Biotechnology and food safety

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1. INTRODUCTION

A Joint FAO/WHO Expert Consultation on Biotechnology and Food Safety was held in Rome from 30 September to 4 October 1996. The Consultation participants are listed in Annex 1. The Consultation was opened by Dr. H. de Haen, Assistant Director-General, Economic and Social Department, FAO, who welcomed the participants on behalf of the Directors-General of FAO and WHO. In his opening remarks, Dr. de Haen also recognized the participation of, and thanked, the Italian Ministry of Health who had graciously provided the venue for the Consultation, the Istituto Superiore di Sanità.

In welcoming the participants, Dr. de Haen recalled the first joint consultation on this subject which was held in 1990. That consultation addressed the assessment of food safety issues related to the use of biotechnology in both food production and processing. Dr. de Haen noted that safety assessment strategies for several food categories and food additives were recommended by that first consultation. In arriving at those strategies, that consultation detailed both general and specific issues that should be considered in making safety assessments.

Evaluation of the safety of a food or food component produced by biotechnology involves a variety of both scientific and technological issues, all of which bear upon the final decision regarding safety. Dr. de Haen pointed out that different approaches to this problem have been developed and used by various national governments, or have been proposed by various international organizations. Additionally, in the years since the first consultation, both FAO and WHO have provided information and guidance on food safety assessment issues through international workshops and technical consultations. The present Consultation had therefore much information from these sources to consider during its deliberations.

Biotechnology provides new and powerful tools for research and for accelerating the development of new and better foods. Dr. de Haen outlined FAO's position that modern biotechnologies should be used as adjuncts to, and not as substitutes for, conventional technologies in solving problems related to food production or processing. Within the past few years, a variety of foods produced using biotechnology have been approved in many countries. Examples are crops such as maize, potatoes, soybeans, tomatoes and oilseeds. The benefits of biotechnology are many and include providing resistance to crop pests to improve production and reduce chemical pesticide usage, thereby making major improvements in both food quality and nutrition. However, just as with any new means of food production, there are potential human health risks that must be considered when foods are developed using biotechnology. It is vitally important to encourage worldwide efforts to develop and apply appropriate strategies and safety assessment criteria for food biotechnology research and to ensure the wholesomeness and safety of the food supply. Dr. de Haen pointed out that this underlines the importance of this Consultation in providing international guidance in this area.

Dr. de Haen reminded the participants that they had been invited to the Consultation as independent experts and that their participation in the Consultation was to be in their individual capacity and not as a representative of any organization, affiliation or government.

Prof. Giuliano D'Agnolo, Deputy Director of the Istituto Superiore di Sanità and Vice President of the Italian Interministerial Biotechnology Commission, added his welcome to the participants and stated that in his opinion the environmental issues related to biotechnology have been well defined, and that the real challenge lies in assessing food safety. There are, of course, other issues including those related to consumer concerns and national regulatory policies.

The Consultation elected Dr. Steve Taylor as Chairman and Dr. M. Toyoda as Vice-Chairman. Dr. Ib Knudsen was appointed as Rapporteur. Dr. Taylor in his response noted that the Consultation had a clear charge to provide advice on safety assessment issues for foods and food components produced by biotechnology. In doing this, the focus must be on science and the need was to reach consensus on the state of the science relative to the various safety issues. Dr. Taylor pointed out that although this might appear initially to be an immense task, the Consultation was fortunate to be able to rely for background on the conclusions and recommendations reached by previous consultations and workshops including the 1990 consultation already referred to by Dr. de Haen.

2. BACKGROUND

The use of biotechnological processes, particularly genetic modification, is extremely important in devising new ways to increase food production, improve nutrient content, and provide better processing or storage characteristics. It follows that when new foods or food components are developed using biotechnology, there are both national legal requirements and consumer expectations for effective systems and procedures to assess the safety of the food or food component for consumption. Traditional food safety assessment techniques, based on toxicological testing as used for food additives, for example, may not always apply to foods or food components produced by biotechnology.

