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Biosafety of Foods Derived by Modern Biotechnology

Proceedings
Basel Forum on Biosafety
18 October 1994

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Basel Forum - Biosafety of foods derived by modern biotechnology

Intention and key issues

The current public debate on risks and benefits of genetically modified food is characterized by a contradictory perception of the impact on human health and the environment. Different levels of understanding of biological mechanisms and an insufficient diffusion of knowledge on the current state of research in safety assessment of genetically modified products might be responsible for the present situation in communication of biotechnology issues.
By offering a **public information platform** to experts working on the safety assessment of genetically modified food the **Basel Forum** would like to meet the need for a **more intensive transfer of "first hand" information**. Current efforts in the safety assessment of foods derived by modern biotechnology are considered in order to response to safety concerns of the public with available scientific data. Potential risks to human health will be the focus of the meeting. The topics will be reviewed by international experts.

The following topics are considered:

(1) A review of the history of genetic modification of agricultural products.

Key issues: Standards in food safety of traditionally produced food
"New risks" induced by gene technology, i.e. pleiotrophic effects
Alterations in nutritional composition

(2) The presentation of an established safety concept for the use of genetically modified microorganisms in food.

Key issues: Measures to ensure safe products (i.e. safety plasmids, GRAS status)

(3) Steps in the safety assessment of genetically modified crops.

Key issues: Toxicity - present state of the art in analytical studies
Health aspects of antibiotic-resistance marker genes

(4) The need for a safety concept for novel food. "Substantial Equivalence" a practical approach.

Key issues: Traditional food sources as counterparts
Applicability - Limits of the "Substantial Equivalence" concept

(5) Regulatory framework for novel food in the European Union.

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Food safety - Food quality. Traditional production and modern biotechnology

Food acquisition, production, modification, and processing technologies form a continuum of allied biotechnologies which trace back to the beginnings of agriculture. These technologies have made use of naturally-occurring genetic variation in an effort to create variety and expand the reach of food sources. Variation among and within agricultural commodities has become accepted and expected in human societies. Rapid technological advance in biology has resulted in the development of new agricultural tools, such as recombinant DNA technology. These technologies may expand the scope of current sources of variation and shorten the time to development for agricultural commodities, and in addition present new opportunities for genetic recombination and the appearance of novel gene products. Public concern over the safety of foods derived from modern biotechnology prompted comprehensive examination of this issue by the International Food Biotechnology Council in 1990. This work resulted in the development of tiered decision trees for determining food safety issues for foods derived from microorganisms, single chemicals and simple mixtures, and whole foods and other complex mixtures. Decision trees consider the genetic origin, composition, and safety of the food; resulting in a decision to accept, reject, or further study the test material. The council´s recommendations stated that food safety evaluations should be closely linked to existing agricultural and processing practices as well as estimation of the regulatory status of comparable foods.

1. The biotechnology continuum spans 10,000 years

Agricultural approaches to food acquisition have occupied the minds and imaginations of human societies for perhaps 10.000 years (Baker, 1978; Edlin, 1967; Harlan, 1992). From early attempts at plant and animal domestication to current efforts involving protein engineering and transformation of foreign DNA segments, modification of living organisms for food production has involved questions central to the survival of humankind. Although technologies employed in these efforts have expanded in scope and complexity since the beginnings of agriculture, their primary focus has changed little.

Transmission of information on food safety for early human communities was undoubtedly critical to their survival and proliferation. In addition to observation of animal feeding behavior, experimental trial and error likely played a major role in the determination of the safety of various plant and animal food sources (Simmonds, 1976; Harlan, 1992). The slow and gradual accumulation of desired plant and animal traits favored by human societies in their domestic strains resulted in substantial genetic change at the population level. In fact, many of our cultivated plant and animal strains have diverged dramatically from their wild counterparts (Hyams, 1971). Continued crossings of desired types, whether conscious or unconscious, hastened the increasingly

widening gap between domestic strains and their wild relatives. It is likely that "backyard" gardens, which might have involved the cross pollination of progeny from selected wild fruits, may represent the first attempt at a technological approach to breeding (Harlan, 1992). These efforts were followed by controlled planting and interpollination, systematic interpollination and selection, and finally by planned improvement for specific characters (Simmonds, 1976). These characters might have been obtained by crosses with wild relatives or systematic crossing and selection for desired type. Animal domestications, which followed the domestication of most plant species, proceeded in a similar manner (Zeuner, 1963). Systematic breeding, which may be generally defined as a scientific and artistic quest toward the development of superior plant and animal strains, has resulted in significant quantitative and qualitative improvement in most of our domesticated food sources (Fehr, 1984; Simmonds, 1979; Allard, 1960). At present, a continuum of techniques for manipulating genetic variability in breeding, such as traditional crossing and selection, mutagenesis, tissue culture, cell fusion, and transformation of cloned genes are all practiced to varying degrees in agricultural production (Crispheels and Sadava, 1994; Goodman et al., 1987).

Our systematic agricultural efforts led to a dramatic increase in food production, which in part may have been linked to a rapid increase in human population. These agricultural beginnings have also been thought to be responsible for the development of art and other crafts not necessarily associated with food production. Perhaps most significantly, these efforts changed the demography of human societies and flourished in stationary populations. Sedentism and agriculture are thought to be closely interrelated, with some models postulating that events surrounding domestication involve a continuum of hunting/gathering and farming. Harlan′s no-model model (Harlan, 1992) affirms this notion, suggesting that in addition to models where cultivation arises to support established populations, the converse may also be true. Regardless of their origins, early human populations, led to the development of cities, which by their nature required the storage of food. Food preservation and storage, two of the most critical biotechnologies of stationary human societies, allowed for further population expansion and co-evolved with emerging food production technologies (Edlin, 1967; Baker, 1978). Thus, the very development and existence of human cultures and societies on this planet has been facilitated through a continuum of agricultural biotechnologies. Our efforts to expand these technologies reflect a desire to shorten development time for certain key steps in the process and incorporate emerging powerful techniques to increase efficiency of our food production systems.

2. Human societies have come to accept and expect genetic variation in food products

Part of the excitement of systematic breeding lies in the awareness of natural variation among living organisms. Genetic differences among individuals in a population, among populations within a variety or species, among wild and cultivated strains, and among species provides the necessary hereditary variation upon which selection may be practiced. Useful genetic variation for plant and animal breeders has come from genetic recombination, introgression of wild sources, spontaneously-occurring mutations, and introduction of foreign germplasm. In this regard, a particularly significant event in the history of food production was the voyage of Columbus and introduction of hundreds of new food plants to and from Europe (Goldblith, 1992). Many crops introduced by early European explorers have become staple foods in Europe, as have many European and Asian food plants in the new world.

