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Hazards of unintentional/intentional introduction of allergens into foods

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Patients with food hypersensitivity always risk developing allergic symptoms after unintentional intake of a nontolerated food, especially when abroad where product labeling is lacking. Even in their normal daily life, allergic patients run the risk of eating nontolerated foods, especially due to insufficient labeling of compound foods, such as precooked meals.

The above examples are inherent features of the lifestyle of an industrialized society and call for better labeling of existing products and restaurant food. Such an effort requires major changes in the thinking and attitudes of several agents in "the food chain" of modern society and is likely to take some time. When new products or processes are deliberately introduced in foods, allergenic substances may intentionally or unintentionally be included (Table 1). In the case of new foods, the patient does not expect the presence of a nontolerated food, and therefore runs an increased risk. For society, there is an opportunity – from the very beginning – to take into account the risks run by food-hypersensitive patients.

Introduction of new allergens into foods

Introduction of allergenic substances can be done deliberately by changing the recipes of compound foods or by genetic manipulation, or unintentionally by quality-control failures (as in contamination somewhere in the production process or in genetic manipulation).

An example of intentional introduction of new allergens into food by change in a recipe was the substitution of green pea for potato as a starch source in a sausage recipe in Norway in 1992. Since the starch source was protein-contaminated, patients allergic to green pea suffered unexpected allergic reactions to the previously tolerated food. An example of contamination comes from our own clinic, where a patient sensitive to hen's egg developed a severe systemic reaction after eating "guaranteed egg-free" meatloaf, subsequent analyses demonstrating high egg content in the food. This contamination was caused by lack of control of the cleaning procedure of the equipment used by the manufacturer.

Manipulation of the genetic code, especially in plants, is gaining increasing interest due to the possibility of increasing the quality and quantity of products (Table 2).

Until now, only a few attempts to reduce or change protein content in order to reduce allergenicity have been made: the best-conducted trial so far intended to reduce allergenicity in rice by antisense coding (1). The allergenicity of the major 16-kDa protein was reduced by 80%, as measured by *in vitro* techniques, a reduction which probably – according to the experience from cow's milk-

Table 1. Introduction of new allergens into foods

Intentional introduction of new allergens into foods	Change in production methods Genetic manipulation
Unintentional introduction of new allergens into foods	Contamination Genetic manipulation

Table 2. Motives for introduction of new genes, especially in plants

Insect protection
Delayed ripening
Virus resistance
Herbicide tolerance
Disease resistance
Modification (yield, oils, etc.)
Change in allergenicity

Adapted from Astwood et al. (7).

allergic patients (2) – would not be sufficient for rice-allergic patients.

Nordlee et al. (3) encoded Brazil nut 2S albumin (with high methionine content) into soybean for nutritional purposes in chicken food. Sera from 8/9 Brazil nut-allergic patients reacted positively in RAST and immunoblot to the genetically modified soybean. Thus, a risk of clinical reaction exists in a Brazil nut-allergic patient who ingests the modified soybean, in which the patient would not expect proteins from Brazil nut to be present.

Calculation of the potential risk of introducing new allergens into foods is not possible. Two factors, however, are very important:

1) the prevalence of clinical hypersensitivity to the food
2) the characteristics of the proteins introduced into the recipient food.

An example of the first factor is mentioned in a study by Nakamura & Matsuda (1). When the prevalence of rice allergy is high, as in Japan, the expected proportion of very sensitive patients reacting to, for example, hypoallergenic rice with a residual content of the 16-kDa protein of less than 1% would also be high, as in cow's milk-allergic infants reacting to hydrolysates (4).

An example of the second factor is the current attempt to introduce fish proteins into potatoes for storage purposes. Such proteins enable the potato to tolerate low temperatures. If – intentionally or unintentionally – Gad c 1, the major (highly heat- and proteolysis-resistant) allergenic protein in cod is introduced into the potato, cod-allergic patients incur great hazards. Although such patients are relatively few in number, the severity of their reactions after intake of cod warrants precaution (5).

Control of the allergenicity of gene-manipulated foods

Altering the genetic code in an organism used in the production of food carries the risk of introducing new allergenic epitopes either from a different species or by creating completely new protein structures. Since very little is known of the possible creation of new allergens by such manipulation, legislation should be strict and should contain guidelines on how a new, potentially allergenic food should be investigated before release on the market. Although at this point completely hypothetic, the following situation may arise. A protein not hitherto recognized as allergenic could be introduced into a food that has highly adjuvant properties. For example, the relatively high allergenicity of the major peanut allergen Ara h 1 (6) might be caused by lectins or high fat content. If a new protein gene were introduced into such a peanut food, the resulting gene product could, quite unexpectedly, prove to be sensitizing in man and thus create new allergies.

Unfortunately, legislation does not exist at present to require national health authorities to assess each food by prior knowledge of the donor and recipient foods, but without *in vitro* or *in vivo* investigation.