The first joint FAO/WHO consultation to address this problem was held in 1990 and was entitled, "Consultation on the Assessment of Biotechnology in Food Production and Processing as Related to Food Safety" (1). That consultation first reviewed the status of biotechnology as used in food production and processing. Foods derived from plant, animal and microbial sources were considered separately. The consultation then discussed foods derived from each source and detailed both general and specific issues to be considered when making a safety assessment of foods produced by biotechnology. Safety assessment paradigms were proposed for each food source. The consultation concluded by recommending safety assessment strategies for both foods and food additives produced by biotechnology. In doing so, the consultation recommended that safety assessment strategies should be based on the molecular, biological and chemical characteristics of the food to be assessed and that these considerations determine the need for, and the scope of, traditional toxicological testing. In this connection, the consultation stated, "This approach leads to a strategy for the evaluation of a product based on a knowledge of the process by which it has been developed, and a detailed characterization of the product itself". With respect to toxicological testing, the consultation considered that, "... classical toxicity tests may have limited application in the safety assessment of whole foods and ... even for materials traditionally evaluated by these procedures, there is a need to review them with a view to developing a more mechanistic

approach to safety assessment" (1). A fundamental conclusion of the consultation concerning modern biotechnology was that, "The use of these techniques does not result in food which is inherently less safe than that produced by conventional ones" (1).

3. SCOPE

The Consultation addressed the evaluation of the safety, for purposes of consumption, of all food and food components produced using techniques involving biotechnology, whether plant, animal or microbial in origin.

The 1990 joint FAO/WHO consultation defined biotechnology as "the integration of natural sciences and engineering sciences in order to achieve the application of organisms, cells, parts thereof and molecular analogues for products and services" (1).

The current Consultation agreed to focus its attention on the provision of recommendations for international guidelines for safety assessment, for the purposes of consumption, of foods and food components which have been produced by techniques that change the heritable traits of an organism, such as recombinant DNA (rDNA) technology.

Excluded from consideration were incidental residues in food resulting from the use of processing aids, or derived from the use of chemicals such as pesticides and veterinary drugs during food production. Also excluded from consideration was the subject of animal feedstuffs, as well as contaminants such as food-borne pathogens.

The Consultation further did not consider environmental safety issues related to the release of food organisms, foods or food components produced using biotechnology, into the environment as these were outside its defined scope. The Consultation also did not consider any issues regarding the labelling of such foods or food ingredients, apart from those considered by the Consultation to be necessary on the grounds of food safety or nutritional value.

4. FOOD SAFETY CONSIDERATIONS

Food safety considerations regarding organisms produced by techniques that change the heritable traits of an organism, such as rDNA technology, are basically of the same nature as those that might arise from other ways of altering the genome of an organism, such as conventional breeding. These include:

- the direct consequences (e.g. nutritional, toxic or allergenic effects) of the presence in foods of new gene products encoded by genes introduced during genetic modification;

- the direct consequences of altered levels of existing gene products encoded by genes introduced or modified during genetic modification;

- the indirect consequences of the effects of any new gene product(s), or of altered levels of existing gene product(s), on the metabolism of the food source organism leading to the presence of new components or altered levels of existing components;

- the consequences of mutations caused by the process of genetic modification of the food source organism, such as the interruption of coding or control sequences or the activation of latent genes, leading to the presence of new components or altered levels of existing components;

- the consequences of gene transfer to gastrointestinal microflora from ingested genetically modified organisms and/or foods or food components derived from them; and,

- the potential for adverse health effects associated with genetically modified food microorganisms.

The presence in foods of new or introduced genes *per se* was not considered by the Consultation to present a unique food safety risk since all DNA is composed of the same elements.

5. SAFETY ASSESSMENT

The concept of substantial equivalence

Food safety is defined as providing assurance that food will not cause harm to the consumer when it is prepared and/or eaten according to its intended use (2).

The report of the 1990 joint FAO/WHO consultation established that the comparison of the final product with one having an acceptable standard of safety provides an important element of safety assessment (1). The Organization for Economic Cooperation and Development (OECD) has elaborated this concept and advocated that the concept of substantial equivalence is the most practical approach to address the safety evaluation of foods or food components derived by modern biotechnology (3). Substantial equivalence embodies the concept that if a new food or food component is found to be substantially equivalent to an existing food or food component, it can be treated in the same manner with respect to safety (i.e. the food or food component can be concluded to be as safe as the conventional food or food component). Account should be taken of any processing that the food or food component may undergo as well as the intended use and the intake by the population.

Establishment of substantial equivalence is not a safety assessment in itself, but a dynamic, analytical exercise in the assessment of the safety of a new food relative to an existing food (4). The comparison may be a simple task or be very lengthy depending upon the amount of available knowledge and the nature of the food or food component under consideration. The reference characteristics for substantial equivalence comparisons need to

be flexible and will change over time in accordance with the changing needs of processors and consumers and with experience.

The assessment of the safety of genetically modified organisms must address both intentional and unintentional effects that may result as a consequence of the genetic modification of the food source. These effects may also arise from food sources derived from conventional breeding. Genetic modification of an organism can result in unintended effects on the phenotype of that organism, such as changes in growth or reduced tolerance to environmental stress, which are readily apparent and typically eliminated by appropriate selection procedures. However, other unintended effects such as alterations in the concentration of key nutrients or increases in the level of natural toxicants cannot be readily detected without specific safety assessment.

