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**Topic 9: Post-Market Surveillance of Allergenicity**

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The development of biotechnology for the production and processing of foods raises the question of the safety of these foods and the evaluation of any risks, including the allergic risk, that their consumption could pose to Public Health (1).

Indeed allergies engendered by foods containing or derived from genetically modified organisms (GMOs) is a special issue on which particular emphasis has been placed. European Union's regulation 258/97 on Novel Foods (2) stipulates that it must be addressed in every application for the authorization to put on the market any novel foods and particularly those containing or derived from GMOs. Assessment of the allergic risk is currently performed using the decision tree approach as described in the ILSI-IFBC recommendations (3). The aim of this paper is to analyse for the different steps of this approach whether human studies may be necessary to assess the allergic risk of long term or high dosages consumption of such novel foods and how post market surveillance could provide such informations in addition of *a priori* (e.g. pre-marketing) safety evaluation by testing methodologies currently used as yet.

One reason for such concern is that incidence of food allergies appears to be constantly and rapidly increasing. Indeed very few epidemiologic data are available ; the true prevalence of IgE-mediated allergic reactions to food and frequency data for allergens are generally unknown. However according to the European Scientific Cooperation Programme SCOOP, task 7.2 (4) the prevalence could be estimated at 3-5% of the general population. This figure may seem low in view of the number of potential allergens, but represents a non-negligible at-risk population, particularly as the severity of the reported incidents is also on the increase. Many such shocks are fatal, especially those provoked by ingestion of peanut-based products. The risk of developing food allergy is especially great in infants, because these allergies generally occur in the first months of life. The special sensitivity of children may be related both to greater uptake of allergens compared with adults, and to immaturity of the local gut mucosal immunity and of the systemic immune system. Indeed prevalence of food allergies in children appears to be higher as it is in adults and figures of 6-8% have been reported. Moreover observations of peanut allergy in young children never directly exposed to peanut before suggests that allergic response can be induced / triggered by sporadic exposures to trace amounts of allergen. Indeed the level of protein necessary to promote an allergic response is still unknown. On the other hand, it must also be noticed that drugs such as  $\beta$  blockers, non steroid anti inflammatory drugs or inhibitors of angiotensin converting enzyme that are used by adults and elderly people may favour the elicitation or the development of food allergy reactions. In the future, at-risk groups of the population exposed to food allergy may therefore also include adult and senior people.

The number of foods incriminated also appears to be on the increase and polysensitizations, e.g. sensitizations to several foods, are now frequently observed. Cross-reactivity between pneumallergens and food allergens of different, sometimes quite distinct, botanic origin, appears to result from common epitopes, that is molecular domains that have similar structural features and are responsible for immunoreactivity (e.g. binding to specific IgE antibodies, which triggers the allergic reaction).

Therefore there is a pressing need to consider biotechnolgy as a possible way of creating new allergens or of unmasking hidden and therefore non bioavailable immunoreactive structures and of increasing the expression/potential of existing ones.

Although allergenicity is part of the whole evaluation of the safety of a novel food, it is considered a specific issue because unlike toxics, food allergy needs several events to occur : a patient with a genetic (atopic) background, an allergen which is "specifically" recognized by IgE and environmental enhancing factors which makes assessment of allergenicity a difficult exercise. The following aspects should be clearly distinguished :

1. The "intrinsic" allergenicity of the foreign protein(s), encoded by the inserted transgene(s) and possibly marker genes, and expressed in edible parts of the plants, or of fragments of these proteins produced during processing.

Indeed once a protein is ingested there is a potential risk of allergy. As far as products of the introduced genes are concerned, the evaluation refers to well identified and characterized compounds. The trait genes as well as the marker genes currently used in the GM plants that have been put on the market or are still under consideration, are always derived from the same origins (e.g. the same transposon). Therefore the proteins they encode are present as foreign proteins in GM foods in the same isoform. It is however noteworthy that in final processed foods, the trait proteins can have been altered and be present under denatured or degraded forms. Therefore a comprehensive *a priori* initial safety evaluation may not be possible.

2. The allergenicity of the whole plant and derived products. In this case it is not the product(s) of the transgene but the incidence of a possible pleiotropic effect of the transgene on the qualitative/quantitative pattern of natural endogenous allergenic proteins that must be taken into account.