The introduction of significant amounts of genetic variation, whether by natural or foreign means, makes the improvement of numerous desirable traits possible. In addition, this genetic variation has allowed for the production of diverse food sources and a diverse selection of choices within each of these sources. Breeders have, for example, developed varieties of fruits, vegetables, and grains with widely varying characteristics, such as seedless and seeded red, green, and white grapes, and green, red, and yellow apples with a myriad of processed uses. Technologies which make use of and manipulate this variation by and large have been judged inherently safe by humankind. Human societies have come to appreciate and expect natural variation for color, flavor, texture, season, and end-use in their food sources. This natural variation forms the basis of a diverse and well-rounded food supply.

3. Evaluating the safety of a diverse food supply: the Decision Tree Model

Public concern over foods derived from modern biotechnology reflect a need for systematic examination of the technologies with which humans produce food and determine food safety. The International Food Biotechnology council (hereafter IFBC) developed guidelines for understanding and communicating the safety of foods derived from biotechnology (IFBC, 1990). This process is facilitated by the use of tiered decision trees which incorporate information on the genetic origin, composition, and safety of the food. These trees take into account the genetic background and procedures of modification, knowledge of the composition of the food, and relevant toxicological data. Separate decision trees have been formulated for microorganisms, single chemical substances and simple mixtures, and complex mixtures and whole foods. This decision-making process may result in a food being considered acceptable, unacceptable, or recommended for further study.

One of the basic assumptions of the IFBC was the observation that our food supply has steadily improved in variety, nutritional quality, safety, and economy during this century. These developments are thought to be directly linked to similar increases in public health. Traditional approaches to plant and animal improvement have played a significant role in these developments. Plant breeders have, for example, substantially increase disease and pest resistance of many crop species while simultaneously increasing yield and quality. In many cases, breeding efforts have resulted in wider adaptation of crop species and proceeded increased variety of fruits, vegetables, and grains in the marketplace. In addition, these efforts have reduced or eliminated naturally occurring toxic compounds such as solanine in potatoes, and cyanide in cassava and certain legumes. To some extent, these efforts have resulted in replacement of endogenous naturally-occurring pesticides and defense compounds in plant s with exogenous chemical application. Use of microorganisms in production of foods such as cheese, yogurt, and bread has likewise resulted in an increase in the supply of healthy food products. In large measure, these practices have been implemented safety and therefore provide a framework for comparing food products derived from emerging biotechnologies such as genetic engineering.

Knowledge of the chemical composition of traditionally-derived foods must, therefore, be acquired if biotechnologically-derived foods are to be evaluated. Many naturally-occurring chemical compounds in food products such as nutrients, microbiological contaminants, and toxins vary greatly both in natural populations and among cultivated varieties (Salunkhe and Desai, 1988; Scoucie et al., 1981; Lawrie, 1985). Knowledge of this variation is unevenly distributed among different foods (IFBC, 1990). Information on

natural toxicants, which may be found in virtually all plants used for human food, is steadily increasing. Given the potential health risk they pose, naturally-occurring toxicants will remain a primary focus of food safety concern.

Genetic variation, because of its implicit acceptance by scientists and non-scientists alike, is not an issue per se in food safety. Methods of varietal development using non-traditional genetic methods such as recombinant DNA technology may offer opportunities for gene introgression not possible in nature; however the novel changes which may result from this work may, like certain novel genetic recombinations which result form traditional technologies, be either disadvantageous or undesired. Introgression of foreign DNA from wild related species and related genera has been widely practiced in plant breeding and has resulted in incorporation of many useful genes for pest resistance (Rick et al., 1977; Goodman et al., 1987). Commonly accepted practices for monitoring commercially-available vegetable and grain cultivars for safety and quality have served and should continue to serve food safety concerns well (Reitz and Caldwell, 1974; Simon, 1988). These changes have been successfully managed by plant and animal breeders throughout this century and should continue to be managed by similar practices in the future.

4. Evaluating the safety of a whole food is inherently more complex than evaluating the safety of a single chemical compound from that food source.

Safety evaluation for food derived from genetically modified microorganisms focus on question as such as whether the microorganism ends up in the food, whether it is free of transmissable antibiotic resistance markers, whether the vectors are free of attributes that would make them unsafe in food, whether the DNA might code for a toxic product, whether the food is free of antibiotics and toxins produced by related microbial strains (Pariza and Foster, 1983). Expression of new gene products in safe microbial hosts should be evaluated. If the gene product is already part of the food chain, little testing is necessary.

Introgression of a well-characterized gene form a complex uncharacterized genome into a defined system may negatively or positively affect the safety< of the food product. Vector design has been identified as a critical factor in maintaining the safety of antibiotic resistance markers which may be used for identifying transformed segments of DNA. In most cases, toxin production by a microorganisms poses no risk following introduction of a gene which does not produce a toxin. Single chemicals and simple chemical mixtures were not found to require any new or additional testing measures since they generally contain safe levels of all undesirable compounds. In addition, these are typically consumed at low levels compared to whole foods.

Whole foods and other complex mixtures to face additional testing. Safety evaluation of genetically modified plant products, microorganisms, and macroingredients should be base on comparisons with traditional counterparts for nutrient content, various expression products, and toxins (IFBC, 1990). In addition, documentation of the nature of the genetic change and an exposure assessment are recommended. Monitored preintroduction consumption by human volunteers, common in traditionally-derived foods, is considered an unimportant and useful addition to this process. If the source of genetic material for whole foods ins another food product, it is likely the confidence in its safety will be increased. Recommendations for food constituent screening involve any

constituent introduced or modified, any constituent of nutritional of safety significance likely to vary in concentration as a result of genetic modification, and other inherent constituents such as any identified or unidentified components naturally present in that food plant of in closely related species of food plants. The standard for compositional comparison for safety must be considered in the range that is normal in any closely related traditional foods. When data from such studies do not establish the safety of a food, feeding studies in animals are recommended. If a a foot contains sufficient quantities of constituents with no dietary history, toxicological testing may be advised. If individual compounds cannot be isolated in sufficient quantity to test their safety in animal studies, the whole food may be used in such a test. These are rearely recommended due to the presence of numerous confounding factors.

