if no sequences can be identified from known foods or other allergens. However, we do not have sequences from all allergens. The data are primarily useful for linear sequence homology but not for conformational homology of IgE binding epitopes. There are still many unknown epitopes in food allergens. It will be beneficial and useful in identifying a sensitive population for studies on allergenicity of the potential allergen.

Sequence homology with known allergens could be taken as an indicator of potential allergenicity of an unknown protein. An 8 amino acid sequence homology may be too simplistic, it ignores conformational epitopes. Amino acid substitutions are not indicative of decreased binding. Shorter and longer sequence matches may allow more flexibility. In both cases, either increasing or decreasing IgE antibody binding could result. It is also necessary to be fully aware of the programs used and the scoring matrices used to determine homology.

7. There is anecdotal evidence that total dietary exposure to a food correlates to food allergy (i.e., prevalence of rice allergy in eastern Asia, fish allergy in Scandinavia, wheat allergy in Europe and the Americas). Does level of exposure in the diet affect the sensitization phase of food allergy? Would exposure to a protein as a minor component of direct dietary consumption lessen the likelihood a protein would either be or become a food allergen? Is there evidence that feed exposure (i.e., soybean meal as an animal feed) can affect the allergenicity of the resulting meat, milk or eggs? For example, does the use of soybean meal as animal feed make the resulting meat, milk or eggs an allergenic risk for a soybean sensitive individual?

Without considering other non-food exposure related confounders in the initiation of food allergic diseases, it is clear that the pattern of exposure to foods during an as yet ill defined period affects the pattern of allergic diseases in the population (i.e., milk, egg, gluten, soy and others). The effects are modified by host and dietary parameters. Age and clinical condition of the host on one hand and dose, frequency, and nature of the protein/allergen clearly are important parameters.

This question has not been systematically studied and human studies are lacking. The effects of different dose feedings are not easily predictable. For tolerance to a particular protein to be induced, the protein needs to be encountered and usually gains access to the immune system via mucosal surfaces. This process, in experimental rodent models, is dose, frequency, age, and protein related. Responding to this question, smaller doses are more likely to sensitize the immune system than to induce tolerance. The definition of "small" and "large" is somewhat arbitrary. For ovalbumin, a small dose is considered 0.001 – 0.01 mg/g body weight and a large dose usually >0.5 (1.0) mg/g body weight given as a single or multiple doses.

Hormone and antibiotic administration to animals has affected food products derived from those animals. Proteins administered to lactating cows are likely to be secreted in their respective milks. If there is any relation to human and/or rodent physiology, the amounts that are secreted into the milk will be small and somewhere in the order of ug/L or less. These amounts taken by allergenic individuals (after pasteurization) may be insufficient to trigger an allergic reaction.

8. Is it feasible to monitor changes in the incidence of human food allergy to stable proteins? How quickly are newly introduced food allergens typically identified after they first become part of the human diet?

Allergenicity, by definition, has been used to identify proteins, peptides, and epitopes that bind to IgE, not that induce IgE production in the susceptible host. What specifically makes a protein allergenic or what contributes to making a protein allergenic is unknown. Several factors have been examined and they include: 1) function (many enzymes have been identified as allergens); 2) glycosylation (certain carbohydrate moieties have been shown to bind to IgE or assist proteins in their ability to bind to surface epithelial receptors permitting access across the intestinal barrier); 3) stability to heat denaturation (however, heat denaturation has been shown both to contribute to and reduce the ability of some proteins to bind IgE) and; 4) susceptibility to enzymatic digestion (variables include the allergen in question and mixtures with other foods to digestibility, differences between gastric and intestinal enzyme simulated stability). A contributing factor is that the longer an intact protein molecule persists in the intestinal tract, the more likely it will gain access to the immune system.

As with all potential allergens, the ultimate criterium will be if the protein or allergen source will become a significant allergen in the genetically susceptible population. As more and more molecules are being identified as allergens that have the ability to bind IgE, the need for a well defined monitoring program of newly introduced products into the marketplace will become necessary to the identification of protein allergenicity.

Even though the Panel agreed that a monitoring program to identify significant allergic problems arising in the exposed population should be pursued, monitoring changes in the incidence of human food allergy to protein molecules will be difficult. The predictive approaches

to determining the allergenic potential of novel foods or proteins should be subject to a case-by-case basis. There is a conceived perception by the public and expressed in the medical literature that there is an increase in allergenicity to foods and food products; however, the scientific evidence is still lacking. Many food intolerances and gastrointestinal symptoms mimic food allergic responses that have no IgE-mediated symptoms. For example, there are a number of food-related gastrointestinal hypersensitivity disorders with an immunologic basis but without evidence of IgE-mediated sensitivity. These include food protein-induced enterocolitis, celiac disease, food-induced proctocolitis, food-induced enteropathy and allergic eosinophilic gastroenteritis in a subset of patients. Only through a detailed clinical history and/or verification by double-blind placebo-controlled food challenges and evidence of IgE to the incriminating product is a diagnosis of food allergy currently sufficient to make the connection between a food protein and allergenicity. Co-administration of other products that may serve as adjuvants, diet changes, normal versus pathogenic flora and other environmental stimuli (smoking, diesel exhaust) all may contribute to the immunogenic, allergenic or toleragenic responses in susceptible individuals.

Monitoring serum levels could also be considered as a method to measure the allergenicity of Cry9C protein. From the toxicology studies performed on both rats and mice, there is a source of serum that could provide evidence for immunogenicity of the Cry9C protein. However, there is a caveat - immunogenicity does not correlate with allergenicity. It is difficult to accurately evaluate the intrinsic potential of proteins to provoke an IgE antibody response to cause allergic sensitization. There is no known amino acid sequence or motif that contributes to a protein being identified as a potential allergen. Co-administration of other products and/or environmental stimuli that may act as adjuvants is likely to contribute to immunogenic, allergenic or toleragenic responses in susceptible hosts.