Given public health, social and economic consequences of food allergy now and in the future, assessing and preventing risks of allergic reactions to (novel) foods is a major challenge that must be met in both cases. In doing this, two distinct aspects must be addressed :

- a) Preventing reactions (e.g. provocation phase of allergy) in allergic consumers, who already know of their allergy. This is partly a communication problem, in which labelling features very strongly but which would benefit of a clear understanding of the molecular basis of IgE recognition and thus of identification of major B-epitopes in allergenic proteins.
- b) Preventing *de novo* sensitisation in genetically susceptible individuals. This requires a better understanding of the mechanisms which help or hinder the development of a specific, IgE-mediated, response to foods. It also needs an understanding of the characteristics of protein structure and function that generate an IgE response, including how they may interfere with other elements of the diet.

Improved knowledge of the basic mechanisms involved in the physio-pathology of food allergy is thus required but it needs to be associated with clinical and epidemiological data to provide informations on questions that still remain unclear such as the thresholds of reactivity and the relationship between the levels of intake and exposure and the development and elicitation of an allergic reaction.

### **Allergenicity of the foreign protein(s)**

The methodology for testing the potential allergenic effects of introduced gene products depends on the origin of the introduced gene according to the decision tree proposed by the IFBC/ILSI (3). In case the source is a known allergen, antisera from allergic individuals can be employed to test the gene product for allergenicity. It has been proposed that negative results should be verified by skin prick tests and food challenge on allergic human patients. Although such an approach is scientifically relevant it must be noticed that experiments on humans can be considered as unethical when performed for marketing authorization of GM foods. Moreover it is also limited by the small number of patients specifically allergic to the relevant conventional food who could be "available" for such a study.

Sensitizations and specificity of serum IgE induced by exposure to the GMOs may vary depending on genetic background of populations and of regional food habits for example.

Whenever possible, evaluations of allergenicity, as measured by the analysis of the IgE binding capacity of the GMO or fragments thereof, should be performed on allergic people from the regions where the novel food is intended to be consumed and compared with the reactions observed on patients from the regions where the GM is grown or produced and who have thus been already exposed to the "new" GM plant and to the food or airway allergens it may contain. Prevalence of allergy in workers or in farmers who have significant occupational exposure to these products would also provide useful informations.

This should permit to assess both aspects of the allergic risk i) induction of new allergy in genetically predisposed "atopic" individuals and ii) elicitation of an allergic reaction in individuals already sensitized to a related protein which could provoke immunologically cross reactions with the "novel" protein(s) present in the GM plant.

To evaluate the allergenicity of the product of a gene from a source without recorded allergenicity it is necessary to turn to other indirect methods. These include animal models, comparison of the amino acid sequence of the novel protein with those of major allergens listed in databanks accessible through the Internet and physicochemical tests.

Each of these methods will be extensively discussed in other papers. I will just emphasize here some aspects that must be critically appraised when they are used for assessment or prediction of allergenicity.

Fragments of a succession of 8 (or more) identical or chemically similar amino acid residues point to the existence of potential common epitopes and, hence, allergenicity. This approach quickly eliminates certain constructs that pose a potential risk. Nonetheless, the absence of common or similar sequences of such length does not strictly guarantee safety because i) available information in databanks is limited to a small number of allergens, ii) these criteria are very restrictive and are limited to linear epitopes. It is worth noting that in the spatial configuration of the protein, short homologous sequences can be brought close together by the folding of the molecule and, thus, participate in the formation of conformational allergenic epitopes. Therefore, if such an approach may be considered relevant it is needed to improve data bases, and to develop algorithms and softwares to compare structures and not only sequences of introduced gene products and known allergens (5).

Assessment of allergenic potential of a protein from its physicochemical properties is based on the assumption that allergenicity is due to the whole intact protein. To allow sufficient amounts of the protein to reach the gut, be absorbed through the intestinal mucosa and then be presented to immunopotent cells, a prerequisite for food protein allergenicity would thus be stability in acidic gastric conditions and resistance to digestion by the proteolytic enzymes present in the gut. Indeed correlation have been established between resistance to proteases and allergenicity for several proteins (6). However, some food protein susceptible to protease activity and extensively degraded during digestion has proved to be as potent allergen as protease-resistant, globular protein. It is also now well established that isolated peptide fragments, even relatively short ones, account for a significant part of the allergenicity of the whole protein (7). Moreover major allergenic epitopes may also be located in hydrophobic regions of the molecule, inaccessible for antibodies in the native conformation of the protein (8). They only become available after unmasking, e.g. after denaturation and/or enzymatic hydrolysis of the protein during the digestive processes. Digestion might thus be a necessary step for elicitation of food allergy and the allergic reaction does not only depend on a major fraction of the protein crossing the intestinal barrier in the native, intact form (9, 10, 11).