An assessment of substantial equivalence can be carried out at the level of the food or food component which will be used as human food. Where possible, a determination of substantial equivalence should consider comparisons as close to the species level as possible in order to allow the flexible use of many types of food products from the species in question (e.g. modified soybean). This will entail consideration of molecular characterization, phenotypic characteristics, key nutrients, toxicants and allergens. For certain food products, comparison at the food product level would permit a conclusion of substantial equivalence even though a comparison at the species level would consider the product to be substantially equivalent except for a defined difference (e.g. oil from herbicide tolerant canola). The approach is to compare the food or food component from the genetically modified organism to the range of values obtained for the traditional counterpart, taking into account the natural variation in range for the host organism and for foods and food components obtained therefrom. The data required to demonstrate substantial equivalence may come from a variety of sources including existing databases, the scientific literature or data derived from the parental and/or other traditional strains/varieties. Regardless of the techniques used to produce new food organisms, attention must be paid to the impact of growth conditions on levels of nutrients and toxicants; for example, in the case of new plant cultivars, attention must be paid to the impact of different soils and climatic conditions.

This comparative approach should lead to one of three possibilities. It may be possible to demonstrate that a genetically modified organism, or a food or food component derived from it, is substantially equivalent to a conventional counterpart already available in the food supply. If it is not possible to demonstrate substantial equivalence, it may be possible to demonstrate that the genetically modified organism or food/component derived from it is substantially equivalent to its conventional counterpart apart from certain defined differences. Finally, it may not be possible to demonstrate substantial equivalence between the genetically modified organism or food/component derived therefrom and a conventional counterpart, either because differences are not sufficiently well-defined or because there is no appropriate counterpart with which to make a comparison.

While there may be limitations to the application of the substantial equivalence approach to safety assessment, this approach provides comparable or increased assurance of the safety of food products derived from genetically modified organisms relative to food products

derived by conventional methods. The Consultation recommended that safety assessment based upon the concept of substantial equivalence be applied in establishing the safety of food products derived from genetically modified organisms.

Further strains/varieties may be derived from genetically modified organisms by conventional techniques, such as traditional animal or plant breeding. Where the genetically modified organisms have been determined to be acceptable as a result of the safety assessment, these further strains/varieties should be assessed on their own merits according to practices applied for the assessment of conventionally-derived organisms.

5.1 Products that are shown to be substantially equivalent to existing foods or food components

Background: characterization of the modified organism

It is necessary to gather information to characterize the genetically modified organism from which a food under consideration is derived. This information is needed before decisions can be taken regarding the parameters to be examined in establishing whether or not substantial equivalence exists between a new food and an existing food. Several of the strategies and guidelines which currently exist (see references, Section 9) to address genetically modified food products were reviewed and the following relevant information from these might be considered:

Host

Origin; taxonomic classification; scientific name; relationship to other organisms; history of use as a food or as a food source; history of production of toxins; allergenicity; infectivity (microorganisms); presence of anti-nutritional factors and physiologically active substances in the host species and closely-related species; and significant nutrients associated with the host species.

Genetic modification and inserted DNA

Vector/gene construct; description of DNA components, including source; transformation method used; and promoter activity.

Modified organism

Selection methods; phenotypic characteristics compared to host; regulation, level and stability of expression of introduced gene(s); copy number of new gene(s); potential for mobility of introduced gene(s); functionality of introduced gene(s); and characterization of the insert(s).

Determination of substantial equivalence: characterization of the food product

A determination of substantial equivalence can be carried out at the level of the food source or the specific food product. This entails a consideration of the molecular characterization of the new food source; phenotypic characteristics of the new food source in comparison to an appropriate comparator already in the food supply; and the compositional analysis of the new food source or the specific food product in comparison to the comparator. The comparison may be made to the parental line/strain and/or other edible lines/strains of the same species, or it can build on a comparison of the derived food product (e.g. protein, carbohydrate or fat) with the analogous conventional food product. The data required to demonstrate substantial equivalence may come from a variety of sources including existing food component databases, type culture collections, the scientific literature or specific analyses carried out on the modified food product with the conventional food product serving as a concurrent control.

Substantial equivalence is established by a demonstration that the characteristics assessed for the genetically modified organism, or the specific food product derived therefrom, are equivalent to the same characteristics of the conventional comparator. The levels and variation for characteristics in the genetically modified organism must be within the natural range of variation for those characteristics considered in the comparator and be based upon an appropriate analysis of data.

