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Series on the Safety of Novel Foods and Feeds, No. 5

REPORT OF THE OECD WORKSHOP ON NUTRITIONAL ASSESSMENT OF NOVEL FOODS AND FEEDS

Ottawa, Canada
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No. 5, Report of the OECD Workshop on the Nutritional Assessment of Novel Foods and Feeds, Ottawa, February 2001

OECD Environmental Health and Safety Publications

Series on the Safety of Novel Foods and Feeds

No. 5

Report of the OECD Workshop on the Nutritional Assessment of Novel Foods and Feeds

Ottawa, Canada
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INTRODUCTION

The OECD Workshop on the Nutritional Assessment of Novel Foods and Feeds was hosted by the Government of Canada in Ottawa, 5-7 February 2001. It was held as part of a programme of work of the OECD's Task Force for the Safety of Novel Foods and Feeds.

The workshop included 79 participants from 19 countries, the European Commission, the World Health Organizations Food and Agriculture Organization (FAO), the OECD's Business and Industry Advisory Committee (BIAC) and the International Association of Consumer Food Organizations (IACFO). The workshop was planned by a steering committee comprising: Ambroise Martin, Agence Française de Sécurité Sanitaire des Aliments (France); François Hervieu, Ministère de l'Agriculture et de la Pêche, (France); Gerhard Eisenbrand, University of Kaiserslautern (Germany); Kenji Isshiki, National Food Research Institute (Japan); Harry A. Kuiper, RIKILT Department of Food Safety and Health (Netherlands); Andrew Chesson, Rowett Research Institute (United Kingdom); Margaret Cheney, Health Canada; Peter Fischer, Health Canada; Paul Mayers, Health Canada; Mireille Prud'homme, Health Canada; Karen McIntyre, Health Canada, Lynne Underhill, Canadian Food Inspection Agency; Elizabeth Vavasour, Health Canada; Peter Kearns (OECD); Tetsuya Maekawa (OECD), and; Clare Chapman, Unilever Research (BIAC). The workshop was chaired by Peter Fischer (Health Canada) and the rapporteur was Nick Tomlinson (United Kingdom).

In planning the workshop, it was recognised that, to date, the activities of the Task Force and previous projects of the OECD have focused on approaches to the safety assessment of novel foods, especially GM foods. While the previous work recognised the need for nutritional assessment where a novel product exhibited a nutritional modification, no specific guidance on nutritional assessment has yet been elaborated. The scope of this workshop therefore focused specifically on the nutritional assessment of novel foods and feeds.

New challenges are expected to arise with the next generation of novel products which will have enhanced or improved nutritional characteristics. The issue for government authorities will not only be how to address the safety of these products, but also how to assess and respond to the nutritional and compositional modifications made in novel products and any related claims which may be associated with them. This will be an issue for all novel foods and feeds with intentional compositional and nutritional changes, not just GM products.

The objective of this workshop was to discuss aspects related to the nutritional assessment of novel foods and novel feeds. More specifically, participants reviewed and made recommendations in the following key areas:

- Nutritional assessment as a tool to substantiate nutritional/efficacy claims and establishing safety;
- The challenges in assessing the nutritional value of future products for which compensatory changes are expected to occur in the plant;
- Whether there is a need to move to a total diet consideration in contrast to the current approach that focuses at the single food/feed product level, and
- The identification of specific novel livestock feed nutritional assessment issues compared with those of novel foods.

OPENING REMARKS ON THE BACKGROUND AND OBJECTIVES OF THE WORKSHOP

by

Dr Peter Fischer
Workshop chairman
Nutrition Research Division, Health Canada

Good morning. I am the workshop chair, Peter Fischer, and on behalf of the Government of Canada, which is hosting this workshop, I would like to welcome you to Ottawa. I hope that while here you will have an opportunity to enjoy our city, which is now in the midst of Winterlude, our annual celebration of winter. Winterlude is centred around the Rideau Canal Skateway, which is just next to this building, and is, at 7.8 km, the longest skating rink in the World.

I would like to give you a little bit of background to the development of this workshop on Nutritional Assessment of Novel Foods and Feeds. The idea for this workshop originated at the first meeting of the Task Force for the Safety of Novel Food and Feeds, held in Paris in 1999. The Task Force is made up of members that are nominated by the governments of the various countries that make up the Organisation for Economic Co-operation and Development (OECD). The OECD membership consists of 29 industrialized countries in Europe, North America and the Pacific, as well as the European Commission. The purpose of OECD is to coordinate and harmonize policies, discuss issues of mutual concern, and work together to address international problems. Most of the work of OECD is carried out by more than 200 specialized committees and subsidiary groups composed of representatives from member countries. The Task Force for the Safety of Novel Foods and Feeds is one of these subsidiary groups.

Members of the Task Force, for the most part, come from ministries or agencies responsible for ensuring the safety of novel foods and feeds, including products of modern biotechnology, such as genetically modified foods and feeds. The members generally have expertise in food and feed safety assessment. Other organizations, such as FAO and WHO also contribute to the work of the Task Force. The Task Force is currently focussed on efforts to promote continued international harmonization in the field of safety assessment of products of biotechnology. The main area of work is the development of consensus documents that provide information on critical parameters of food safety and nutrition for each food crop.

A major issue for the future is the development of strategies for managing the safety assessments of the next generation of genetically modified products, which are expected to be on the market in the next decade. Included are products with agronomic applications, along with food crop varieties that can withstand specific environmental stresses, functional foods with higher levels of specific nutrients, such as beta-carotene, and products with medical applications.

The activities of the Task Force and previous projects of the OECD have focussed on approaches to the safety assessment of novel foods. One of the main achievements was the development of the Report

"Safety Evaluation of Foods Derived by Modern Biotechnology - Concepts and Principles, released in 1993. The main concept presented was that of "Substantial Equivalence". It was recognized that some products, however, do not have relevant comparators, and the first steps towards developing strategies to deal with these were developed at an OECD Workshop in Oxford, UK in 1996. In 1997, another OECD Workshop at Aussois, France examined the experiences that various countries have had in applying substantial equivalence in safety assessments, and it was concluded that this concept provides equal or better assurance of the safety of foods derived from genetically modified plants when compared to foods derived through conventional methods.

In the work that was done previously, there was a recognition that there is a need for nutritional assessment where a novel product exhibited nutritional modification, however, no specific guidance on how such nutritional assessment might be carried out was provided. This workshop, therefore, focuses on the nutritional assessment of novel foods and feeds, especially on how we are to deal with the next generation of novel products that will have altered nutritional characteristics. The issue with these novel products is broader than just assessing their safety. We will also have to assess their nutritional and compositional modifications, as well as associated claims of their beneficial effects, in terms of both nutritional safety and efficacy. This will be an issue for all novel foods and feeds with altered nutritional characteristics and composition, not just for genetically modified foods.

Thus, the objective of the workshop is to discuss aspects related to nutritional assessment of novel foods and feeds. Specifically, participants will be asked to review and make recommendations in the key areas listed on the slide:

1. Nutritional assessment as a tool to substantiate nutritional/efficacy claims and establishing safety

2. The challenges in assessing the nutritional value of future products for which compensatory changes are expected to occur in the plant

3. Whether there is a need to move to a total diet consideration in contrast to the current approach that focuses at the single food/feed product level

4. The identification of specific nutritional assessment issues for novel livestock feed compared with those of novel foods

The program will consist of the keynote presentation by Dr. Harry Kuiper, followed by a plenary session on food modification in plants and nutritional assessment of derived novel foods. In the afternoon there will be two simultaneous breakout sessions, one on tools for nutritional assessment and the other on metabolic pathway modification in plants. Tomorrow, there will be a second plenary session on single trait versus total diet considerations and issues related to novel feeds versus novel foods. This will be followed by two more simultaneous breakout sessions, one on single trait versus total diet considerations and the other on differences between the nutritional assessment of novel foods versus that of novel feeds. Finally, on Wednesday morning, we will have the closing plenary session during which the breakout session reports will be presented.