Moreover, the test conditions, and notably the pH of the medium (pH 2), are harsh and do not correspond to the real conditions of digestion, or to individual variability in evolution, distribution

and regulation of pH values and the kinetics of secretion of proteolytic enzymes and release of products. In addition, performed on the isolated protein, it does not take into account the incidence of the food matrix in which the allergen is present.

Further testing in appropriate animal models, for instance the Brown Norway rat model or any other relevant animal model (e.g. guinea pig, rat or mouse of different strains) can be considered. In the case of a novel protein or of a new GM plant, appropriate treatments may be needed in order for the product to be administered under relevant form and doses to expect any IgE or Th2 type immune response being induced. Animal studies are not yet considered relevant models that can be extrapolated to humans, because the method of experimental sensitization may be quite different from the conditions of oral sensitization in atopic humans and specificity in the antibody responses is a function of the species and of the individual animal. Moreover, inbred strains of laboratory animals are not representative of the genetic variability of the population and, thus, will not express the diversity of the human IgE response. In the study of Brazil nut allergenicity, tests on animals even led to 2S albumin being considered as a minor allergen, or even as a tolerogen (12).

Moreover, it is vital to respect the strict identity between the foreign protein expressed by the transgene in the plant which will be ingested by the human consumers and the protein used in the evaluation tests on animals. The recombinant proteins are generally expressed by transgene at very low levels, and direct extraction of the test protein from the transgenic plant will not yield the large quantities required for testing. Instead, the test protein is generally produced directly by a genetically modified microorganism into which the corresponding transgene has been introduced, and which is able to synthesize it at much higher yields than the plant. However, small structural variations can occur depending on the producing organism. Such variations can arise in the protein's primary sequence as a result of point mutations, or may be caused by post translational modifications which could affect the degree of methylation, phosphorylation or glycosylation. Such changes can influence the protein's biologic properties and the pharmacologic activity, notably its immunoreactivity and allergenicity (13).

All these indirect approaches do not reflect the real conditions of sensitization of atopic consumers in the every day life situation of intake and exposure and especially for at risk groups like elderly people and children. Each of them provide some useful informations and their use can lead to a body of convergent presumptions which may be not sufficient to draw a definite conclusion on the (non) allergenicity of the novel protein. Such a situation occurred in the recent example of the maize StarLink™ where the current state of knowledge regarding structure and chemical properties of allergens and the uncertainties concerning the exposure to Cry9C protein via the food chain with regard to a possible, but unknown, threshold of reactivity precluded any definite conclusion. The FIFRA Panel concluded that it is a priority to gather clinical and historical data, in individuals either who reported to have experienced adverse effects after consuming food that might have been made from StarLink™ corn or who have significant occupational exposure to StarLink™ corn or corn products (14).

### **Allergenicity of the whole GM plant/food**

This aspect is rarely dealt with in dossiers for the authorization of a novel food. The question is whether a GM plant or derived food can present a different qualitative or quantitative composition in endogenous proteins that can be allergens naturally occurring in the conventional plant.

Alterations of genes involved in and/or of genes regulating processes entirely different from those expected from the genetic modification itself may occur because of the only insertion event. The location where the transgene is inserted within the plant genome is not controlled, and this single genetic modification may interfere with the expression of other genes and affect numerous

uncontrolled and nonrelated phenotypic characteristics. Such an indirect pleiotropic effect is a specific issue that needs to be addressed. The insertion event may alter the functioning of other genes e.g. those encoding natural endogenous allergenic proteins. As a consequence, it might over express one or several endogenous allergenic protein(s) or express it (them) in a modified form. The fear may then be that the allergenicity of the GM plant is increased or modified compared with that of the corresponding classical commercialized variety. The whole genetically modified plant itself (or a food derived therefrom) can then be considered a novel hazard and particularly could present a novel allergic risk which would be inherent to the process.

This issue is related to substantial equivalence and to unintended effects of the genetic modification which could have biological / toxicological significance in a long term consumption of the whole GM food.