In conclusion, the biotechnological continuum initiated at the dawn of agriculture and continuing on through modern genetic engineering has used variation to expand the scope and reach of food sources. New technologies may expand the range of current sources of variation and shorten development time for agricultural commodities, while at the same time present new opportunities for appearance of novel gene products. Decision tree models, which consider the origin, composition, and safety of foods represent a significant step toward evaluation of food safety issues in the era of modern biotechnology.

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Safety assessment of genetically modified microorganisms and their products

1. Background

Until a few decades ago, food has allways been assessed for its safety for human consumption by permanent trial and error, i.e. by its history of a long and safe use. Over the millennia since the invention of agriculture about 10.000 years ago, mankind has by this "instinctive" strategy accumulated a wealth of experience on the production, properties and nutritional qualities of traditional food. In the first place, there was a permanent fight against microbes which tended to spoil precious resources. In the cause of this fight, microbes were detected which by spontaneous fermentations transformed specific raw materials (e.g. milk, meat, vegetables, fruits and fruit extracts) into microbiologically stable, well tasting products like sour milk, cheese, sauerkraut, soy sauce, wine, beer and others (1).
These originally spontaneously, now intentionally and on an industrial scale manufactured items were and still are consumed in part together with the used live microbes. In fact, the mean consumption of live microbes with fermented food by the Swiss population is estimated to be about 30.000 million per person per day, based on the consumption statistics of the Swiss Nutrition Report. This compares to only 100 million consumed with drinking water, air, and other, mostly pasteurized or cooked food. In the human intestine, about 10.000.000 million living bacteria are already present. Obviously, mankind possesses a natural protection against these microbes which developed during a many million years lasting evolution.
The scientific assessment of food safety became necessary when traditional food was being transformed with new technologies leading to a new composition or new ingredients (e.g. UHT heating, heat sterilization, chemical preservation, irradiation, and now genetic engineering). The traditional food was the necessary reference which in itself, however, had most of the time not been evaluated by critical scientific investigation asked for with novel food. To solve this dilemma, several countries introduced in their food legislation the definition of traditional food items and their general recognition as a safe (= GRAS) food if a long history of safe use was evident (2).
However, we have to realize that this GRAS definition can by no means be taken as an absolute definition of a zero risk. This has to be applied to traditional and novel food. If we use the traditional food as a reference, we can define different levels of novel food regarding its relatedness with the reference food. One recent concept (see contribution by Dr. Jonas) defines three levels of relatedness: 1. substantial equivalence, 2. sufficient similarity and 3. insufficient similarity (3). It is paramount to any safety discussion and evaluation to use the same scientific instruments for novel. eg. genetically modified food as for its traditional counterpart or reference. On the basis of all these ideas, it is clear that the final outcome of a safety assessment will therefore always have a certain uncertainty or - positively speaking - plausibility component. In other words, it must be our task to arrive at the lowest possible risk attainable at the present state of scientific knowledge and technology to obtain the highest possible plausibility of safety.

2. Genetically modified microorganisms in food

Microorganisms traditionally used for the production of fermented food have been the subject of genetic modification for a series of purposes for the following reasons:

1. they are generally recognized as safe (GRAS) and provide a proper refence material,
2. there is ample experience to handle them on a large industrial scale,
3. their taxonomy, biochemistry, genetics and molecular biology are very well understood, at least for some genera like Saccharomyces or Lactococcus/ Lactobacillus,
4. their behaviour in the environment (soil, water, food, intestine etc.) is also very well studied in many species, an important fact if it comes to release of genetically modified microorganisms with food, and last not least
5. there is a substantial market potential.

Another advantage in the evaluation and assessment of the safety of genetically modified microorganisms in food is the fact that only a limited number of microorganisms is used for food fermentations as evident from the following list of genera (4):

1. Gram-negative bacteria: Acetobacter (vinegar), Zymomonas (ethanol).

2. Gram-positive bacteria: Brevibacterium (cheese, amino acids), Lactobacillus (bread, cheese, yoghurt, pickles, sausages), Lactococcus (sour milk, butter, cheese), Leuconostoc (sour milk, butter, cheese, vegetables, wine), Micrococcus (suasages, amino acids), Pediococcus (soy sauce, silage), Propionibacterium (Swiss cheese), Staphylococcus (sausages), Streptococcus (yoghurt), Streptomyces (sausages, enzymes, antibiotics).

3. Yeasts: Candida (kefir), Kluyveromyces (kefir, enzymes), Saccharomyces (wine, beer, bread, bakers yeast, soy sauce), Schizosaccharomyces (alcoholic beverages, enzymes).

4. Moulds: Aspergillus(soy sauce, enzymes, citric acid), Monascus (colored rice), Mucor (cheese, enzymes), Penicillium (cheese, salami, antibiotics, enzymes).

Many economically important species out of these genera are currently heavily investigated regarding genetics and genetic engineering potential. Methods of natural and artificial gene transfer (eg. conjugation, electroporation) are available. The number of vectors developed for homologous and heterologous gene expression is almost weakly increasing. Lactococcus lactis and Saccharomyces cerevisiae are almost as well genetically managable as Escherichia coli, to name the two most important ones (5, 6).

3. Specific purposes of genetic modification of food microorganisms (4,5,6)

The tasks can be summarized as follows:

- Optimization of the function(s) of a single component culture,
- Combination of properties from different biological systems in one microorganism.

In principle, genetic engineering is therefore used to optimize the control of biochemical reactions already known and present in traditional food which per se have a long history of safe use in their original genetic and food environment.
Examples in Saccharomyces cerevisiae are constitutive maltose utilization, growth on starch with the aid of an enzyme system stemming from Schwanniomyces occidentalis or S. diastaticus, secretion of legume lipoxygenase, secretion of barley beta-1,3-1,4-glucanase, reduction of diacetyl by an alpha-acetolactate dehydrogenase from Acetobacter pasteurianus, expression of malolactic enzymes and lactic dehydrogenase from lactic acid bacteria.
In lactic acid bacteria, examples include stabilization of technologically important functions by transfer of the corresponding genes from labile and conjugative plasmids into the chromosome (protease, lactose metabolism, citrate uptake), construction of bacteriophage resistant starter cultures by recombination of different phage resistance mechanisms from different strains in one strain, establishment of starter cultures with high proteolytic activities to accelerate cheese ripening and aroma production, construction of starter cultures excreting bacteriocins and peptide antibiotics to inhibit pathogenic contaminant bacteria in food and fodder, expression of amylase activity for better silage fermentations.
The main products of genetically modified microorganisms to be used in food are food grade enzymes like chymosin, proteases, amylases, beta-galactosidase, lysozymes, glucanases. In addition we have to assume that other food ingredients like aminoacids, vitamins, citric acid, nisin may already be manufactured with gentically optimized cultures including genetically modified ones (see the tryptophane debacle). In this respect it has to be mentioned that at least 30 heterologous proteins have been expressed in Lactococcus lactis. In Saccharomyces cerevisiae, a recent review (6) lists 39 human proteins, 23 proteins from other mammals and higher eukaryotes, 11 viral proteins, 8 proteins from other fungi including food grade enzymes, and 5 bacterial proteins. If these products are sufficiently purified and free of the producing microbes, safety evaluation and assessment may be easy and not controversial at all.