During the whole program, there is ample time for discussion, so I encourage you to all participate actively.

My last task is to acknowledge the work of the steering committee whose names appear on the slide. It is through their hard work, including several conference calls at odd times of the day for many of us that this workshop came about.

BACKGROUND

The basic concepts for the safety assessment of foods derived from genetically modified organisms have been developed in close collaboration under the auspices of the Organisation for Economic Co-ordination and Development (OECD) and the United Nations World Health Organisation (WHO) Food and Agricultural Organisation (FAO). A first joint FAO/WHO consultation in 1990 that resulted in the publication of the report 'Strategies for Assessing the Safety of Foods Produced by Biotechnology' in 1991 paved the grounds for the development of an international consensus on a basic approach for the safety assessment of foods derived from genetically modified organisms by the OECD's Group of National Experts on Safety in Biotechnology in a meeting in Bergen, Norway in 1992. Conclusions of the Group were published in a report on 'The safety evaluation of foods derived by modern technology – concepts and principles'. It was recommended to conduct the safety assessment of a genetically modified food on a case-by-case basis, where possible, through comparison to an existing food with a long history of safe use. This basic concept, later denominated *the concept of substantial equivalence* was refined in two subsequent workshops organised by WHO in Copenhagen in 1993 and in 1995, respectively, and a further joint WHO/FAO consultation on the safety of foods derived from modern biotechnology in Rome in 1996.

An OECD Workshop on the Toxicological and Nutritional Testing of Novel Foods, held in Aussois in 1997 (OECD 1998), concluded that the selection of key nutrients and toxicants should be based on the structure and function of the inserted gene(s) and the crop species under consideration, and that the selected components should be representative of essential biochemical/physiological pathways in the organism. It was, however, also noted that further development of alternative approaches for the detection of unintended effects, including profiling techniques should be considered.

The G8 summit in Cologne in June 1999 requested the OECD Working Group on Harmonization of Regulatory Oversight of Biotechnology and the OECD Task Force for the Safety of Novel Foods and Feeds to undertake a study of the implications of biotechnology and other aspects of food safety and to provide recommendations on how to improve the approach to these issues through international and other institutions. Responding to this request was one of the first objectives of the OECD Task Force on Novel Foods and Feeds. Other, longer term objectives of the task force include the development of consensus documents on individual crops species to help foster consensus on the determination of specific components appropriate for the comparison of the novel food to its counter part, and more generally on the safety assessment methods that can be used with novel foods and feeds when the concept of substantial equivalence can not be applied. Consensus documents have been prepared on soybeans and oilseed rape, others are in progress.

The Codex Alimentarius Commission at its 23rd Session in 1999, decided to establish an *Ad Hoc* Intergovernmental Task Force on Foods Derived from Biotechnology to develop standards, guidelines or recommendations, as appropriate, for foods derived from biotechnology or traits introduced into foods by biotechnology. The first meeting of the Task Force was held in Japan in March 2000. FAO and WHO expressed their intention to organise a series of scientific expert consultations to support the work of the Task Force. In June 2000, a Joint FAO/WHO Consultation on Foods Derived from Biotechnology was held in Geneva (WHO, 2000). It addressed the overall safety aspects of foods derived from genetically modified plants and focused on the applicability of substantial equivalence as a general guidance for

scientific risk assessment. It was noted that *substantial equivale*nce was a concept used to identify similarities and differences between the genetically modified food and a comparator with a history of safe food use which subsequently guides the safety assessment process. A consideration of compositional changes was not the sole basis for determining safety. Safety can only be determined when the results of all aspects under comparison are integrated. It was concluded that the concept of *substantial equivalence* was developed as a practical approach to the safety assessment of genetically modified foods. It should be seen as a key step in the safety assessment process although it is not a safety assessment in itself as it does not characterise hazard. Rather it is used to structure the safety assessment of a genetically modified food relative to a conventional counterpart.

The present OECD workshop on the nutritional assessment of novel foods and feeds is intended to build on conclusions reached at the Joint FAO/WHO Expert Consultation on Foods derived from Biotechnology held in June 2000. One fundamental conclusion reached was that 'there were presently no alternative strategies that would provide a better assurance of safety for genetically modified foods than the appropriate use of the concept of substantial equivalence. This conclusion was based on the recognition that whole foods do not lend themselves to the standard safety evaluation principles (WHO 1997) used for additives and other chemicals and that quantitative assessment of risk of individual whole foods from any source cannot be achieved. Assessing the safety relative to existing foods offered the best means of assessing the safety of genetically modified foods.

The 2000 FAO/WHO consultation agreed that some aspects of the steps in the safety assessment process could be refined to keep abreast of developments in genetic modification technology, in particular for the safety and nutritional assessment of genetically modified crops with more complex traits. New methodologies, such as profiling techniques, may offer the means of providing a more detailed analytical comparison. Profiling methods that are being developed for possible use in the safety assessment of genetically modified crops include micro-array technology to obtain comparative gene expression profiles, proteomics that will help to compare the levels of proteins in specific tissues, and metabolic profiling. However, it was recognised that much more developmental work was necessary before such methods could be validated. A brief overview on each of these methods is given below.

Micro-array technology is based on hybridisation of mRNA to a high-density array of immobilised target sequences, each corresponding to a specific gene. The small-scale analysis of expression-levels of a large number of genes allows the comparison of gene expression profiles of the modified organisms and the comparator. Availability of genetic sequences will provide a first lead for further investigations into putative health effects from observed differences. In order to interpret data from profiling analysis it is, however, necessary to establish what types of changes in gene expression patterns naturally occur within crop species, under different cultivation conditions. The generation of a considerable amount of baseline data will be required to develop a better understanding of the natural limits of variation in expression levels before such methods can be routinely used for the safety assessment of genetically modified crops. Furthermore, in the context of the interpretation of such data for risk assessment, it has to be considered that mRNA levels do not necessarily reflect protein levels. Moreover, the rapidly increasing knowledge on plant genomes will provide information on gene insertion sites, which will help to anticipate possible unintended effects due to the gene insertion. In the (near) long-term, site-directed insertion using homologous sequences may reduce the risk of unintended side effects of the genetic modification due to the insertion event.

Another approach uses two dimensional gel electrophoresis methods to study cellular proteins to provide information on the presence of specific proteins and their relative levels. The method also allows isolation of individual proteins for further characterisation. First concepts for protein chip-based approaches are also under development. Major technical hurdles remain to be overcome: proteins may constantly change in their secondary, tertiary and quaternary structures, depending on transfer and

expression in different tissues and cellular compartments, which may profoundly influence their electrophoresis behaviour and molecular mass.

Chemical fingerprinting techniques, including off-line liquid chromatography nuclear magnetic resonance (LC-NMR) are being developed to provide an overview on relative levels of individual compounds in plant matrices. Fingerprints of metabolite levels in the genetically modified organism should primarily be compared with those of (i) isogenic control lines grown side-by-side under identical conditions in one plot and at multiple sites, and (ii) an extended range of commercial varieties of that crop, in order to interpret the biological relevance of any significant difference found between the modified organism and its parental line.

In addition to the need to further develop each individual method, there are a number of overarching issues that will need to be addressed before such methods can be used on a routine basis. These include: standardisation of sample collection, preparation and extraction procedures, standardisation and validation of measurements, and addressing the limited availability of data on profiles and natural variations.

The FAO/WHO consultation held in June 2000 paid particular attention to nutrition related issues. It was noted that the improvement of the general knowledge base between disease and diet was desirable, and that this might be achieved through establishment and use of monitoring systems.

The ability to change nutrient levels in crop plants through plant breeding, including the use of recombinant DNA techniques, has the potential to result in broad changes in at least two ways: (1) the intended modification in plant constituents could change the overall nutrient profile of the plant product and this change could affect nutritional status of the individual; (2) unexpected alterations in nutrients could also affect nutrient profiles of the product and the nutritional status of people. Although the genetically modified plant components may be assessed as safe individually, the impact of the change on the overall nutrient profile must be determined.