This aspect appears to be a real issue in terms of allergenicity. It is specific to every new product and to each new genetic modification event. Therefore it should be addressed on a case by case basis for all applications of GM plants intended to be used as novel foods.

Unintended effects of the genetic modification can be detected then identified using modern analytical-, biochemical-, and molecular techniques (15). As an example, comparison of the allergen repertoire of GM vs conventional plant/food can now be performed using new methodologies such as proteomics, e.g. separation of proteins by high performance 2-dimensional gel electrophoresis, then detection of allergens on immunoblots of the gels probed by allergic patient sera (16, 7). Allergen spots can then be characterized by their molecular weight and isoelectric point. Identification of allergens which are affected, disappearing, over expressed, modified or neo synthesized, by an indirect effect of the the introduction of the transgene can be done after extraction from the gel and purification using mass spectrometry analyses and microsequencing.

Animal studies with whole GM plants may also be appropriate in such cases where there is reason to suppose that the introduced trait(s) may have altered the composition of the plant, i.e. in case GM plants are not substantially equivalent to the conventional counterpart. Actually this the case in most GM plants particularly when introduced genes encode products that are expressed and remain present in the plant. As already noticed for assessment of allergenicity of isolated trait protein, such chronic feeding tests or long term tolerance studies with animals do not reflect the conditions of sensitizations of atopic humans exposed to the GM food in the every day life conditions. Animal feeding trials with whole food products lack sensitivity and specificity, because of the impossibility to administer high doses of the test product through the animal diet, and because numerous uncontrolled factors may influence the final result.

### **Post-market surveillance**

If it is feasible to demonstrate that no adverse effect can objectively be evidenced using all the testing procedures available as yet, it is impossible to scientifically provide any definite proof of the absence of any risk of toxicity which corresponds to the social demand. In order to detect possible long term unintended effects of novel foods in which no presumption of toxicity or allergenicity has been evidenced during the pre-marketing safety evaluation procedure, post-market surveillance (PMS) thus appears to be necessary. It must be emphasized that PMS must then be considered as a tool for risk assessment and not only for risk management even if the informations collected through PMS, as any other objective/scientific datas, may have consequences on some aspects of risk management.

PMS must not be considered as a substitute for proper *a priori* testing methodologies, but as a complementary approach which could bring useful informations on the occurrence of such

unintended effects and particularly on new allergies after exposure to GMOs in the every day life conditions. However such an epidemiologic survey is difficult to organize and the hope to get reliable and unambiguous conclusions in terms of statistically significant impact of the exposure to a GMO product on disease processes or outcomes is low because of the multiplicity of factors affecting the burden of disease in the general population. It is therefore generally much criticised.

Indeed it is difficult to unambiguously relate a subtle, rare, unexpected adverse effect with the consumption of a GM food in the general population. However it does not seem to me that post-market surveillance should be considered as naive or utopic.

First if such a surveillance is not organized properly by regulatory bodies in charge of public health and with the petitioner, it will anyway be performed in an uncontrolled, subjective manner by consumers and media with no guarantee of reliability. In the FIFRA report on StarLink™ maize, the Panel recalled that in self-reported reactions, it is well known that patient history often cannot be confirmed (14). In the same document it was mentioned that less than 40% of reported food allergic reactions can be confirmed when patients are subjected to double-blind placebo-controlled food challenges and that reports of adverse reactions to foods are more frequent following publicity about a specific product. It is also what is happening with the galloping spreading rumour that the increasing prevalence of food allergy to soybean is linked with the consumption of GM soybean.

Second, as far as allergy is concerned, it does not affect the general population but only an at-risk group of atopic individuals. These people are particularly aware of the different factors that may interfere with their health, they are used to read labels and keep themselves well informed about new ingredients, modification in composition of newly commercialized foods, regulations,... just because it may be life-threatening for them. Moreover they are organized in Associations that can be reliable and efficient relays to pass and to get back the informations and will certainly be very keen to carefully scrutinize any possible impact of GM foods on occurrence of allergic reactions as they already do with conventional foods and to participate in such a kind of post-market surveillance.