Phenotypic characteristics

For plants this would include: morphology, growth, yield, disease resistance, and other characteristics which would normally be measured by plant breeders for a given crop.

For microorganisms this would include: taxonomic characterization (e.g. traditional culture methods, ribotyping, physiology etc.), colonization potential, infectivity, host range, presence of plasmids, antibiotic resistance patterns, and toxigenicity.

For animals this would include: morphology, growth, physiology, reproduction, health characteristics and yield.

Compositional comparison

The compositional analysis of a genetically modified organism, or a specific food product derived therefrom, should provide sufficient information on composition to allow an effective comparison to a conventional comparator already available in the food supply, for the purpose of determining substantial equivalence.

Critical components are determined by identifying key nutrients and toxicants for the food source in question. Analyzing a broader spectrum of components is in general unnecessary, but should be considered if there is an indication from other traits that there may be an unintended effect of the genetic modification.

Key nutrients are those components in a particular food product which may have a substantial impact in the overall diet. These may be major constituents (fats, proteins, carbohydrates) or minor compounds (minerals, vitamins). The determination of the key nutrients to be assessed may be influenced in part by knowledge of the function and expression product of the inserted gene.

Key toxicants are those toxicologically significant compounds known to be inherently present in the species, such as those compounds whose toxic potency and level may be significant to health (e.g. solanine in potatoes if the level is increased, selenium in wheat). The determination of the key toxicants to be assessed may be influenced, in part, by knowledge of the function and expression product of the inserted gene.

In determining key nutrients and toxicants, differences among consumption patterns and practices in various cultures and societies must be recognized. The key nutrients and toxicants to be examined may differ in different regions, so they should be determined using consumption data for the target region. The more critical the nutrient or toxicant, the more attention needs to be paid to the implication of comparative differences when establishing substantial equivalence. Thus, some conclusions from the substantial equivalence determination may not be equally valid in all regions. However, this should not require a complete reassessment of safety in a new jurisdiction, but only consideration of those aspects that can be justified on health grounds, such as the impact of the specific nutrient content based upon composition and intake.

In addition to analysis of key nutrients and toxicants, the extent of the analysis for unintended effects will, in part, be determined by the nature of the intended alteration and by the data from molecular and phenotypic characterization. Additional tests may be necessary if these analyses point to possible unintended effects (e.g. allergenicity).

Outcome of assessment: establishment of substantial equivalence

Products which are demonstrated to be substantially equivalent to an existing counterpart are regarded as being as safe as that counterpart and no further safety considerations than for the counterpart are necessary.

5.2 Products that are substantially equivalent to existing foods or food components except for defined differences

When a food product is determined to be substantially equivalent to an existing counterpart except for defined differences, it was concluded by the Consultation that further safety assessment should focus only on those defined differences. Typically the defined differences will result from the intended effect of the introduction of genetic material that encodes for one or more proteins that may or may not modify endogenous components or produce new components in the host organism. This category could also include products

from genetic modification and that have been shown to produce an unintended substance(s) if that unintended substance(s) is clearly defined. The safety of introduced DNA and messenger RNA (mRNA) *per se* is not an issue. However, the stability of introduced genetic material and the potential for gene transfer are relevant issues in the assessment. The potential for gene transfer is addressed in Section 6.2. Stability of introduced genetic material should be addressed during both the molecular characterization and the performance evaluation of the genetically modified organism in the development process. These processes minimize the likelihood of unintended effects in subsequent generations.

The Consultation considered that the majority of genetically modified products will result from the introduction of genetic material and therefore concentrated on the safety assessment of these types of products. However, the approaches described herein are equally applicable to the assessment of the safety of products which have been genetically modified by other means. The approach to assessing the safety of food products having inserted genetic material should focus on the gene product(s) and their function, including the products produced as a result of their function. The introduced genetic material will typically encode one or more proteins. The safety assessment should concentrate on both the safety of the expressed protein(s) as well as the products produced as a result of the expressed protein(s). These products will most likely include; fats, carbohydrates or modified or new small molecule components (modification of endogenous components or production of new components).