It will be important to determine if the overall nutrient profile of a genetically modified food has been changed and if dietary intake patterns are altered by the introduction of foods from genetically modified plants. The introduction of a significant nutritional change in a food may require post-market assessment to determine whether the overall diet has been altered and to what degree, before an assessment of the impact on nutritional status can be made.

Genetically modified foods have the potential to improve the nutritional status of individuals and provide products with enhanced functionality for populations in developed and developing countries. The major issues relate to possible nutritional imbalances and the introduction of unexpected alterations in nutrients and other compounds. The change in nutrient levels in a particular crop plant may impact overall dietary intake. In such cases, it would be important to monitor changes in nutrient levels and bioavailability in such foods and evaluate their potential effect on the nutritional and health status of consumers. However, an assessment of the impact on nutritional status of consumers is important for all significant dietary changes and is not specific to the introduction of genetically modified foods.

SECTION I – FUTURE MODIFICATIONS IN PLANTS AND NUTRITIONAL ASSESSMENT OF DERIVED PLANTS

The workshop considered three papers that addressed potential future developments in plant breeding and the nutritional assessment of such products. The abstracts of the presentations are enclosed in Appendix 1. The workshop considered the types of crops currently under development that could potentially be commercialised in the next ten years. Amongst these crops, many of which are already undergoing field testing, were: corn, soybean, tomato, potato, canola (oilseed rape), rice, wheat, barley, alfalfa, lettuce, flax, coffee, grape, pear, apple, melon, pepper and plum.

Whereas previous products had been aimed mainly at developing improved agronomic traits, the next generation of products could bring direct consumer benefits. Many of these products will involve increasingly complex modifications to plant metabolic pathways. As an example, the workshop heard about the development of 'golden rice'. The development of this crop began with consideration of the metabolic pathway in rice and a how the pathway could be altered to express β carotene in rice endosperm. The synthesis of β carotene in rice endosperm requires the addition of four additional plant enzymes, although a bacterial enzyme can be used in place of two of these enzymes. The appearance of unexpected xanthophylls in some of the early transformed varieties illustrates the importance of scrutinising unexpected effects when assessing the safety of the plants with altered metabolic pathways.

The workshop also considered the nutritional assessment of the next generation of functional foods. In the developed world, nutritional deficiency is now less of an issue. In these countries people are now buying food more on taste or convenience, as a result, diets are sometimes not optimal. This has led to an increasing interest in improving the functionality of foods to enhance health. It was suggested that rather than using a disease-based model of health, the emphasis should be switched towards a 'well-being' based model. However, it was recognised that there is a gap between adequate and optimal nutritional status. Consumers clearly want improved health, but identifying the contribution individual foods make will require the development of global biomarkers. It was also recognised that individual nutrients will not have the same health effect in the entire population, and the effect in individuals will vary with a number of factors, for example, age.

It was suggested that one approach that could be adopted in the future was the application of microarrays to compare the genetic profile of healthy and ill individuals. However, since the real interest is in changes at the phenotype level rather than the genetic level, the use of proteomics and metabolomics should provide more pertinent information. The workshop recognised that these new techniques will require sophisticated data processing technologies. It was noted that the use of more specific and quantitative biomarkers will be at least in the short term, the logical transition to the full nutritional assessment of the impact of a food with altered nutritional properties.

Although the application of new techniques may improve the precision with which nutritional changes can be assessed, it was recognised that many products will potentially be exported to countries where the capacity for analysing data may be less developed.

SECTION II – SINGLE TRAIT VERSUS TOTAL DIET CONSIDERATIONS AND ISSUES RELATED TO NOVEL FEEDS

The workshop considered four papers that addressed the relative merits of assessing single traits versus total diet, post market monitoring and animal feed assessment. The abstracts of the presentations are enclosed in Appendix 1. The workshop recognised that the level of complexity of the nutritional evaluations had increased in recent years although as in other areas the higher the resolution, the greater the heterogeneity of the results. Many factors are now considered, including interactions between nutrients. The spectrum of metabolic efficacy and safety of a nutrient can range from inadequate, through optimal to toxic. However, in many cases the impact of an inappropriate diet can take 30-40 years to manifest itself in terms of health effects. In addition there are many variables that need to be considered. Consumption patterns can vary widely between population groups and between individuals. The dietary composition can also vary with time. As an example levels of selenium are increasing in Finland whereas in the UK they are falling. It was considered that the outcomes of nutritional assessments are generally insensitive and can be biochemically, physiologically or temporarily remote. There is a need for biomarkers, although these are often non-specific and readily confoundable. It was suggested that the total diet consideration should be an integral part of the risk assessment but it needs to be recognised that such an approach has significant resource implications. In this context it was essential to differentiate information that is essential to the safety assessment process from information that would be nice to know.

One approach to the nutritional assessment of novel foods was the use of food consumption patterns. The workshop heard that the cluster analysis of food consumption data in France has identified five or six consumer groups. The health impact of a specific novel food could be very different in each of these groups. Another approach that might have some value is the use of post market monitoring. Such monitoring could be used to confirm intake assumptions made during the original pre-market assessment.

Finally the workshop considered issues associated with animal feeds. The workshop heard that studies with the first generation of GM crops had found no significant differences in composition or efficacy as an animal feed. In some studies the fate of DNA had been studied in considerable detail. Although small fragments of plant DNA had been found in many animal tissues, no rDNA had been detected. The biological significance of such DNA fragments is unclear. When looking at the next generation of crops, it was suggested that a more detailed analysis of key nutrients would be necessary. In addition, there may be some circumstances where feeding studies, looking at performance, health and quality could usefully complement existing safety assessment procedures. Consideration also needs to be given to the issue of by-products used in animal feed, particularly, where the by-products are derived from compositionally altered crops.

SECTION III - DISCUSSION

Several broad themes emerged during the workshop and the four breakout sessions.

Nutritional assessment as a tool in an integrated safety assessment

All novel foods should be subject to a pre-market safety assessment. This should include a nutritional assessment. It was recognised that the tools for the nutritional assessment of novel foods need not be any different to those used for assessing conventionally derived new products in the market place.

It was recognised that the efficiency of absorption and systemic utilisation of a food component is dependent on many dietary variables. The accurate estimation of the efficiency of absorption and systemic utilisation of novel components should be part of the nutritional assessment of any product. Furthermore, existing methods for measuring these aspects are equally appropriate for both conventionally developed and novel food products, although it was recognised that there may be some limitations in the methods currently available.

The elements of nutritional assessment should follow a logical progression through compositional analysis, morphological and physiological analysis in the form of in-vitro tests, animal studies and clinical analysis through human studies. However, not all products need to go through this entire progression, step by step.

Where post market surveillance is considered necessary it could incorporate active elements such as conducting studies of consumption and impact on total diet and passive elements such as consumer questions directed towards company customer careline and sales statistics.

The safety assessment of novel foods or feeds should not attempt to incorporate the validation of potential health claims for the product under consideration. It was also recognised that whilst there was a need for guidance on health claims, this was considered to be outside the remit of the Task Force for the Safety of Novel Foods and Feeds.

It was considered important that the impact of a new product on the total diet be assessed on a case by case basis regardless of whether it is conventionally derived or produced using novel processing. It was considered that there was a need for more work to develop biomarkers that quantitatively assess biochemical and functional intermediates and endpoints, particularly those that reflect changes at the mechanistic level.

The nutritional assessment of novel foods should focus on the whole food and not just the novel component. The assessment should also consider target and at risk groups of the population and recognise population diversity. Foods should be safe for everyone in their intended use, not just target groups.

The implications of cumulative changes in the nutrient profile of conventional crops was seen as an important issue which should be evaluated so that the significance of a large change in nutrients introduced by a single modification could be placed in context.