Certainly the fundamental difficulty in to draw and prove a direct causal correlation between health hazards and the consumption of a novel food or to bring sufficient consistant evidence of the absence of apparition of such side effects. Developing a concept and a suitable and qualified method to solve this problem is urgently required. Major difficulties occur with regards to :

- The low frequence and/or intensity of adverse effects that are to be expected, particularly when allergy is concerned, e.g. emergence of new allergies (i.e. to trait proteins) or increased prevalence of allergy to foods already recognized as allergenic (i.e. allergy to GM foods vs conventional corresponding foods). The latest case is all the more difficult since the base level of allergy to the conventional food in the general population is itself generally unknown. To overcome this difficulty requires to carefully design the target population to survey in order to get sufficiently consistant data for a statistical interpretation. The programme should define the size of the "sample" but also its relevant characteristics in terms of age, sex, geographic and social repartition, on their known previous health history in order to focus on the most exposed at-risk groups. Observation of occuring cases of occupational allergy in workers employed in biotechnology companies may be useful as a first warning sign of the allergenic potential (e.g. sensitizing and triggering capacity of recombinant novel proteins and GM crops).
- The collection, validation and record of reported cases of allergic reactions that must be carefully controlled for their relevance and veracity. As noted by the FIFRA Panel on StarLink™ maize, perceived food allergy is probably 10 times greater than actual food

allergy. A systematic approach is required in order to come to the correct diagnosis of food allergy, including clear identification of the food eliciting the reaction and of the quantity ingested, description of the symptoms and the timing of reaction, clinical previous history of the patient. Confirmation by determination of specific IgE, skin tests or food challenges may be needed to determine if the reported cases can be considered possible, probable or confirmed food allergy.

- The traceability of the GM crop and of all products derived therefrom all along the whole food chain. Such a postmarket surveillance can only be achieved through the development and organization of procedures ensuring the traceability of novel food products as part of a quality assurance policy applicable to all agribusiness sectors including production, processing and commercialisation of the final food products containing the novel ingredient. This complete traceability is a major issue to address. It may be very difficult because of the great number of products that can be used as foods as such or be incorporated as well defined and labelled (major) ingredients in final food products or be used as technological additives and be present at low amounts in processed foods where they are not indicated and where consumers are not expecting to find them. The presence in foods of such hidden or masked compounds that can be allergens precludes the following of any PMS and the compliance of any diet for the prevention of adverse reaction in allergic consumers.

The PMS programme should be initiated by the notifier as part of the risk assessment of long-term accumulated effects, in fulfilment of the conditions under which the GMO crop will gain consent. It should be designed to incorporate both general surveillance and case-specific monitoring. The notifier should provide details on the executing bodies, the reporting of adverse effects to the competent authorities, the methods to identify and confirm such effects, and measures that enable the protection of consumers health (and environment).

The notifier should disclose detailed detection methods to facilitate the post marketing control of products derived from the GMO crop. In addition, samples of the GMO product and relevant details of nucleotide sequences should be made available by the notifier to the competent authorities. Detection of foreign DNA is certainly not appropriate in processed foods and complementary analytical techniques for detection of the foreign protein, either intact or after denaturation/degradation occurring during the processing may be needed. Immuno chemical methods using specific antibodies could be very useful since they are reliable, sensitive, relatively costless and easy to apply by numerous laboratories including industry and control laboratories. The challenge is to obtain sufficient sensitivity and specificity when applied to various food matrix. Should the antibodies prepared have a sufficient affinity / specificity, the pattern of degradation products occurring during the different steps of the industrial processes could be achieved. These data would then be used to defining and developing a second generation of tests for the detection of the most frequent and characteristic residual peptidic fragment(s) present in the end products and therefore of those compounds that could be reliable and stable markers of the use of the transgenic proteins.

The manufacturer is responsible for the general organisation of the PMS in collaboration with other partners in order to ensure a circulation of information in both way. A validated information on the presence of novel foods or novel food ingredients in foods available on the market place should go down to the food industry then to the public (e.g. general population or at-risk groups, directly or through the intervention of associations) via national or european competent authority in charge of food safety. A follow up of the actual intake, including quantitative estimation by the different at risk groups must be set up by the manufacturer through its commercial network or most likely by specialized panels/committees in charge of the survey of consumer behaviour and spending. Associations may serve as effective relays between food industry and consumers but they also

may have an effective role to play between consumers and physicians in order to permit the informations on reported cases of allergic reactions to a new food to go back to the manufacturer and to the competent authority. As previously stressed the validation of the alleged allergic adverse effects must be done under the responsibility of local physicians and the recording of the documented cases should be coordinated and centralized by a competent clinician specialized in allergology/epidemiology who will establish the relationship with the consumption of the novel food in association with the competent authority. The objective is not to achieve a complete epidemiological study which would be quite impossible because of the difficulties already mentioned but to set up an alarm network to gather partial but validated answers in order to get preliminary warning signs on a relationship between consumption of food derived from biotechnology and increased allergic reactions. As a consequence it might also be concluded that there is very likely no allergic risk. Indeed PMS also offers some advantages to the companies: if the intake of the novel food product was over-estimated in previous considerations and no unexpected negative effects were evidenced, they may extend its use without new toxicologic studies