4. Safety assessment

A prerequisite of the use of genetically modified organisms is the proof that the intended technological function is working under production conditions. In addition, specific harmful effects on human health and the environment have to be excluded on the basis of the state of science and technolgy of detection. Whereas the safety assessment of isolated and purified producst may be simple if the product is identical with a known compound (e.g. chymosin), the situation is quite complex if live genetically modified microorganisms are present in the food. In this case, the organisms are released with the particular food item into the environment and are eventually consumed by man (and animals).

The necessary basic elements of a safety evaluation are the following:

1. *Identity and knowledge of the recipient microorganism.*
   Species/strain identity, taxonomical position, pathogenicity for man/animals/plants, function and behaviour in food including GRAS status, behaviour in human body and environment. This body of knowledge is necessary to judge the genetic modification to be introduced. In that sense, the unmodified recipient organism is the reference material.There seems to be consent that only microorganisms placed in the lowest risk catagories (no risk or harmless) of the different systems should be applied for food production.

2. *Identity and source of the introduced genetic material.*
   Determination of the complete nucleotide sequence enables the exclusion of known protein toxins and pathogenicity factors and the identification of the genetic control elements and their identities with traditionally used elements and functions. It also allows a prediction of a possible migration of the introduced genetic material within the microbial community if released into the environment.

3. *Absence of pathogenicity and toxicity in the genetically modified microorganism.*
   The absence of allergenicity may not be achievable if a molecule is expressed known to be allergenic in the firstplace. Antibiotic resistance markers should not be released with viable microorganisms into food and fodder.

4. *Fate of genetically modified organisms in the environment.*
   Growth, proliferation and survival rates in the food, in the human/animal body, on plants, in air, water and soil should be known to compare it with the traditional recipient.

5. *Nutrional properties of the produced food.*
   It must be known whether the nutritional composition is significantly changed compared with the traditional product.

A very detailed discussion of different safety assessment systems (WHO, OECD, EBO, FDA) is given by Simon and Frommer (2). Regarding these 5 different sets of data, it becomes selfevident that there can only be a case-by-case evaluation of the use of genetically modified microorganisms and their products in food. As stated above, if the genetically modified microorganism delivers the required functions and behaves otherwise like the traditional reference organism a safety evaluation and assessment is possible.
If in the case of the evaluation the traditional organism turns out to represent an until now not recognized risk, this risk will have to be eliminated in accordance with the requirement we ask for in genetically modified organisms.
The current safety discussion and evaluation procedure in the public and the media will be examplified with the three products on the market, the genetically modified yeasts and the different chymosin preparations.

I would like to emphasize that the safety assessment is only one, but probably the most limiting step in the development of genetically modified microorganisms for the use in food production:

- realization of the genetic modification in the laboratory
- proof of technological function and suitability
- safety assesment for human consumption
- safety assessment for the environment
- legal acceptance
- acceptance by the market and consumer.

This elaborate procedure will only allow economically strong and competitive, and publicly well accepted products to have a chance of realization. As in other industries, increased legal constraints will work against small and medium sized companies and favour large enterprizes.

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Safety assessment of genetically modified plant products. Case study: *Bacillus thuringiensis*-toxin tomato.

Introduction

Genetic transformation of plants broadened the range of genes that can be inserted into existing crops, as recombinant DNA techniques can bridge the barriers between widely different species. Traits for insect and virus resistance, herbicide tolerance and delayed ripening of fruits have been introduced in various food plants. Many aspects of genetic manipulation by means of novel biotechnology are not new, and to a great extent, already experienced before. In conventional plant breeding selection might have guarded safety, although it was not recognised as such. Nevertheless, recDNA techniques enable breeders to express proteins in plants that were never part of it before. As a consequence, the unfamiliarity with this technology leads to questions about the safety and nutritional value of the novel food. Considerations, which have led to national and international consultations on the necessity of additional regulation for genetically modified plants and derived foodstuffs. As yet, the evaluation of genetically modified plants has for a great part been limited to yield and open field behaviour of which the requirements are laid down in the Directive 90/220/EEC. While the food safety testing of transgenic food plants is still in a phase of exploration.

Novel food regulation in the Netherlands

Recently, an amended proposal for a European Parliament and Council regulation of novel food products and ingredients has been issued which sets the framework for the European Union (EU)-market introduction [1]. At the European level, however, no uniform specific guidelines for safety testing have yet been developed. In spite of that considerable numbers of genetically modified organisms and derived foodstuffs are expected to reach the Dutch market soon.
In 1993, therefore, a legislation for novel foods has been adopted which will be effective till a definite EU-regulation has been published. The Dutch 'interim' legislation provides regulations in order to warrant the safety of novel foods before being brought onto the market. Thereto the existing Food Commodities Act was modified and extented with a regulation for: (i) foodstuffs composed of or produced by genetically modified organisms and (ii) foodstuffs with novel chemical properties, or which contain novel ingredients or ingredients with novel chemical properties. The safety assessment of these categories of food must be generated by, or for, the producer, which will be evaluated by an independent institution. In this context the approval for marketing is a two step procedure which takes place under responsability of the Ministry of Welfare, Health and Cultural Affairs. The Provisional Committee on Safety of Novel Foods is involved in the evaluation of safety aspects, and the Novel Foods Committee of the Food Commodities Act Advisory Committee considers aspects such as the ethics of potential applications, public perception, and regulatory and marketing policy (i.e. labelling). The 'closed-dossier'