The challenges in assessing the nutritional value of future products for which compensatory changes are expected to occur in the plant from which the food is sourced

It was considered that the approach to the safety assessment of products with intentionally modified metabolic pathways was fundamentally the same as for the first generation of GM crops. Nevertheless, it was also recognised that the differences relative to its conventional counterpart would be greater and that there was a greater potential for the introduction of unintended effects. Therefore, there is a need to develop that provide greater precision in the identification of unintended effects.

Where a nutritionally altered product is developed, consideration must be given to the nutritional implications of product substitution, particularly where the new product may have significantly altered levels of some nutrients.

Whether there is a need to move to a total diet consideration in contrast to the current approach that focuses at the single food product level

Frameworks have been developed for the premarket assessment of novel foods. Applicants develop data to support the safety and nutritional quality of their novel food. Each food is evaluated on a case by case basis however, the food is eaten as part of a diet which is complex and varied. There is a need to determine the extent to which each novel food impacts on the total diet.

It was agreed that manufacturers of novel foods have a responsibility to assess the impact of their product on total exposure to any bioactive substance contained therein. The methodology is not exclusive to novel foods but is the same as that used in determining exposure to chemicals and nutrients contained in existing foods. To carry out this assessment, it is essential to have validated data on food consumption patterns, nutrient intakes and in some instances, nutritional status. Accurate and up-to-date tables of food composition are also required.

There was a discussion on how beneficial bioactive substances with upper safe levels of intake should be handled. When considering the foods that could contain these, should public health be a consideration so that the greatest benefit is achieved by the most people? There was no consensus on this issue.

Novel products targeted at certain groups should be tested in those groups but since there can be no guarantee that they will only be consumed by the target group these foods should not pose an unacceptable risk to others in the population. If a food is intended for the general population, it should be tested in a group representative of the population. The use of labelling to ensure that the product primarily reaches the target population was discussed. It was pointed out that such label statements should not be in the form of health claims.

The identification of novel livestock feed particularities compared to those of novel foods

The goal of feed safety and efficacy assessment is to produce safe, high quality food products. To date, a combination of compositional analysis and feeding trials have been used in the assessment process. It was noted that while humans generally have a varied diet, animals do not.

There is developing literature on both compositional and animal feeding trials that demonstrates that existing novel feeds are not different in terms of nutrient composition, digestibility and performance (Baltimore Animal Science 2000, Flachowsky et al 2000).

The same tools used to assess these feeds can be used in the assessment of the next generation of novel feeds. In addition, suitable in vitro techniques and/or animal feeding trials to evaluate specific traits may be indicated on a case-by-case basis.

The same concerns regarding unintended effects in novel foods apply to novel feeds. Nutritional assessment including possible use of an agreed bioassay (with rapidly growing species) and livestock feeding trials, may be used as an indicator of unintended effects on a case-by-case basis.

Novel feeds in development may include:

- those with traits to enhance animal production efficiency, e.g., low phytate plants,
- by-products of plants altered to serve a food purpose,
- by-products of non-food plants for industrial purposes.

Safety and nutritional assessment of each of these feeds presents different challenges. The assessment of the next generation of genetically modified plants should be built upon the core characterisation of the modification.

The workshop was aware that a number of studies investigating possible transfer of genetic material from animal feed had been completed and that further studies were on going. All of these studies had demonstrated the absence of novel DNA or protein fragments in food products obtained from animals.

SECTION IV - CONCLUSIONS AND RECOMMENDATIONS

The workshop concluded that the nutritional assessment of novel foods and feeds should be seen as an integral part of the safety assessment process.

The Workshop noted the conclusions from the recent Joint FAO/WHO Expert Consultation on Foods Derived from Biotechnology. It was agreed that the appropriate use of the concept of substantial equivalence, that is, as a comparative approach focussing on the determination of similarities and differences between the modified food and its conventional counterpart, provided a robust tool for the safety assessment of existing GM products. However, some aspects of the steps in safety assessment process could be refined to keep abreast of products being developed by genetic modification technology.

Substantial equivalence was seen as a starting point, not an end point, in the assessment process. It is still a valid tool for assessing novel foods and feeds with nutritionally modified characteristics, since the recipient species provides a baseline for a safety assessment, which is still relevant with the new generation of modifications.

The nutritional implications of the novel product need to be assessed, and this should take into account the total diet of the intended market segment. The contribution to the total diet of many novel products may be minimal. However, there may be a need for new method development. In particular it was recommended that techniques such as the use of micro-arrays, proteomics and metabolomics could potentially enhance current nutritional assessment approaches. It was recommended that further research effort should be directed to developing and validating these methods. The assessment should be the same for novel and conventionally derived foods.

The workshop welcomed the fact that the Codex Committee on Food Labelling and the Codex Committee on Nutrition and Foods for Special Dietary Uses are developing definitions, conditions for use and scientific criteria for the validation of health claims.

There was a need for better methods to measure food consumption patterns and usual intakes of populations. There was also a need for further research to identify the mechanisms' underlying differences in bioavailability of nutrients within conventional and novel foods.

There was a need for methods including biomarkers to determine nutritional status of populations and to validate food consumption data. It was recommended that the OECD Secretariat should be invited to develop a questionnaire to establish what biomarkers are already under development in member countries.

There was a need to update and expand food composition tables and to include information on non-nutrient bioactive food components such as carotenoids, flavonoids, and sterols. There was also a need to take into account existing databases on toxins and anti nutrients.

As part of the premarket assessment, the applicant should generate sufficient data to estimate the total exposure to the novel food and its active principle(s). The methodology could be the same as that used to estimate exposure to any substance in foods, such as food additives, agricultural chemicals etc.

When generating data the applicant should identify the intended uses of the food and the anticipated impact on the diet in terms of the contribution of key nutrients and other bioactive substances when used at expected levels of consumption.

Novel products targeted to a specific group of the population should be tested in that group. Products intended for consumption by the general population should be tested in a sample representative of the general population.

Novel products intended for use by a specific population subgroup should not pose an unacceptable risk to the rest of the population.

Label statements could be used as a risk management tool to direct the food to the target population however, such an approach may not be appropriate if consumption would put non-target groups at an unacceptable risk. These statements should not be in the form of health claims.

Postmarket surveillance should not be required on a routine basis. However, it should be required for example when there are issues related to consumption by general or target populations, concerns about displacement of other foods, or concerns about exceeding upper safe levels of intake of the bioactive constituent.

Compositional analysis of key nutrients, antinutrients and toxicants is an important element of the safety assessment process – as important for animal feeds as human foods. The workshop supported the development of OECD Consensus Documents on commodities and emphasised the importance of including data on by-products. Within the consensus documents, consideration should be given to inclusion of data on the use of commodity feedstuffs in aquaculture.

In the case of nutritionally modified crops and their by-products, feeding trials with all categories of target animals would not be required as part of the safety assessment process. Feeding studies with an appropriate representative fast growing species should be sufficient to detect unexpected effects not captured by compositional analysis.

To support a claim for an enhanced feed trait would require testing in the appropriate animal species or categories.

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APPENDIX I - ABSTRACTS OF PRESENTATIONS

KEYNOTE PRESENTATION

PANEL 1

PANEL 2

RECENT INTERNATIONAL DEVELOPMENTS IN ASSESSING SAFETY AND NUTRITIONAL ADEQUACY OF NOVEL FOODS AND FEEDS

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Safety Assessment of Genetically Modified Foods

Scientific principles for the safety evaluation of foods and food components obtained by modern biotechnology developed by OECD and FAO/WHO are widely accepted as appropriate regulatory assessment systems (1-5). The safety of these new foods can be determined by comparing the properties of these foods with those of analogous conventional foods, which are assumed to be safe based on long-term experience (concept of *Substantial Equivalence*). The concept of Substantial Equivalence is a *guiding* tool to identify similarities and differences, which should be subject of further toxicological or nutritional investigation. The concept is only applicable in case of the existence of a conventional counterpart, and does not provide an absolute safety warrant for the new product. In fact knowledge of the actual safety of our daily consumed foods is still limited. Application of the concept of Substantial Equivalence has worked well for the *first generation* of products with improved agronomic properties, obtained by insertion of a relatively small number of genes, and for which a suitable counterpart could be identified.