The safety assessment of proteins should focus on the structure, function and specificity of the protein(s) and its history of use in foods, if any. Information on these should be evaluated prior to deciding whether and what type of safety evaluation may be appropriate to assess the safety of the protein(s). Proteins in general do not raise significant safety concerns due to the large protein component of the human diet. The typical eukaryotic cell contains tens of thousands of different proteins. Genetic polymorphism (the occurrence of more than one allele of a gene) also contributes to the diversity of proteins in the diet. Generally proteins that are currently consumed or functionally similar to proteins known to be safely consumed (including minor variations in structure or function), would not raise safety concerns (5). Variation in proteins may also result from post-translational processing, for example glycosylation or methylation patterns of the host plant. Proteins that are not functionally similar to proteins known to be safely consumed should be assessed relative to their potential toxicity and allergenicity. A very limited number of proteins are known to be toxic to vertebrates and those proteins, including bacterial and animal toxins, have been well characterized (6). Proteins that would raise a safety concern can be identified by knowing the source, amino acid sequence and function of the introduced gene(s)/protein(s). Sound scientific practice dictates that toxic proteins should not be introduced into food. If a gene is obtained from a source known to produce a mammalian protein toxin or if the introduced protein shares significant amino acid homology to a known mammalian protein toxin, an acute gavage or other *in vitro* or *in vivo* tests should be considered to provide assurance that the introduced protein is not toxic to mammals. Proteins that are transferred into food products should be assessed as to their potential allergenicity as described in Section 6.1. to provide assurance that allergenic proteins are not transferred.

Structure, function and specificity

Generally, there will be significant knowledge on the structure, function and specificity of proteins introduced into foods through genetic modification. This information is key to determining what safety assessment is warranted as well as elucidating what products will be produced as a result of the biological activity of expressed protein(s). For example, a protein that performs the same or similar function (e.g. enzymes) as an endogenous protein will not likely raise a significant safety concern. Likewise, for a protein such as the insecticidal proteins from *Bacillus thuringiensis* that are active against target insects but not mammals, fish or non-target insects, information on the specificity and mode of action is important. *In vitro* studies showing binding of the insecticidal protein to gut tissue of target insects but lack of binding to mammalian tissue clearly provides important information to determine what additional data on protein safety is warranted.

Generally, the function of proteins that have been introduced into foods through genetic modification have been well characterized and these proteins are not known to exert toxic effects in vertebrates. If such well-characterized proteins do not exhibit unusual functions, further safety testing will generally be minimal. Demonstration of the lack of amino acid sequence homology to known protein toxins/allergens and their rapid proteolytic degradation under simulated mammalian digestion conditions, is appropriate to confirm the safety of these proteins as well as proteins that are not substantially similar to proteins that are known to be safely consumed. Demonstration of proteolytic digestion under both gastric and intestinal conditions (7) supports the expectation that the protein would likely be degraded during food consumption/digestion. The conditions for these digestions (gastric at low pH and intestinal at neutral pH) support the expected digestion of the introduced protein, including digestion by those individuals that have modified gastric conditions, such as achlorhydria, in which the gastric pH is elevated. For a protein that is not rapidly digested, additional testing may need to be considered. The potential allergenicity of introduced proteins should be assessed as described in Section 6.1.

Certain groups of proteins or food products produced from the introduced proteins may require additional consideration, depending on the function of the protein or food product produced. Certain groups of proteins are known to exhibit antinutritional effects (e.g. lectins and protease inhibitors). Because processing may reduce or eliminate the toxic effects of these proteins, many foods that contain these toxic substances are deleterious when eaten raw but safe when properly processed. Sound scientific practice dictates that such toxic protein components should not be introduced into new food products, unless the resulting food is processed in a manner that would render the food safe.

Proteins may be introduced that are enzymes and produce products such as carbohydrates, fats and oils, or small molecule components. Developments that affect carbohydrates will often be modifications of food starches, which are likely to affect the content of amylose and amylopectin as well as the branching of amylopectin. Such modified starches are likely to be functionally and physiologically equivalent to starches commonly found in food and thus not raise any specific safety concerns However, if a food source organism is genetically modified to produce high concentrations of an indigestible

carbohydrate that normally occurs at low concentrations, or to convert a normally digestible carbohydrate to an indigestible form, nutritional and physiological questions may arise that must be addressed.

Some alterations in the composition or structure of fats or oils, such as an alteration of the saturation of unsaturated fatty acids, may have significant nutritional consequences or result in marked changes in digestibility. Such changes may warrant a change in the common or usual name of that product that reflects the new composition of the substance. Additionally, safety questions may arise as a result of the presence of fatty acids with chain lengths greater than C22; fatty acids with cyclic substitutions; fatty acids with functional groups not normally present in fats and oils; and fatty acids of known toxicity, such as erucic acid.

The concept of substantial equivalence can be applied to assess the safety of these components of the food by comparing them to similar components present in other existing foods. For example, a canola (a low erucic acid rapeseed oil) variety was recently developed that produced high levels of lauric acid, a fatty acid not normally found in canola (8). This fatty acid has a history of safe consumption as a significant component of edible tropical oils. Therefore, substantial equivalence at the component level was used to assess the safety of this product. The expected uses and patterns of consumption were also assessed in the overall safety assessment of this product. The "common or usual" name of this product was changed to reflect the compositional changes and altered uses.