principle is applied to the evaluation process, however, a release of a public summary is foreseen. The regulation endorses the recommendations of both the Health Council and the Nutrition and Food Council who proposed in their advisory reports that foods, obtained by means of recDNA technology, should be evaluated on the basis of a case-by-case approach using a decision-tree system in which toxicity tests tend to predominate [2].
To arrive at a safety evaluation four decision trees have been set up: (i) simple substances and chemically defined mixtures, (ii) plant foodstuffs, (iii) foodstuffs of animal origin and (iv) foodstuffs and foodstuff ingredients derived from microorganisms, cell extracts and enzymes. The decision trees are mainly those of the International Food Biotechnology Council (IFBC) proposal with an extra one for products of animal origin [3]. The Dutch variant stipulates an exact characterisation of the DNA insert and pays special attention to effects of novel foods on the nutritional status of the consumer. Related to this, marker genes coding for antibiotic resistance when incorporated in a stable way, are deemed admissible. However, the most important difference between the Dutch decision tree for e.g. food plants and the IFBC counterpart is that the former demands a 90 day feeding trial for each new product. The Dutch decision tree only exempts those foodstuffs that have the place of insertion characterised to such an extent that it can be established that no detrimental effects to the metabolism occur that may affect food safety. Although a decision-tree system looks very straightforward, it leaves still some room for interpretation.

Safety evaluation of the *Bacillus thuringiensis*-toxin tomato

Criteria for safety evaluation of novel foods are far from settled. In view of proposed guidelines, it can be anticipated that evaluation strategies for e.g. transgenic plants will show major differences. Growing agreement exists on considering the newly expressed proteins as additives of which the toxicity and exposure levels should be estimated. Whereas, among others, secondary effects in transgenic plants should be analysed based on either an analytical and biochemical approach or on toxicologic testing of the novel variety, taking its traditional non-transgenic 'counterpart' into account. It is obvious that case studies are needed which results may be valuable in designing a science-based, practical and internationally harmonised strategy for the risk assessment of novel foods of vegetable origin.
In 1991 an EU co-sponsored research project (AGRF-0039) was initiated entitled '*Opportunities of transgenic food crops for the consumer and the food industry in the Community*'. Partners in the project are Plant Genetic Systems (Ghent, Belgium); RIKILT-DLO (Wageningen, the Netherlands), in cooperation with the Agricultural University of Wageningen, and with the University La Tuscia (Viterbo, Italy); SME Ricerche (Piana di Monte Verna, Italy), and the University of Genova (Genova, Italy). The project concerns the molecular, biochemical and toxicological characterisation of insect-resistant tomatoes obtained from the control tomato line TL001 by *Agrobacterium* mediated transformation using cotyledons as the explants. Thereto, the vector pPSO216 was used that comprised two chimeric genes between the T-DNA border repeats. The chimeric *neo* gene consisted of the promoter of the T-DNA TR1' gene and the coding region of the *neo* gene encoding neomycin phosphotransferase II (NPTII). Whereas the chimeric *Bacillus thuringiensis* (*Bt*) gene consisted of the woundstimulated promoter of the T-DNA TR2' gene and the coding region of the C-terminal truncated *Bt*2 gene, called *IAb*6 derived from the coding region bt884 encoding the insecticidal crystal protein CRYIA(b) (MW 66-68 kDa). Based on entomological and agronomical criteria the insect-resistant transformant RLE13-0009 was chosen for a risk assessment.
The food safety evaluation of the insect-resistant transformant was designed in a way that answers could be given to a number of appropriate questions: (i) does the CRYIA(b) pro-

tein exert a similar toxic action in mammals as observed in larvae of target insects; (ii) do the newly expressed proteins cause adverse effects; (iii) are they immunogenic and/or potentially allergenic, and (iv) does the transgenic phenotype induce alterations in the nutritional composition or in levels of natural toxins that could compromise human consumption.

The nature of the genetic modification has been analysed with respect to size and number of inserted genes as well as to size and levels of transcripts and proteins in different organs of the plant. Enzyme-linked-immunosorbent assays (ELISA) were used to estimate the levels of CRYIA(b) protein in mature transgenic Bt-toxin tomatoes, in extracts of sliced fruits incubated overnight in protoplast medium containing 1 mg/l 2,4-D, and in processed products. Levels of NPTII were quantified using Western blot and dot blot analysis. In the harvested transgenic Bt-toxin tomato variety RLE 13-0009 the CRYIA(b) protein was typically expressed at levels of about 7.5 ng/mg of protein, and in induced fruits at levels of about 25.4 ng/mg of protein with a nominal content of 0.8% protein of fresh weight tomatoes.

As sufficient amounts of recDNA proteins cannot be easily extracted from tomato tissue, a number of toxicologic and binding studies has been carried out with CRYIA(b) protein purified from the overproducing recombinant *Escherichia coli* strain K514 (pGI502). Possible binding of CRYIA(b) to gastro-intestinal tract tissues from mammals has been studied thoroughly, since in larvae of target insects binding seems essential prior to the onset of toxicity. After feeding rats single oral doses of CRYIA(b), corresponding to a human daily consumption of approximately 2000 kg of Bt-toxin tomatoes, no binding of CRYIA(b) or histopathological damage could be observed in any tissue segment of the gastro-intestinal tract of treated animals, in contrast to what was found in the midgut of larvae of the target insect *Manduca sexta* force-fed with CRYIA(b). *In vitro* binding of CRYIA(b) to intestinal tissue sections of mice, rats, Rhesus monkeys and humans was examined immunocytochemically, but no specific binding could be observed. Whereas, midgut tissue sections of *Manduca sexta* larvae incubated with CRYIA(b) showed an uniform binding in the brush border membrane over the entire length of the epithelium. The degradation behaviour of CRYIA(b) studied under simulating human gastro-intestinal conditions indicated clearly a two-step process. At pH 2 in the presence of pepsin the protein was rapidly cleaved to yield 15 kDa polypeptides, and extensive fragmentation to smaller fragments (<< 10 kDa) was seen after continued incubation at pH 8 with chymotrypsin and trypsin. The NPTII protein on the contrary appeared completely digested at pH 2 in the presence of pepsin. Moreover, the digestability of CryIA(b) was studied in rats, fistulated in the ileum, and immunoblot analysis of collected chymus revealed a rapid and extensive breakdown of the protein.