The Concept of Substantial Equivalence has been criticised, as being a poorly defined principle, primarily focussed on the chemical analysis of the new food (6). However, a toxicological and nutritional assessment of newly expressed products and of the modified food is an integral part of the assessment procedure. Data on these aspects may however not always be available in the public domain. Issues of further consideration are: (i) suitability of the comparator, (ii) detection possibilities for unpredictable changes in metabolic pathways of organisms as a result of the genetic modification (unintended effects), (iii) natural variations in levels of key nutrients and toxins, (iv) acceptable degrees of differences in composition between the modified and non-modified food from the health point of view, and (v) uniformly applied protocols for the assessment of substantial equivalence.

These issues are addressed by the OECD Task Force for Novel Foods and Feeds, which is involved in the process of preparing Consensus Documents for food crops, covering agronomical, phenotypic and compositional characteristics (7).

Present approaches for the detection of the unintended effects are based on single compound analysis. Such methods have their limitations with respect to unknown antinutrients and natural toxins, especially in less well known crops. In order to increase the probability to detect unintended effects alternative *profiling* methods are under development, which allow for the screening of potential changes in the metabolism of genetically modified organisms at different integration levels, i.e., at the genome, at protein expression and at the formation of primary nutrients and secondary metabolites (8).

Assessment of novel foods and feeds with enhanced nutritional properties

A major issue has been raised by the OECD Task Force for the Safety of Novel Foods and Feeds, and by the FAO/WHO Expert Consultation held in June 2000, i.e. the need for the development of

strategies for the safety and nutritional assessment of the *next generation* of genetically modified foods with specific agronomical applications, or with improved functional or health characteristics (9, 5). Examples of the latter category are genetically modified rice containing β-carotene ("golden rice"), food crops containing oils with altered fatty acid profiles, and many other products in the pipeline (10). Many of the new traits in these food products are controlled by insertion of multiple genes, and therefore suitable traditional counterparts may not be available.

The assessment of this type of new food should be focussed on the *simultaneous* characterisation of inherent toxicological risks and nutritional benefits. This requires a *coherent and multidisciplinary* approach, incorporating molecular biology, toxicology, nutrition and genetics. Important issues to be addressed are: (i) scientific evidence for nutritional/health claims, (ii) beneficial and toxicological dose-ranges of selected compounds, (iii) target population(s), (iv) impact on overall dietary intake and on the nutritional status of consumers, (v) nutrient-gene interactions and polymorphism, (vi) interactions between food constituents and food matrix effects, and (vii) possibilities for effective post-market surveillance.

The introduction of quality traits in animal feeding products, for instance increased lysine content, may introduce specific considerations for safety assessment. Safety evaluation of this type of feed must take into account any risks for the animals consuming the feed and any indirect risks to the consumer of animal derived products.

In general, knowledge of working mechanisms of bioactive compounds with presumed enhanced nutritional or health improving/protecting effects is still fragmentary. Classical toxicological, nutritional and kinetic studies may answer some of the questions related to safety and nutritional margins, in parallel with animal feeding trials with whole foods/feeds, taking however the limitations of these types of studies into account. But new innovative techniques like the DNA micro-array technology and proteomics are needed in order to characterise the complex interactions of bioactive food components at the molecular-cellular level. Large-scale screening of the *simultaneous* expression of a large number of genes and of synthesised proteins will provide relevant information concerning the complex relationships between human/animal exposure to bioactive food constituents and their specific effects (11, 12). Moreover insight can be gained in individual variabilities in biological responses (polymorphism), as well as in food-matrix oriented interactions. This type of information is a prerequisite before such foods should be allowed on the market.

This workshop has the challenging task to design integrated *risk/ benefit* assessment paradigms and specific test requirements for new foods and animal feeds with enhanced nutritional or health improving/protecting properties.

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THE PIPELINE FOR FUTURE AGRICULTURAL PRODUCTS

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Historical features of GM crops

The first wave of GM crops, the ones on the market now in the USA, Canada and a few other countries, were geared primarily to agronomic production. These include herbicide resistance (to provide alternative forms of weed control for farmers) and insect resistance (to provide alternative forms of insect pest control for farmers). As such, the GM varieties benefit primarily the originating institutions and, to a lesser extent, the farmers growing the new crops.

Consumers appear to gain little from these products, yet are being asked to assume an uncertain or at least undetermined degree of risk. Naturally, consumers are reluctant to assume any risk for which there is no apparent compensating benefit. The industry response has been to develop products for which there is clear and direct consumer benefit (the ecological and health benefit *via* the reduction in agrichemical usage with certain herbicide tolerant GM crops is neither clear nor directly evident to most consumers). The newer GM products under development and in testing include a substantial number of nutritionally enhanced or fortified foods and feeds, many of which are designed to appeal directly to consumers.

New products in the pipeline

As of November 2000, in the US alone, there were1372 field trial permits or notifications for environmental releases of GM plants with altered quality characteristics (typically those with nutritional implications and consumer appeal). The EU has fewer total environmental releases (1649 as of September 2000), but the trend in Europe toward GM plants with modified quality aspects is just as clear.

As well as an obvious shift to nutritional traits, there is a considerable increase in the number of species being tested. The early GM products in commercial production were primarily in major field crops such as corn, soybean, and canola. While those species still dominate, other major food species like wheat and rice, as well as lesser species, ranging from apples to lettuce, have been subject to genetic modification and modified lines are now undergoing environmental release trials.

Equally evident is the increase in institutions involved in developing and field testing GMOs. The big multinationals are still dominant, but many smaller companies, universities and government agriculture institutes have produced and are testing nutritionally modified GMOs.

The new scientific fields of genomics and proteomics will have a major impact on the rate and range of new food GMOs. The complete genome of a higher plant, *Arabidopsis*, has now been elucidated. Substantial progress in the genomic analysis of a major food crop, rice, is also evident. The completion of the human genome project will also impact significantly on plants. These developments allow the rapid characterisation and cloning of nutritionally useful genes for transfer to deficient food and feed species. It also facilitates the characterisation of similar genes from a range of species. Homology permits scientists to choose the species from which to isolate a particular gene for a desired function. This allows the circumvention of requiring genes to be taken from cultural or ethically ‘sensitive’ species, such as humans, swine or pathogenic organisms.

The increase in these parameters means effective regulatory oversight must accommodate and account for increasing numbers of clients, applications, species and trait complexity.

Context: GM vs. conventional breeding technology

The objectives of increased nutritional composition of foods and feeds have existed for years. Plants, animals and microbes have been genetically modified (in the scientific, if not the regulatory sense) over thousands of years to increase not only production, but also nutritional value. More recent conventional breeding methods like induced mutagenesis, including ionising irradiation, has given the world hundreds of new cultivars, many with nutritional improvements. 'Conventional' mutation breeding has given us, for example, corn with an enriched amino acid profile. Such cultivars are not scrutinised as GMOs, even though the genetic changes are not as well characterised as those in GM corn with a similar phenotype.

As well, most of our most common food crops naturally carry at least some antinutritional chemicals, remnants of prehistoric life in the wild where such compounds often provided a protective advantage. These potentially hazardous chemicals, for example alkaloids in potatoes or tomatoes, occasionally appear in modern cultivars from conventional breeding.

In spite of the genetic uncertainties of conventional breeding, and the occasional atavistic regression churning out excessive quantities of nasty (but natural) chemicals, the existing regulatory system seems effective at identifying and eliminating these rogue cultivars before they do any real damage.