In addition, labeling of products containing foreign, unexpected proteins of potentially allergenic origin should emphasize the presence and quantity of these, enabling the consumer in general and the allergic patient in particular to avoid nontolerated foods.

How should genetically modified foods be evaluated for allergenicity?

Astwood et al. (7) have suggested that the modified food should be evaluated only if the source of the introduced gene is allergenic. Tests should initially be *in vitro*, such as RAST, ELISA, or immunoblotting using sera from patients with a convincing case history, or take the form of positive double-blind, placebo-controlled food challenge (DBPCFC) with the source food. If the tests are negative, the authors suggest that the protein source (the donor plant) need not be labeled as the source but may or may not continue to be evaluated *in vivo*. A positive outcome of *in vitro* or *in vivo* tests (skin prick test [SPT], DBPCFC) requires labeling as the source, according to the authors.

This approach may be correct, provided that the test systems used are of sufficient quality – a requirement only rarely fulfilled in allergens of plant origin (8). In many cases, the sensitivity and specificity of the test systems are too low to distinguish between allergenicity and nonallergenicity, thus carrying the risk of introducing modified foods with high allergenicity into the market, or of excluding clinically harmless foods from the market. Some possible pitfalls are listed in Table 3.

To ensure maximal safety before introducing a genetically modified food into the market, we

Table 3. Pitfalls in evaluation of allergenicity in genetically modified foods

Item	Outcome
Patient material (serum, SPT) not thoroughly evaluated (no DBPCFC)	False-negative response in test (sensitivity insufficient) False-positive response in test (specificity insufficient)
Test material not thoroughly evaluated (lack of knowledge of major allergens in donor and/or recipient food)	False-negative response in test (sensitivity insufficient) False-positive response in test (specificity insufficient)
Cross-reactivity between families of plants (including donor and/or recipient food)	Clinically irrelevant responses obtained Clinically relevant responses missed
Genetically modified foods have altered sensitizing potential	Not tested for in this setup

Table 4. Flowchart for investigation of genetically modified foods for allergenicity before release to market

Allergenic source of introduced gene	
↓	
In vitro testing (RAST, ELISA, immunoblotting)	
↓	
In vivo testing (SPT, DBPCFC)	
All negative ↙	↘ Any positive
Label: "Contains proteins from (food). A reaction in patients allergic to (food) cannot be excluded."	Label: "Contains allergenic proteins from (food) and should not be eaten by patients allergic to (food)."

need a diagnostic setup using high-quality patient material (DBPCFC-positive patients, preferentially monosensitized to the food in question, according to the European guidelines [9]) and high-quality test systems (with data on sensitivity, specificity, and known predictive values), to be performed in independent laboratories (Table 4). This would probably require new legislation in this field.

Conclusion

At present, too little is known of how we should deal with the risk of introducing potentially allergenic proteins into foods considered safe for patients with food hypersensitivity. There is a great need to improve the quality of the methods used to test for potential allergens. Until these needs have been met, rigorous labeling is mandatory.

References

1. Nakamura R, Matsuda T. Rice allergenic protein and molecular-genetic approach for hypoallergenic rice. Biosci Biotechnol Biochem 1996;60:1215-21.
2. Høst A. Cow's milk protein allergy and intolerance in infancy. Some clinical, epidemiological and immunological aspects. Pediatr Allergy Immunol 1994;5:5-36.
3. Nordlee JA, Taylor SL, Townsend JA, Thomas LA, Townsend R. Investigations of the allergenicity of Brazil nut 2S seed storage protein in transgenic soybean. In: OECD workshop on food safety evaluation. OECD Environmental Health and Safety Unit, 1995:121-5.
4. Halken S, Høst A. How hypoallergenic are hypoallergenic cow's milk-based formulas? Allergy 1997;52:1175-83.
5. Hansen TK, Bindslev-Jensen C, Stahl Skov P, Poulsen LK. Codfish allergy in adults. Specific tests for IgE and histamine release vs. double-blind, placebo-controlled challenges. Clin Exp Allergy 1996;26:1276-85.
6. Burks AW, Williams LW, Helm RM, Connaughton C, Cockrell G, O'Brien T. Identification of a major peanut allergen, Ara h I, in patients with atopic dermatitis and positive peanut challenges. J Allergy Clin Immunol 1991; 88:172-9.
7. Astwood JD, Fuchs RL, Lavrik PB. Food biotechnology and genetic engineering. In: Metcalfe DD, Sampson HA, Simon RA, editors. Food allergy: adverse reactions to foods and food additives. 2nd ed. Blackwell Science, 1997: 65-92.
8. Bindslev-Jensen C, Poulsen LK. *In vitro* diagnostic methods in the evaluation of food hypersensitivity. In: Metcalfe DD, Sampson HA, Simon RA, editors. Food allergy: adverse reactions to foods and food additives. 2nd ed. Blackwell Science, 1997:137-51.
9. Bruijnzeel-Koomen C, Ortolani C, Aas K, et al. Adverse reactions to food. Allergy 1995;50:623-35.