To test for systemic effects of CRYIA(b) upon passage through the intestinal wall, and for adverse immune reactions, daily doses of purified CRYIA(b) were fed via drinking water *ad lib.* to mice and rabbits for 30 days. At relatively high dose levels corresponding to a human daily consumption of 60-500 kg of transgenic Bt-toxin tomatoes, no differences were observed in standard toxicological test parameters. In serum of treated rabbits no antibodies against CRYIA(b) could be detected, nor was the total immunoglobulin (IgG) content elevated with respect to controls. No histopathological damage was observed in organs and intestinal tissues of treated animals. There were no indications for immunotoxic effects of CRYIA(b) as judged from histological examination of spleen, lymph nodes and Peyer's patches. In addition, human red blood cells were tested for the hemolytic potential of CRYIA(b), but no hemolysis was observed.

The question whether genetic manipulation may result in secondary metabolic changes which could be of toxicologic significancy, has been evaluated by two approaches. First, chemical analyses were made of components related to the nutritional composition of Bt-toxin tomatoes compared to non-transformed control lines, and found to be unchanged and

within published ranges. Moreover, levels of the glycoalkaloid a-tomatine were similar in control and transgenic tomatoes (range: 1.4-1.7 mg/kg).
The field tested transgenic Bt-toxin tomato line RLE13-0009 and the respective controle line TL001 were selected for a 91 day feeding trial in rats. The field trial manifested no significant differences in vegetative growth and harvest characteristics between transgenic Bt-tomatoes and the controls. Three groups of 12 male and 12 female weanling Wistar rats were fed respectively a control semi synthetic animal diet (Muracon SSP TOX), the same diet supplemented with 10% (w/w) of lyophilized Bt-toxin tomatoes containing 40.6 ng CRYIA(b)/mg of protein, or with 10% (w/w) of lyophilized control tomatoes. The macro- and micronutrient composition was equalized in all diets: 7.5% E(energy) fat, 20% E protein, 41.5% E carbohydrate and 10.4% fibre (w/w). The amounts of supplementary minerals and vitamins were deduced from the actual levels in freeze-dried tomatoes. The average daily intake of tomato powder over the 91 days period corresponded to 200 g of tomatoes/kg body weight, equivalent to a daily human consumption of 13 kg tomatoes. There was no feed refusal or unusual behaviour in any of the animals. No significant differences in the other parameters under study have been noticed between the different diet groups, and no macroscopic abnormalities were found. The weights of liver, kidneys, spleen, and thymus, expressed as percent of body weight, did not show differences in treated animals compared to controls. Microscopic histological analysis included in this study did not reveal signs of pathologic effects related to transgenic Bt-toxin tomato feeding. The results of the 91 days feeding trial in rats obtained up till now are reassuring with respect to food safety of insect resistant Bt-toxin tomatoes.

Toxicologic considerations

In case the encoded product is a foreign food protein a toxicologic evaluation will be required in keeping with guidelines for additives (e.g. JECFA). The given example of insect-resistant Bt-toxin tomatoes shows the necessity of such an approach. Extensive testing of the CRYIA(b) protein revealed that its specific insecticidal action does not occur in mammals. *In vivo* and *in vitro* binding experiments in intestinal tissues from rodents, Rhesus monkeys and humans indicated the absence of specific binding sites for the protein. Even at exaggerated dose levels, corresponding to 2000 kg of fresh transgenic Bt-toxin tomatoes, no adverse effects could be observed in laboratory animals, and no evidence was found for immunotoxicity of the CRYIA(b) protein. Beside the knowledge of toxicity and exposure levels of the encoded proteins the safety evaluation should also be based on the OECD-formulated concept of substantial equivalence [4].
Related to this latter aspect, a 90 Day feeding trial with complex novel foods as a substantial part of the test diet may pose problems with regard to the conventional testing procedures for additives. Apparent toxic effects may result from nutritional imbalances caused by large quantities of test material to the basal rodent diet, rather than from the inherent toxicity of the transgenic food plant. On the other hand, safety testing of complex food products in rodents may offer cumulative toxicity as a means of detection. In order to avoid these problems the application of a semi-synthetic rodent diet with interchangable nutrients, adapted for the nutritional requirements of rats and deduced from the actual levels in transgenic Bt-toxin tomatoes, was studied. Although the given example demonstrated the feasibilty of this approach, in view of the diversity of varieties and risks dealt with, the choice of an analytical approach as customarily performed to screen for secondary effects in transgenic plants appears to be more justified.
With respect to safety evaluation of Bt-toxin tomatoes other aspects have still to be investigated: (i) the posttranslational modification of CRYIA(b) protein obtained from fermentations with recombinant bacterial strains may be different from the one expressed in transgenic food plants, which possibly results in a modified toxic profile and

immunogenicity. On the other hand, the lack of posttranslational modification could also induce toxicity; (ii) the long term use of Bt spore preparations in the field as insecticides has not revealed evidence for allergic reactions in workers. Despite this, studies on the allergenic potency of CRYIA(b) should be carried out, in particular because of the potential exposure of the general population to Bt-toxins via transgenic plants. Testing systems to investigate the allergenic potency of foreign food proteins are not yet available, however. A major problem in the development of useful and validated test systems is the considerable variation in sensitivity to sensibilisation and subsequent allergic reaction in individuals.

Regulatory considerations

Most experts on regulatory aspects of foodstuffs derived from genetically modified plants agree on a case-by-case approach as the most efficacious strategy. A case-by-case approach allows to include the latest scientific findings in the evaluation, thereby guaranteeing maximum safety of the novel food. On the other hand, it may require more efforts to safeguard uniformity of evaluation. In any case, the criteria for the evaluation of transgenic plants are largely comparable to those used for food additives. In case of transgenic plants the identity of the non-transgenic control plant must be known, and the host plant needs to be a GRAS (Generally Regarded As Safe)-organism. The DNA insert must be fully characterised and located, and devoided of any toxic element harmful to humans. It is most likely that methods to analyse nutrients, naturally occuring toxicants as well as antinutritional factors will be used in order to identify possible secondary metabolic changes in plants as a result of foreign gene insertion, rather than animal feeding trials.
An analytical approach based on single component analysis has its limitations, however. Information on the composition of most food crops and derived products is fairly limited. Also knowledge on the variation of components in different varieties and in different environments or stages of development is still in its infancy. New ways of chemical analysis should therefore be explored. Metabolic profiling, determining compositional patterns of the whole food product using techniques such as NMR, LC-MS and CZE(-MS), may be a good alternative to traditional chemical analysis. Moreover, databases should be set up to supplement existing data in relation to food components with the purpose to gain more insight into both the composition of plant varieties and the variation in composition depending on variety, stage of cultivation or climate conditions. Next to the method of metabolic profiling, a differential analysis at the DNA and/or mRNA level would be, at least in theory, of great value. However, fundamental knowledge on the functioning mechanisms at DNA level is largely lacking. In case these new analytical approaches can not generate sufficient data to establish safety or if they indicate significant compositional differences compared with traditional 'counterpart' crops, additional animal feeding trials can still be considered to assess safety of the transgenic food plant.