Conclusion

No one, whether from industry or government, is interested in releasing a potentially harmful product. Our common and collective responsibility to society is to effectively identify and eliminate hazardous foods and feeds, regardless of the method used to create them. While it is not possible to guarantee absolute safety of any product, we must be able to provide reasonable assurance that new foods and feeds are at least as safe as those currently seen as safe. This is as true for products of conventional breeding as it is for GM products.

As we consider and evaluate nutritionally enhanced GM foods, can we learn from our experience and history with products of conventional breeding? Is there a hazard threat differential between a food modified using conventional breeding vs. the same trait developed using GM techniques? If so, let's identify and regulate it accordingly. If not, regulatory prudence dictates that we concentrate our efforts on the product and not on the method of breeding.

GOLDEN RICE: ENGINEERING THE ß-CAROTENE BIOSYNTHETIC PATHWAY INTO RICE ENDOSPERM

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Rice (*Oryza sativa*), a major staple food, is usually milled to remove the oil-rich aleurone layer that turns rancid upon storage, especially in tropical areas. The remaining edible part of rice grains, the endosperm, lacks several essential nutrients, such as provitamin A (ß-carotene).

Vitamin A deficiency causes symptoms ranging from night blindness to those of xerophthalmia. In Southeast Asia, it is estimated that a quarter of a million children go blind each year because of this nutritional deficiency. Furthermore, vitamin A deficiency exacerbates afflictions such as diarrhea, respiratory diseases, and childhood diseases such as measles, causing 1 to 2 million deaths annually among children. In an approach to overcome this problem, we carried out work to introduce provitamin A-biosynthesis into rice endosperm by genetic engineering.

The synthesis of ß-carotene in rice endosperm requires the complementation with four additional plant enzymes: phytoene synthase (PSY), phytoene desaturase (PDS), zeta-carotene desaturase (ZDS) and lycopene ß-cyclase (ß-LCY). To reduce the transformation effort, a bacterial carotene desaturase (CrtI) which can substitute the two plant desaturases, can be used.

cDNAs from *Narcissus pseudonarcissus* coding for the carotenogenic enzymes PSY and ß-LCY, both placed under the control of the rice endosperm specific glutelin (Gt1)-promoter, as well as a bacterial (*Erwinia*) gene, coding for CrtI under 35S promoter control, were introduced into rice plants (TP 309) by using *Agrobacterium*-mediated transformation. We obtained T_0 seeds exhibiting a clearly visible yellow colour, due to the carotenoid accumulation. Among these, provitamin A (ß-carotene) was predominant, followed by the xanthophylls lutein and zeaxanthin, as revealed by HPLC analyses. This resulted in a carotenoid complement that is qualitatively not dissimilar to the one observed in green leaves. To have the full carotenoid pattern, including provitamin A and the xanthophylls, may be nutritionally more advantageous, considering the role of zeaxanthin and lutein in preventing the eye's macula degeneration. The appearance of the xanthophylls (and of ß-carotene in some of the experiments) was unexpected, since our transformation did not comprise the corresponding hydroxylase (lycopene ß-cyclase). Our preliminary evidence suggests that later enzymes in the carotenoid biosynthesis pathway are induced by products derived from the transformation. The results obtained will be discussed and details will be given.

NUTRITIONAL ASSESSMENT FOR THE NEXT GENERATION OF FUNCTIONAL FOODS

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Food represents one of life's great delights, simultaneously stimulating, exciting, comforting, reassuring and rewarding virtually every sensation. Furthermore, the luxurious food marketplace has increasingly provided consumers with another, more philosophical allure, free choice -the opportunity to choose the foods they want to eat when they want them. For nutrition to compete for consumer choice in this environment of immediate, personal gratification, it must do better than promise possible reductions in the risk of distant diseases for generalized segments of the population.

For many decades, clinical scientists have used biochemical markers that reflect disease states and their reversal. Increasingly, scientists have searched for similar markers that predict the risk of diseases. In nutrition especially, the search has been to identify markers that reflect the nutritionally responsive aspects of health and preventing disease. However, unlike diseases, which in many cases can be ascribed to a single defect or dysfunction, optimal health is the success of a myriad of aspects of metabolism and is reflected in many metabolites, not just one biomarker. To accurately predict or reflect health and especially its improvement through foods, assessment techniques must expand in three dimensions: analyze individuals rather than populations, accurately measure metabolism systematically rather than single bio-markers, and analyze repeatedly the entire response to diet rather than take a single snapshot in the fasted state. Recent advances in analytic chemistry, microelectronic engineering and bioinformatics have developed a host of new technologies that could address such a challenge.

Capabilities will emerge from these new analytic approaches that were not conceivable five years ago. These include: Highly parallel bioassays, separation times fast enough to approach real-time sensors, and data capture and analyses that constitute such broad and comprehensive analysis of the system variables that they approach a global description of the biological response. The next generation of bio-analysis promises more than just faster and cheaper data. Limits to the availability and processing of information will change dramatically. The resulting increase in information will profoundly extend investigative powers in both breadth and time. In breadth, nutritionally relevant data will encompass all of metabolism, and in time will approach continuous monitoring.

The future role of foods and nutrition in health and preventive medicine will depend on the ability to analyze as a function of time the myriad metabolic responses of an individual to the food or nutrient. Only then will it be possible to understand the relation between nutrient intakes and metabolism. For example, it is the variation of an individual's metabolism in response to food consumption that will predict most of the nutritional effects on the risk of chronic and degenerative diseases in that individual. Current availability of analyses for fatty acids, amino acids, glycolytic intermediates and proteins provides clear evidence of feasibility. It is now necessary to mobilize the appropriate industrial and academic partners to such an enterprise.

SINGLE TRAIT VERSUS TOTAL DIETARY CONSIDERATIONS OF THE IMPACT OF NOVEL FOODS AND FEEDS FROM A NUTRITIONAL PERSPECTIVE

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The decision trees for the evaluation of novel foods, and related guidelines appreciate the difficulty of the assessment of novel foods and ingredients in the context of the whole diet, either before or after they are placed on the market. They appreciate that "alternative approaches for the testing assessment of the wholesomeness of foods and major food ingredients are needed, and the ultimate strategy for combined nutritional-toxicological testing will extend from initial tests (in vitro and in vivo) in animal models to studies in humans, if needed". Despite this awareness that there is a need to consider the impact of a novel food or modification in the context of the "normal" consumption pattern of the food, no specific approach or solution to this issue has evolved.

The systematic safety and nutritional evaluation of a novel trait involves a well-defined or explicitly modified protocol for toxicological safety, and, if they are needed, hypothesis generated studies to evaluate further potential toxicity or desired functional and metabolic outcomes. These studies are conducted with a well-characterised controlled diet and with an equally rigorous control of known potential confounders. This approach would be needed to provide the basis of any claim, which might be made for the product. The product would have been assessed in a dietary context, but in a very limited dietary context. Opportunities have been taken to test some novel foods and ingredients in free-living individuals, but systematic evaluation against a defined diversity of diets has not been pursued.

In the total diet context, consideration must be given to the composition, and in some instances the stability of that composition, of the diet. Compositional analysis can, as well as informing decisions on substantial equivalence, help determine what, if any, further studies of metabolic efficacy and safety are needed.

The introduction of novel products and their use in diverse diets should also be considered in the context of human variability (metabolic maturation, growth, gender, lifestyle, and genetic variability affecting primary and secondary metabolites).

Novel modifications and ingredients offer many opportunities to affect the bioavailability and metabolism both of the novel ingredient and of other substrates. Some of these are conjectural, others have been demonstrated. Total diet considerations include the composition of the background diet, and the impact of other dietary components, and of the dietary matrix, on the digestion, intestinal absorption, systemic utilisation or deposition, metabolism and excretion of a novel ingredient and on substrate metabolism in general.

Thus broader considerations than a single trait would indicate the risk of impaired efficacy. Whereas one would not expect anyone to develop a "Futile Food" in which two or more novel modifications negate the effects of each other, it is possible that consumers will select a "Futile Diet". Just as important is the possibility that in the context of the adequacy, or otherwise, of the total diet, nutritional adequacy or safety might be compromised.