Genes may be introduced into organisms that encode one or more proteins that result in the production of a new or modified small molecule component in the host organism. The safety of these products should be assessed based on the knowledge of the product produced, the characteristics of the product and the history of safe use of the same or similar product in other foods. Some of these products may require additional testing, including appropriate *in vitro* or *in vivo* testing, depending on the uniqueness of the product and the knowledge of its function and similarity to existing products used in food. The Consultation recognized the difficulties in performing *in vitro* and *in vivo* testing with whole foods and recommended that any additional testing be carefully designed with very specific objectives and using validated methods.

5.3 Products that are not substantially equivalent to existing foods or food components

Up to the present time, and probably for the near future, there have been few, if any, examples of foods or food components produced using genetic modification which could be considered to be not substantially equivalent to existing foods or food components. Nevertheless, it is conceivable that with future developments in biotechnology, products could be developed which could be considered to have no conventional counterpart and for which substantial equivalence could not be applied. For example, there could be products derived from organisms in which there has been transfer of genomic regions which have perhaps been only partly characterised.

If a food or food component is considered to be not substantially equivalent to an existing food/component, it does not necessarily mean it is unsafe and not all such products will necessarily require extensive testing. Such a food or food component should be evaluated on the basis of its composition and properties. However, a sequential approach to assess the safety and wholesomeness of these foods should be considered. First, it will be necessary to characterise the product based on information as described in Section 5.1. This includes details of the host organism, the genetic modification and inserted DNA, as well as properties of the modified organism/product with respect to phenotype and chemical and nutritional composition. Where a modification has involved the insertion of genomic regions which have been poorly characterised it will also be important to consider the donor organism.

The results of this initial characterization and the role that the product is to play in the diet will determine whether further safety testing is needed. Although many protocols exist to test food ingredients, these methods were not designed to test the safety of complex whole foods. In particular, the use of animal feeding studies has many limitations because of the insensitivity of the test system in the detection of low level effects, problems of diet balancing and the problem of assigning adverse effects to specific major foods or food components. Despite these limitations, there are no alternatives at the present time, and if animal studies are deemed appropriate, their objectives should be clear and care taken in the experimental design.

Because of these difficulties, a tailored testing programme should be devised for these products on a case-by-case basis depending on the information generated during the initial characterization. This could involve testing as described under Section 5.2 for products having new inserted traits such as new proteins, fats or carbohydrates. A combination of *in vitro*, and specific *in vivo* animal models may need to be employed to further assess the safety of the product. Particular attention needs to be paid to bioavailability of new food components as well as wholesomeness. With respect to nutritional aspects, human studies may need to be carried out, especially where the new product is intended to replace a significant part of the diet. These should only be carried out when animal studies have shown that the product is not toxic. Attention should be paid to sensitive segments of the population. Furthermore, it will be important to take into account regional variations for foods which will have international distribution.

Because there are presently no satisfactory animal test methods which can be employed for these types of products and other types of novel foods and food components, attention should be paid to the development of appropriate methods.

Experience gained in assessing new foods which are not substantially equivalent to existing foods will serve in subsequent evaluations of similar types of products.

6. SPECIAL ISSUES

6.1 Allergenicity

A food allergy is an adverse reaction to an otherwise harmless food or food component that involves the body's immune system in the production of antigen-specific IgE[1] to specific substances in foods. Surveys suggest that up to one-third of all adults believe that they, at one time or another, have had food allergies. Yet, true food allergy is estimated to affect less than 2% of the population (9). Children are at greater risk with up to 5% of infants having food allergies which are often outgrown. Allergic reactions can occur virtually to any food, though most reactions are caused by a limited number of foods. The 1995 FAO Technical Consultation on Food Allergies concluded that the most common allergenic foods associated with IgE-mediated reactions and on a worldwide basis were fish, peanuts, soybeans, milk, eggs, crustacea, wheat, and tree nuts (9). These commonly allergenic foods account for over 90% of food allergies, although an extensive literature search has revealed more than 160 foods associated with sporadic allergic reactions. Gluten-containing cereals (wheat, rye, barley, oats and spelt) were also specifically added to the list established by that FAO Technical Consultation because of their implication in the etiology of gluten-sensitive enteropathy.