General conclusion

In assessing the safety of transgenic plants as food following elements must be issued: (i) the specific genetic modifications involved; (ii) the characteristics of DNA inserts and expected gene products; (iii) the role of expression products in physiological processes; (iv) possible secondary metabolic changes occuring as a result of gene manipulation, and (v) levels of exposure to be expected in various processed foods. It is emphasized that the risk assessment of novel foods should take place within a general framework with case-by-case variations. The challenge for toxicology is to design such flexible and tailormade evaluation strategies for transgenic plants, taking the often long history of safe use of tradi-

tional 'counterpart' crops into consideration. New analytical approaches combined with *in vitro* toxicologic test systems have great opportunity to achieve these objectives.

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Safety determination of the *kan*^{r} marker gene for use in tomato, cotton and oilseed rape

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OECD food safety concept "Substantial Equivalence"

Introduction

The safety of food for human consumption is based on the concept that there should be a reasonable certainty that no harm will result from intended uses under the anticipated conditions of consumption. Substantial equivalence is a concept that embodies the idea that existing organisms used as food or as a source of food can be used as the basis for comparison when assessing the safety for human consumption of a new food or of a food component that is modified or new. Substantial equivalence is not the application of a fixed set of rules; rather, it is a concept which can be applied flexibly. It is a concept that is applicable to a wide range of "novel foods" and not only to those produced by biotechnology.

In applying modern biotechnology in food production or processing, the starting point will usually be an existing food source organism. It is this aspect that facilitates the safety evaluation of foods derived by modern biotechnology and makes the concept of substantial equivalence the most practical approach to their safety evaluation.

The food safety of a food or food ingredient produced by genetic modification is dictated by a number of factors but principally by: the safety aspects of the deliberately introduced changes; and the safety aspects of any secondary or unintentional changes as a result of the genetic modification. The concept of substantial equivalence can be applied to address all of these concerns.

The Concept of Substantial Equivalence

Demonstration of substantial equivalence takes into consideration a number of factors such as:

knowledge of the composition and characteristics of the traditional or parental product or organism;

knowledge of: the characteristics of the new component(s) or trait(s); transformation techniques including the vector(s) and any marker genes used; possible secondary effects of the modification; and characterisation of the component(s) or trait(s) as expressed in the new organism; and

knowledge of the new product/organism with the new component(s) or trait(s), including a comparison with the conventional counterpart(s).

Application of Substantial Equivalence to Foods from Genetically Modified Organisms

In evaluating the food safety of a genetically modified organism or a product obtained from a genetically modified organism, the first stage is to establish whether there are any secondary effects from the modification. This is done by establishing whether, apart from the deliberately introduced changes, the genetically modified organism is substantially equivalent to the parent organism used as host for the modification. This will involve consideration of the phenotypic and analytical characteristics of the genetically modified organism and the host. Clearly this approach cannot detect all secondary effects but it is anticipated that secondary effects of any safety significance will be revealed in changes to the phenotypic characteristics of the host or to analytical characteristics such as gross composition, natural toxicant and nutrient levels. Where secondary effects are suggested, their nature and their safety implications will need to be followed up.

Having established that, apart from any deliberately introduced changes, the genetically modified organism intended for use as food is substantially equivalent to the parent organism, and if the parent is an acceptable food organism, the next stage in the evaluation is to consider the safety of the deliberately introduced changes. It is necessary to establish whether any novel gene products will be present in any food or food products obtained from the genetically modified organism. The nature of any inserted genetic material must be fully characterised so that all potential novel gene products can be identified. Some novel gene products may be expressed only in non-edible parts of the genetically modified organism or during phases of growth during which the organism is not used for food purposes. Others may be destroyed during the preparation of food ingredients from the genetically modified organism. If it can be shown beyond reasonable doubt that these novel gene products are not present in the food as consumed, they are of no further food safety concern.

If the food as consumed contains novel gene products, or altered levels of existing gene products, these will need to be the focus of a specific safety evaluation. Data may be available in the literature relating to the safety of the isolated gene product. Provided that it can be shown that the gene product expressed in the genetically modified food organism is substantially equivalent to an acceptable component of food at the levels anticipated, then no further safety evaluation of the gene product is required. Where substantial equivalence to an existing acceptable food component can not be established, the novel gene product will need to be evaluated.

Finally, it is important to determine whether the food from the genetically modified organism is substantially equivalent to comparable existing foods. This will provide valuable reassurance regarding the safety implications of any natural toxicants and antinutritional factors that might be present. If the levels in the food as derived from the genetically modified organism are within acceptable ranges and substantial equivalence is established, then they are of no additional food safety concern.

Case Study - Genetically Modified Lupin

Genetically modified lupins are a useful example to consider because the lupin seeds from the genetically modified cultivar might themselves might be used for food or the seeds might be processed to give a range of products including: oil, meal, fibre and protein. There is also the possibility that the genetically modified cultivar might be crossed with other varieties using conventional breeding techniques and that the crosses might be used as a source of food products. For study purposes it is assumed that the lupin is modified by the inclusion of three genes one of which modifies the composition of the oil so that it resembles sunflower oil; one, nptII, which confers resistance to kanamycin and a third, expressed only in the leaves, which produces Bt toxin.

It is for the developer to consider whether to seek food safety clearance for a specific processed product, for all processed products obtained from the seeds of the genetically modified cultivar, or for all processed products obtained from the seeds of cultivars obtained by conventional breeding from the modified cultivar. The concept of substantial equivalence can be applied to all cases.

The first stage in the safety evaluation - whatever the scope of the clearance sought - will be to consider whether there are secondary effects that will need to be addressed later in the safety evaluation. Comparison of the modified and parent cultivars in respect of agronomic characteristics and performance will reveal whether there have been gross changes to the plant's metabolism. It is then necessary to look at the chemical composition of the seeds of the parent and the modified cultivar. If, apart from the plant's resistance to antibiotics and pests and the unusual fatty acid profile of the seed oil, the modified cultivar is sufficiently similar to the parent then it might be infered that there have been no secondary effects from the modification and one can proceed to the next stage of the evaluation.