As yet, PMS-experiences on foods only include novel foods with nutritional or functional claim such as novel fat replacers and phytosterols. Although there was no concern of allergy Olestra<sup>TM</sup> can be used as an example which illustrates some general features of PMS such as the need of a consumer follow up and of a structure to collect and record the reported adverse effects.

Marketed by Procter and Gamble, Olestra is a mixture of polyesters prepared by esterifying sucrose with long chain fatty acids isolated from edible fat and oils. It has the organoleptic and chemical properties of fat, but is not hydrolyzed by gastric and pancreatic enzymes and is not absorbed intact from the gastrointestinal tract. For this reason, it does not provide energy in the diet, and can serve as a zero calorie replacement for fat in a variety of foods (e.g. potato and corn chips) and may, thus, make up a significant part of the diet.

Safety assessment required determination of the size and frequency of consumed "novel" foods, the context of consumption, and whether the opportunity of a reduced intake of energy would prompt consumers to increase their total consumption of such low fat and non-fat foods or to eat these foods instead of fruits and vegetables. This is a safety concern among the general population and among identified subgroups who might have either particular dietary patterns (i.e. children, teenagers and young adults, women from low-income families, and vegetarians) or specially high metabolic nutritional needs for nutrients where availability can be affected by a fat replacer (i.e. children, teenagers, and pregnant or lactating women). In such groups, greater effects than those measured in the pre-marketing nutritional studies, or effects not seen in the studies, could occur. Through a postmarketing surveillance program Olestra exposure and frequency of consumption have been monitored as well as the spontaneous reporting of alleged undesirable effects. In addition, prospective epidemiologic studies were conducted to determine the nature, severity, incidence and prevalence of any effects on nutritional status and undesirable gastrointestinal effects among individuals who eat Olestra foods under free-living conditions (29). After a period of 30 months the manufacturer had to submit the collected information to the FDA for further evaluation.

## **Conclusions**

Allergenic foods and constituents of food responsible for allergenicity seem to be widespread and unlimited in number. New allergens are constantly appearing and it is not easy to provide a simple, universal and definite answer to the question: "what makes an allergen an allergen?" (18). The outstanding challenge is to understand why a common glycoprotein which is an innocuous

antigen is also an allergen for some groups of people, or why it may suddenly or progressively become a much more potent allergen than usual.

No structure can be described as being solely and intrinsically allergenic, and the number of allergenic epitopes determined and identified on a particular molecule varies with the methodology used. In addition to the structural characteristics of the potentially immunoreactive component, other factors can modify allergenicity. One such factor is linked to the individual. In the definition and determination of an epitope, there is an essential association between the potentially reactive fragment of the protein, which is well defined and stable, and the binding region of its corresponding IgE antibody, which is variable in affinity and specificity because of the genetic heterogeneity of the population. Another factor appears to be associated with changing eating habits. The immunoreactivity of a food may be affected by the fact that 1) the food is first ingested by the young infant, 2) is consumed in larger amounts than it used to be and 3) may be processed and presented with different textures, i.e. associated with lipids in emulsions. It is therefore essential that the food industry does not generate new epitopes on food constituents, or market forms with higher allergenicity as a result of processing or presentational alterations.

Different allergens may share analogous sequences which could represent preferential sites for binding to antibodies and in particular to IgE. These homologies may occur in related molecular species of the same family and be partly conserved during evolution. They may also, however, be present among apparently unrelated compounds, and hamper a coherent approach to predicting allergenicity. No reliable test is as yet available for definite detection of minor allergens or the allergenic potential related to minor allergens. As a consequence, even if no indication has yet suggested that novel foods, and particularly recombinant proteins expressed by genetically modified organisms, would be more (or less) allergenic than the corresponding traditional foods, care should be taken in interpreting and applying the results of the different predictive procedures currently available.