Allergic reactions to foods due to antigen-specific IgE usually begin within minutes to a few hours after eating the offending food. Very sensitive persons can experience a reaction from exposure to trace quantities of the offending food. Life-threatening reactions can occur in some individuals particularly following large exposures to the offending food. An individual allergic to a specific food must avoid that food, in part through careful reading of food labels. This is because no treatment is yet available to prevent specific allergic reactions to food.

Almost all food allergens are proteins, although the possibility exists that other food components may also act as haptens[2]. While the crops from which staple foods are derived contain tens of thousands of different proteins, relatively few are allergenic. The distribution of those proteins varies in different parts of the plant and can be influenced by environmental factors such as climate and disease stress. Conventional breeding introduces additional protein diversity into the food supply. However, variations in the protein composition of our diet brought about through conventional crop improvement practices have had little, if any, effect on the allergenic potential of our major foods. In contrast, altered dietary preferences can have significant implications for the development of food allergies. For example, allergy to peanut (groundnut) occurs at a significant frequency in North America and Western

[1] IgE, or immunoglobin E, is a protein that recognizes an allergen. It circulates in the blood, and becomes fixed on the surface of specific cells (basophils and mast cells). When IgE on the cell surface binds to allergen, this triggers the release of chemicals which cause allergic reactions.

[2] Haptens are small molecules which may react with body proteins and cause these proteins to become allergenic.

Europe but not in other countries where peanuts are less commonly eaten. Also, recent food introductions, such as kiwi fruit, have proven to be additional sources of food allergens. These observations provide confidence that there are not a large number of potential allergens in the food supply, but show that new allergenic foods are sometimes introduced into the marketplace.

Because of the above, a clear need exists to pay particular attention to allergenicity when assessing the safety of foods produced through modern biotechnology. The difficulties of predicting potential allergenicity of foods derived from genetically modified plants, animals, and microorganisms requires the examination of a number of parameters which are common to many food allergens. These characteristics facilitate the identification of potentially allergenic gene products, although a single criterion is insufficient to confirm allergenicity or lack thereof. Relevant criteria include:

a. Source of transferred genetic material: Particular caution must be exercised if the source of this material contains known allergens.

b. Molecular weight: Most known allergens are between 10,000 and 40,000 molecular weight.

c. Sequence homology: The amino acid sequence of many allergens is readily available.

d. Heat and processing stability: Labile allergens in foods that are eaten cooked or undergo other processing before consumption are of less concern.

e. Effect of pH and/or gastric juices: Most allergens are resistant to gastric acidity and to digestive proteases.

f. Prevalence in foods: New proteins expressed in non-edible portions of plants, for example, are not of a concern in terms of food allergy.

In the assessment of gene products, the amino acid sequence should be compared against the database(s) of all known allergens, in order to screen for immunologically significant sequence similarities. Gene products from sources with no allergenic history and that lack immunologically significant sequence identity to known allergens should still be subjected to physicochemical evaluation. If a gene product is found to have the physicochemical characteristics of an allergen, caution must be used and regulatory agencies may wish to consider some appropriate action. For example, a gene product from an organism not commonly consumed could be expressed in a common food, exhibit a relevant sequence similarity to a known food allergen, and be resistant to acid and protease degradation. The concern in that case would be that the allergenicity of the product would only be noted following exposure of a reasonable population number. Such an association between a modified food and allergic reactions would in all probability be more likely to be recognized if the food was identifiable. Comprehensive stepwise approaches to the assessment of potential allergenicity employing the above principles are available (10, 11). The

Consultation noted that, unfortunately, reliable animal models for the assessment of the allergenicity of genetically modified foods do not presently exist, although the development of such models is to be encouraged.

Clinical reagents and test subjects should be available to conduct a valid assessment of the potential of a gene product obtained from an allergenic food to be an allergen for an individual sensitive to the food which was the source of the gene product. Thus, new proteins produced from genes derived from allergenic foods should be first subjected to *in vitro* assays (12) which use sera from individuals documented as being sensitive to the food that is the source of the gene, in order to identify if allergens have been transferred. Negative or equivocal results from *in vitro* assays should be followed by using approved *in vivo* skin prick tests with sensitive test subjects. Absence of allergens from known allergenic foods may be further confirmed by appropriately designed and approved challenge procedures in sensitive subjects (12). Foods that fail to elicit positive results in *in vitro* or *in vivo* tests should be treated like any other food in regards to allergenicity. Foods that are found to contain an allergen transferred from the organism which provided the DNA should not be considered for marketing approval unless they can be clearly identified in the marketplace and this identity would not be lost during distribution or processing. Labelling approaches may not be practical in all situations, and the specific problem of consumers who cannot read labels or who may not be provided with labels should be taken into account.