If the proposed food use is restricted to the fibre from the seeds of the modified cultivar it is necessary to consider whether the novel gene products are found in the fibre. If the Bt toxin gene is under the control of a leaf-specific promoter and the toxin can be shown not to be present in the seeds, it is of no further concern. By virtue of the processing, the novel oil fraction and the APH(3')II enzyme confering antibiotic resistance will be absent from the fibre and of no safety significance. If substantial equivalence is shown between fibre from the seeds of the modified cultivar and fibre from the seeds of conventional cultivars, it is presumed to be as safe without the need for further testing.

If the proposed food use is for the refined oil from the seeds of the modified cultivar, it is necessary to consider whether the novel gene products are found in the oil. The APH(3')II enzyme will not be present and will therefore not pose a safety risk, nor will the Bt toxin. The refined oil will, however, contain the novel oil produced as a result of the other inserted gene. It will be necessary to compare the seed oil from the modified cultivar with sunflower oil and with the composition of edible oils generally. If substantial equivalence is established, then the oil is regarded as safe for consumption as conventional sunflower oil without further testing.

If clearance is sought for all edible products derived from the seeds of the modified cultivar, all forseeable products (ie: oil, meal, fibre and protein isolate) are evaluated using the approaches described above. If, however, the proposal relates to the seeds as well as to any edible product derived therefrom, a different approach is necessary and this will focus on the seed. The seed contains both the novel oil and the APH(3') enzyme, but not the Bt toxin. Historical data will confirm the safety in use of the oil since it is substantially equivalent to sunflower oil. Evidence of the safety of the enzyme will be needed but will take into account that the enzyme will be degraded rapidly in the gut even if it is not degraded during any processing of the lupin seeds. It will also take into account that enzymes are not usually toxic, that they are very specific in their action and that this particular enzyme requires a cofactor for activity. Having established that the enzyme does not pose safety risk, that the oil is substantially equivalent to sunflower oil, that there is no Bt toxin in the seed, and that there are no unexpected changes as a result of the modification, the seeds are regarded as as acceptable for use as food or as a source of food ingredients as the seeds of conventional lupin cultivars.

In many cases, having introduced a genetic modification into an organism, the developer will wish to develop further cultivars from the organism using traditional approaches. The main concern here is that the presence of the novel gene construct or the novel gene products may initiate latent genes in the organism with which the genetically modified organism is crossed. To preclude this possibility it will be necessary to show, over several generations, that the modification is stable; it will also be necessary to show that, over a period of time, no secondary effects of the modification are revealed. If this can be done there is no reason why clearance to a range of cultivars should not be given.

Conclusion

Over the past few years in the UK a range of genetically modified organisms and their products has been evaluated and others are under evaluation. These include products of microbial, plant and animal origin. The approach which we have adopted is the comparative one described above - although we may not always have called it substantial equivalence. Practical experience leads us to concur with the report of the OECD working group that the concept is the most practical approach to the food safety assessment of the products of modern biotechnology. In most instances we do not anticipate that animal tests will be necessary to establish the safety of foods produced from genetically modified organisms, chemical, biochemical and genetic data should suffice.

Suggestions for further reading

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Regulatory framework for novel food and novel food ingredients in the European Union

The paper points out that the Commission proposal for a European Parliament and Council Regulation was made in the context of the present situation in the food sector of the European Union, where foodstuffs can generally be placed on the market without any pre-marketing assessment or authorisation under the responsibility of the manufacturer. Hardly any Member State has a general legal provision which would require a scientific assessment before the placing on the market of a foodstuff and only few Member States (in particular the UK and at the Netherlands) have developed special procedures for the placing on the market of novel foods.

However, with the recent emergence of a new range of materials, processes and technologies, including modern biotechnology and genetic modification techniques - aiming for example at improving the nutritional and dietary aspects of foodstuffs or at promoting greater technical efficiency in processing or distribution - the Commission considered it desirable that "novel foods" resulting from these innovations should undergo a safety assessment and, in certain cases an authorisation procedure.

The objective of the proposal is therefore both increased consumer protection and to ensure the smooth running of the internal market by avoiding the emergence of trade barriers.

After the presentation of the state of discussions in European Parliament and Council, the paper deals with the three key aspects of the proposal: the scope of the proposed regulation, the procedure for the placing on the market of novel foods and the question of labelling.

The proposed Regulation covers all novel foods and novel food ingredients, including but not only foods derived by modern biotechnology. In order to fall under the scope of the Regulation two conditions have to be met: the food or food ingredients has not hitherto been used for human consumption to a significant degree in the European Union and it falls under one of the categories mentioned in the proposal. It is explained that while foods and food ingredients containing or consisting of genetically modified organisms are always covered by the Regulation, those simply produced from genetically modified organisms are covered in principle but are excluded if their substantial equivalence to conventional foods or food ingredients can be established. Additives are excluded because specific authorisation procedures already exist.

As to the procedure for the placing on the market of a novel food or food ingredient, a pre-marketing assessment with different responsibilities assigned to Member States and the commission and the possibility for objections is foreseen. After an initial evaluation carried out by a national food assessment body a food either gets a "green light" and can be placed on the market, or, in the case of objections, become subject to a full assessment by the Scientific Committee for Food and to an authorisation procedure. This procedures

allows for an efficient "sorting out" between easy, straightforward products and those requiring a full assessment. In the case of foods containing genetically modified organisms, an environmental risk assessment is integrated in the authorisation procedure.

Finally, the paper explains the Commission's approach to labelling. The general labelling requirements laid down in Community legislation, in particular Directive 79/112/EEC, apply to all novel foods. According to Community legislation processes are nor generally labelled unless their use has an impact on the final product.

Therefore, the Commission is in favour of a functional levelling of novel foods. The Consumer has to by systematically informed of any significant differences with regard to nutritional composition, conditions of correct use, presence of an unexpected allergen, et. Between the novel food or novel food ingredient and the equivalent conventional food or food ingredient. The concrete labelling requirements can only be decided on a case by case basis. A generic undifferentiated label stating for instance "product of gene technology" would not provide the consumer with any meaningful information on the nature and characteristics of the product but would simply stigmatise the use of a particular technology.

Moreover, it would be extremely difficult to enforce and therefore become meaningless, given the different stages of transformation and given the functional labelling approach adopted by the Union's main trading partners.

The paper ends with an assessment of the proposal in the light of the international approaches taken in this area and underlines the importance of international harmonisation.