Whereas classic screening would demonstrate acute unintended outcomes, processes to look for unintended outcomes from chronic and cumulative exposure and use need to be developed based on informed insight. Customary outcomes for systemic evaluations of these issues are in general insensitive

and non-specific, and this limits the ability to evaluate novel foods in a general context. Interest exists in generating better markers for the nutritional efficacy and safety assessment of food components, which could be used in the free living and total dietary context.

However, these would still be demanding on resources. It would not seem possible to produce a generic definitive guideline for such approaches and their use would need to be determined in specific and strategic contexts. The overall process would require informed risk assessments of the potential hazards, but screening protocols could be devised for evidence of early adverse events, which could arise from novel components and modifications to foods. These would be complementary to processes being considered in post market surveillance.

POST MARKET MONITORING OF NOVEL FOODS (AND FEEDS)

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An important objective of the so-called Novel Food Regulation (Regulation (EC) N° 258/97 of the European Parliament and of the Council of 27 January 1997 concerning novel foods and novel food ingredients) is, in order to protect public health, to ensure that novel foods and novel food ingredients are subject to a **safety assessment before** they are placed on the market within the Community. That means that the risk management should be based on a system that is as comprehensive as possible.

In its report[1] of 17 May 2000 the OECD Task Force for the Safety of Novel Foods and Feeds noted that "to protect the consumer and animal health, it is accepted that novel foods and feeds should be **fully assessed** before being placed on the market. If the assessment identifies safety concerns, the product will not be approved for commercial use. Some member countries, therefore see no justification for the use of post market surveillance."

On the other hand, post market surveillance is a commonly used tool, for example, in the risk management of pharmaceuticals. Also, in many areas, industry is using, frequently, post launch monitoring programmes to judge the success of their products. Such activities certainly provide additional data. However, the relevance, quality and reliability of such data depends very much on the initial question and the available methods to collect and evaluate such data.

The FAO/WHO[2] expert consultation on the safety aspects of genetically modified foods advised that "monitoring to establish links between diet and disease is desirable. However, many chronic health effects are multi-factorial and it was recognised that observational epidemiological studies would be unlikely to identify any such effects against a background of undesirable effects of conventional foods. Experimental studies, such as randomised controlled trials (RCTs), if properly designed and conducted, could be used to investigate the medium/long term effects of any foods, including genetically modified foods. Such studies could provide additional evidence for human safety, but would be difficult to conduct. In this respect, it is also important to recognise the wide variation in diets from day to day and year to year."

The question to be addressed is, whether and how post market monitoring could be used in risk management of novel foods (and feeds)? In particular, whether post market monitoring could be useful for the assessment and management of long term and unintended effects of foods derived from genetically modified organisms?

For example in the United Kingdom, the Advisory Committee for Novel Foods and Processes (ACNFP) has been looking at the feasibility of monitoring novel foods after they have reached the market, in order to provide additional reassurance to consumers on the safety of such foods. Following a number of meetings involving various organisations (like major supermarkets, Greenpeace and the Consumers'

1. *Report of the OECD Task Force for the Safety of Novel Foods and Feeds*, C(2000)86/ADD1 of 17, May 2000

2. *Safety aspects of genetically modified foods of plant origin*, report of a joint WHO/FAO Expert Consultation on Foods Derived from Biotechnology, 29 May – 2 June 2000

Association), the initial conclusion was that it was essential to test the robustness of data collection procedures.

It appears that there is some consensus that post market surveillance will give rise to new data and knowledge. However, there are severe doubts whether the questions and methods for collection of the relevant data are available. Moreover, even if there is a question concerning the safety of a novel food, in particular a food or food ingredient that consists of, or contains, or is derived from, a genetically modified organism, in general, it has to be asked, whether an answer could be found prior to the introduction of that novel food.

As stated earlier the objective of the authorisation procedure for novel foods and novel food ingredients was to ensure that only safe products would be placed on the market. Of course, it is not possible to guarantee absolute safety forever. Therefore, such regulations must have a safeguard clause and we should consider appropriate complementary measures like post market surveillance to ensure proper risk management.

Thus, risk management may include post market monitoring for example in order to:

- Achieve more detailed knowledge about possible occurrence, impact and significance of potential human health effects identified during the risk assessment;
- Monitor changes in nutrient levels, associated with the introduction of foods likely to have a significant impact on the nutritional status;
- Facilitate the evaluation of their effect on human nutritional status;
- Some hope that the post market surveillance might also contribute to identifying the possible occurrence of adverse effects of genetically modified foods or food ingredients on human health, which were not anticipated in the risk assessment.

Whether post market surveillance is the appropriate complement to an authorisation of a novel food or novel food ingredient can only be decided on a case-by-case basis. Every time, it is necessary to ensure that the appropriate procedures for data collection are available and that these data are useful and sufficient to answer the open questions. If safety questions can not be answered sufficiently in the risk assessment, the risk managers would have to make a balanced decision. In cases of severe doubts, the authorisation of a novel food has to be refused or if the right means are available and it can be justified in the light of the anticipated risk, a complementary obligation like post market surveillance could be used in the risk management.

NUTRITIONAL ASSESSMENT OF NOVEL FOODS: FOOD CONSUMPTION PATTERNS IN A NATIONWIDE REPRESENTATIVE POPULATION AS A TOOL IN NUTRITIONAL RISK ASSESSMENT

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Nutritional assessment must examine both sides of food constituent intakes, risks linked to insufficient intake and linked to excessive intake. As far as a food, novel or not, it is not the single source of a constituent in the diet, cumulative intakes from the various sources must be taken into account to ensure global risk assessment. Therefore, nutritional assessment must examine intrinsic properties of the food, as well as the possible global result of the insertion of the food in the total food pattern of a population. It could be useful that such methodology would be applied very early in the development process of the novel food. In this global approach, many difficulties are encountered, due to the definition of the nature of risks to be analysed, the determination of safety limits determined for the constituents and the paucity of data in some cases on the amounts provided by other sources.

- the nature of risks : acute or short-term risks can be easily assessed by classical methodologies of toxicology. However, consumer risk perception actually takes into account long-term risks so that traditional consideration of cancer development cannot be the unique endpoint to be considered. Cardiovascular disease, endocrine disruption, immunological modulation and cognitive impairment are also endpoints to which many people are aware. In this way, some studies (such as CARET or ATBC) underlined that high, though toxicologically safe, dosages of nutrients can induce deleterious effects at the population level which could not be predicted.
- many national or international organisms around the world have developed sets of safety limits for human consumption concerning some essential nutrients. Examining reported adverse effects, they have determined either LOAEL or NOAEL, then, by using empirical safety factors to take into account human diversity and long-term consumption, they have derived limits for consumption. These limits are used as reference values in the interpretation of methodologies described below.
- the huge developments in technological processes dramatically increases the sources of (possibly concentrated) interesting nutrients: improvements in industrial food technologies (sometimes with sophisticated procedures such as high pressure or active packings) enhances the actual amount of essential or interesting nutrients in traditional foods; on a longer time basis, plant or animal selection by classical methods (and obviously use of GMO), as well as improvements in agricultural practices lead to the same results. Food fortification and dietary supplements are the most visible concentrated sources. Functional products (foods or ingredients) are now a new way to classify many of these products, based on physiologically driven concepts, rather than on intrinsic chemical composition. All these paths of human nutrition improvement can be considered as equally legitimate. Besides essential nutrients such as vitamins and minerals, there is actual focus on many non-nutritive constituents with potential health benefits, for which dietary intakes from traditional foods is poorly known. Therefore, long-term consequences of these new constituents are generally not assessed in most of epidemiological studies.

Keeping in mind these limitations, the safety assessment of novel foods can use nation-wide representative individual consumption data, using methodological tools for which there is still a large place for improvements. The recent use in France of Monte-Carlo simulations and cluster analysis with representative data will be briefly described.