Finally, assessment of the allergic risk of novel foods should be subject to case-by-case critical appraisal and approval, by National and/or European committees in charge of consumer protection and food and environmental safety.

The predictive approach to determining the allergenic potential of novel foods should be allied to mandatory implementation of monitoring of the potential post-marketing impact of these new foodstuffs on public health. Such monitoring can only be achieved through the development and organization of procedures ensuring the traceability of novel foods products as part of a quality assurance policy applicable to the whole food chain. Epidemiologic survey of any increasing prevalence of food allergy or emergence of new allergies in relation with the intake and exposure of "novel" allergens derived from GMOs should mobilize all agribusiness sectors (producers, processors, distributors), physicians, scientific and regulatory committees in charge of public health as well as at risk groups of consumers and associations of allergic patients.

## **References**

1. Wal J.M., Pascal G. Novel foods and novel hazards in the food chain. In Risk Assessment in the Food Chain of Children. P.J. Aggett and H.A. Kuiper Eds. Nestlé Nutrition Workshop Series, Pediatric Programme, 1999, Vol. 14, pp. 235-59.
2. Official Journal of the European Communities L 253, vol. 40,16 september 1997.
3. Metcalfe D.D., Astwood J.D., Townsend R, Sampson HA., Taylor SL., Fuchs RL. Assessment of the allergenic potential of foods derived from genetically engineered crop plants. *Crit Rev Food Sci Nutr.* 1996;36(S):S165-S186.

4. Scientific Cooperation Programme in the EU. The occurrence of severe Food Allergies in the EU. Report of experts participating in Task 7.2. April 1998.
5. Wal J.M. Strategies for assessment and identification of allergenicity in (Novel) Foods. *Int Dairy J.* 1998;8:413-23.
6. Astwood J.D., Leach J.N., Fuchs R.L. Stability of food allergens to digestion in vitro. *Nature Biotechnol.* 1996;14:269-73.
7. Wal J.M. Assessment of allergic potential of (novel) foods. *Nahrung / Food* 1999;43:168-74.
8. Maynard F., Jost R., Wal J.M. Human IgE binding capacity of tryptic peptides from bovine  $\alpha$ -lactalbumin. *Int Arch Allergy Immunol* 1997;113:478-88.
9. Haddad Z.H., Kalra V., Verma S. IgE antibodies to peptic and peptic-tryptic digests of  $\beta$ -lactoglobulin: significance in food hypersensitivity. *Ann Allergy* 1979;42:368-71.
10. Spuergerin P., Walter M., Schiltz E., Deichmann K., Forster J., Mueller H. Allergenicity of  $\alpha$ -caseins from cow, sheep, and goat. *Allergy* 1997;52:293-8.
11. Selo I., Negroni L., Yvon M., Peltre G., Wal J.M. Allergy to bovine  $\beta$ -lactoglobulin : specificity of human IgE using CNBr derived peptides. *Int. Archs Allergy Immunol.* 1998;117:20-28.
12. Melo V.M.M., Xavier-Filho J., Silva-Lima M., Prouvost-Danon A. Allergenicity and tolerance to proteins from Brazil nut (*Bertholleria excelsa* H.B.K.). *Food Agric. Immunol.* 1994;6:185-195.
13. Bernard H., Meisel H., Créminon C., Wal J.M. Phosphorylation is a post translational event which affects IgE binding capacity of caseins. *FEBS Lett.* 2000;467: 239-44.
14. FIFRA Scientific Advisory Panel Meeting, Report on Assessment of Scientific Information Concerning StarLink Corn, November 28, 2000, Arlington, Virginia, USA.
15. Kok E.J., Keijer J., Van Hoef A.M.A., van der Wal-Winnubst E.N.W., Henkens M.H.C., Kuiper H.A. mRNA fingerprinting of transgenic food crops. Report of the demonstration programme on Food Safety Evaluation of Genetically Modified Foods as a Basis for Market Introduction. The Hague january 1998. P.37-49.
16. Burks AW, Fuchs RL. Assessment of the endogenous allergens in glyphosate-tolerant and commercial soybean varieties. *J Allergy Clin Immunol* 1995;96:1008-10.
17. Suttie JW, Ross AC Eds Assessment of the nutritional effect of Olestra.. *J Nutr.* 1997;127(8) Supplement.
18. Aas K. What makes an allergen an allergen. *Allergy* 1978; 33:3-14.