Monte-Carlo simulations are becoming a routine tool in the risk assessment of chemicals in toxicology. They can also be used for nutrients. Using this method, it is possible to calculate the distribution of total intake of a given nutrient in the population, assuming different hypotheses concerning either the amounts of the nutrient added to foods, the type of foods to which the nutrient has been added, or the fraction of the market covered by this food. For example, extreme hypothesis can be 100 % of the market, which considers that some people would systematically look at and eat this type of foods. A more realistic hypothesis for vitamin enriched food (for example) can use the percentage of the market actually taken by this type of food in a country: in this hypothesis, we also used random construction of this percentage among different foods and random attribution to eating occasions. The interest of such approaches is the consideration of extreme consumers, which is particularly important for safety assessment. The quality of data on extreme consumers largely depends on the duration of dietary records and the number of people included in the survey. However, it is possible to modelize the patterns of long-term extreme consumers on the basis of data from extreme consumers on a given day. Monte-Carlo simulation has been recently used in France either by industry (to propose amounts of fructooligosaccharides that could be added in various foods without any risk) or Public authorities (to determine the safe level of vitamin D to be added in milk products).

However, such simulations cannot take into account behaviour modifications which could be induced by health claims supported by the new products (obviously, many nutritionally modified novel foods are conceived to support claims and gain increased parts of the market). Pre-market analysis could be completed by post-market analysis, using purchase data from household surveys that are currently performed in many countries for industrial uses and are also used by nutrition scientists. These data allow for verification of the coherence and validity of the hypotheses that have been retained for the pre-market analysis.

Whatever refinements of these methodologies may be, they suffer from the limitation of considering the whole population, thus assuming that everybody has the same basal risk. The study of food patterns, and modelization on food patterns, could give more precise data. Using statistical techniques such as principal component analysis, coupled with cluster analysis, it is possible to separate groups within a population, only on the basis of their consumption of some categories of foods. In France, 44 food categories were used leading to the identification of five or six consumer groups (according to the database used). The groups are *a posteriori* also characterised by age, gender, and socio-economic status. For example, in the French population, we identify “diversified small eaters”, “hurried small eaters” and “monotonous big eaters”. For nutrient intakes, these groups are also characterised by nutrient adequacy or inadequacy, as compared to RDA (recommended daily allowance), obesity prevalence and very different theoretical health risks for degenerative diseases. The health impact (beneficial or deleterious) of a novel food could be clearly different in these groups, due to the differences in initial risk or to associations with other nutritional or lifestyle factors. The future use of biological markers could improve such analyses. However, a large part of the progress will rely on international comparisons with harmonised methodologies to develop eco-epidemiology and gain a better knowledge in the links of long-term nutrition to long-term health. Such efforts are currently done at the European level (Efcosum and Dafne programs).

Finally, in these studies, the principal limitations may arise not from food composition tables, lack of biomarkers or statistical techniques, but, overall, from a conceptual limitation of the human mind to embrace complex multifactorial processes. In this way, periodic dietary and health surveys are necessary not only to allow better pre-market assessment but also to identify new problems.

ROLE OF NUTRITIONAL ASSESSMENT OF GMO IN FEED SAFETY ASSESSMENT

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Introduction

In addition to feed safety assessment including safety for consumers, animals and environment, nutritional assessment of feeds produced using recombinant DNA techniques is necessary. Therefore, we need effective systems to assess GMO's from the nutritional point for animals. The assessment system should be cheap and reliable; the results must be representative and acceptable.

Proposal for nutritional assessment

From the nutritional point of assessment we have to distinguish in GMO's of the 1st and the 2nd generation:

1stGeneration: Feed plants are characterised by changed tolerance or resistance to insects, herbicides, pesticides or other influencing factors with minor changes in nutrient content (e.g. Bt-corn, Pat-corn, Gt- soybeans etc.)

2ndGeneration: Feeds are characterised by substantial changes in the content of valuable or undesirable major (e.g. protein, amino acids, fat, fatty acids, starch, sugar, lignin) or minor ingredients (e.g. vitamins, minerals, enzymes, anti-nutritive ingredients).

In the case of GMO's of the first generation we do not have to expect significant changes in nutritional value because of the substantial equivalence between isogenic and transgenic plants, but we need some experiments for acceptance of GMO's in the society.

A complex nutritional assessment seems to be necessary with the second generation of GMOs. Table 1 shows a proposal to assess GMO's of the 1st and 2nd generations from the view of animal nutrition. Furthermore, the same recombinant DNA construct should not be nutritional assessed in each plant, but only in the most important feed plants. In vitro studies could be favourable for plants of lower significance, but with the same recombinant DNA. Experimental conditions (species, category and number of animals per group, duration of feeding, diet composition etc.) should be discussed and proposed from expert groups.

A combination of nutritional and safety assessment in animal experiments is recommended.

Table 1: Proposal for nutritional assessment of GMO's

Parameters	GMO of 1st Generation	GMO of 2nd Generation
– Determination of important ingredients		
• Crude nutrients	+	++
• Nutrient content modified (e.g. amino acids, fatty acids, minerals, vitamins, enzymes etc.)	–	++[2)]
• Undesirable ingredients modified (e.g. plant ingredients as lignin, inhibitors, glucosides etc.; or secondary substances as mycotoxins, pesticides etc.)	(+)	++[2)]
– Digestibility, Balance studies, Availability of modified nutrients in target animal species	(+)	++
– In vitro studies to assess nutritional value	(+)	(+)
– Long term feeding experiments with target animal species/categories		
• Animal performances and quality of foods of animal origin	(+)	++
• Animal health, welfare	(+)	++
• Fate of modified protein and/or DNA[1)]	(+)	(+)

– not necessary + recommendable [1)]for scientific reasons
(+) could be favourable ++ necessary [2)]for modified ingredient/s

Experiments at our Institute

In 1997, at our institute, we started with the nutritional assessment of GMO's of the first generation. Composition of feeds, digestibility, feeding experiments, animal health and performance, quality of foods of animal origin and fate of DNA were included in our studies (Table 2). Recently some results were presented (Flachowsky et al. 2000).

Up to now we did not find significant differences between feeds from isogenic or transgenic plants of the first generation. The so-called substantial equivalence could be demonstrated. Therefore only limited measurements are recommended for nutritional assessments of GMO's of the first generation (Table 1).

The concept of substantial equivalence is unrealistic for GMO's of the second generation, where substantial changes are aimed at composition and nutritive value. Nutritional assessment of GMO's of 2nd generation could follow the proposal given in Table 1.

Rules for nutritional assessment of genetically modified feeds should be discussed and proposed by special groups.

Table 2: Investigations using GMO's of the first generation which have been carried out at the Institute of Animal Nutrition of the FAL Braunschweig, Germany (always compared with parental hybrids)

Investigation	**Bt-corn seeds silage**	**Pat-corn seeds silage**	**Pat-sugar beets beets leaf silage**	**Gt-soybeans Full fat beans**
Ingredients				
Crude nutrients	x x	x x	x x	x
Amino acids	x -	x -	- -	x
Fatty acids	x -	x -	x -	-
Minerals	x -	x -	x -	x
Fibre fractions	x -	x -	- -	x
Mycotoxins	x -	- -	- -	-
Animal experiments				
Poultry				
Broiler	B/F[2)] -	- -	- -	-
Layers	B/F[2)] -	B/F -	- -	-
Pigs	B/F[1)2)] -	B/F -	B/F -	F[1)2)]
Ruminants				
Sheep	- B	- B	- B	-
Growing bulls	- F[2)]	- -	- -	-
Dairy cows	- B[2)]	- -	- -	-

x: Measurements, -: No data
B: Digestion or Balance studies
F: Feeding trials with performance registration
[1)]not yet finished
[2)]including studies of the fate of DNA (Einspanier et al. 2001)

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