6.2 Gene transfer from genetically modified plants[3]

The Consultation noted that the most relevant food safety issue concerning gene transfer is the potential consequence of the transfer of an introduced gene from material derived from a genetically modified organism to microorganisms in the gastrointestinal (GI) tract, in such a way that the gene can be successfully incorporated and expressed, and result in an impact on human or animal safety.

Marker genes are inserted into genetically modified plants to facilitate identification of genetically modified cells or tissue during development. There are several categories of marker genes, including herbicide resistance genes and antibiotic resistance genes. Antibiotic resistance markers have been utilized during the transformation/selection process in the development of the vast majority of genetically modified plants. Their continued use in plants remains critical to the production of genetically modified plants. The Consultation therefore focused on these particular marker genes.

With respect to the potential for gene transfer from genetically modified plants to microorganisms in the GI tract, the Consultation supported the conclusions and

[3] The Consultation was unaware of antibiotic resistance genes currently being used as a marker for the genetic modification of animals intended for food use. Therefore, the transfer of genes from food derived from genetically modified animals was not specifically addressed. However, the same principles considered for the transfer of gene(s) from the food derived from genetically modified plants would be equally applicable.

recommendations of the 1993 WHO Workshop entitled "Health Aspects of Marker Genes in Genetically Modified Plants" (13). That workshop, as well as this Consultation, focused on the potential for transfer of antibiotic resistance genes since these genes are the most likely to raise safety concerns if they were to be transferred and expressed in gastrointestinal microflora. Were this to occur, it could potentially affect the therapeutic efficacy of antibiotics. In regards to genetically modified plants, the WHO Workshop concluded that "there is no recorded evidence for the transfer of genes from plants to microorganisms in the gut" and that there are no authenticated reports of such bacterial transformation in the environment of the human gastrointestinal tract. The first of these conclusions was based on the judgement that transfer of antibiotic resistance would be unlikely to occur given the complexity of steps required for gene transfer, expression and impact on antibiotic efficacy. In order for gene transfer to take place, the following events would need to occur:

- the plant DNA would have to be released from the plant tissue/cells and survive in the presence of the hostile environment of the GI tract, including exposure to gastric acid and nucleases;
- the recipient microorganisms would have to be competent for transformation;
- the recipient microorganisms would have to bind the DNA to be transferred;
- the DNA would have to penetrate the cell wall and translocate across the cell membrane;
- the DNA would have to survive the restriction/modification system developed by the microorganism to degrade foreign DNA; and,
- the DNA would have to be integrated into the host genome or plasmid, which requires at least 20 base pairs in a complete homologous DNA sequence for significant recombination at both ends of the foreign DNA.

The likelihood that foreign DNA would persist in a microorganism would be significantly enhanced under conditions that would exert selection pressure. Such conditions are generally considered to be restricted to antibiotic selectable markers and then only under the conditions of oral therapeutic use of the corresponding antibiotic. Only when an antibiotic resistance marker is under the control of an appropriate bacterial promoter would the antibiotic resistance gene potentially be expressed and thereby provide a selective advantage to a recipient microorganism. Antibiotic markers under plant promoters would not be expressed in a microorganism; therefore, in this situation the presence of the antibiotic would not provide a selective pressure.

The Consultation concluded, consistent with the WHO workshop, that as the possibility of horizontal gene transfer is considered to be vanishingly small, data on such gene transfer will only be needed when the nature of the marker gene is such that, if transfer were to occur, it gives rise to a health concern. In assessing any potential health concerns, the

human or animal use of the antibiotic and the presence and prevalence of resistance to the same antibiotic in gastrointestinal microflora should be considered.

Given that the likelihood of transfer of a gene from a genetically modified plant to a microorganism in the GI tract is remote but cannot be entirely ruled out, the Consultation recommended that FAO/WHO convene an expert consultation to address whether there are conditions or circumstances in which antibiotic marker gene(s) should not be used in genetically modified plants intended for commercial use and, if so, to define those conditions/circumstances. For example, the Consultation noted that the antibiotic vancomycin is critical in the treatment of certain bacterial diseases where multiple antibiotic resistance is prevalent, due to the lack of alternatives.

In Section 5.2 the Consultation discussed issues related to assessing the safety of expressed proteins. In addition to the factors considered in that section, the specific issue related to the use of antibiotic marker genes expressed in the plant, is the potential to adversely effect the therapeutic efficacy of orally administered antibiotics. Factors that should be considered in the assessment of potential impact on such antibiotic efficacy, include:

- the function and specificity of the expressed product (typically an enzyme);
- the digestibility of the expressed protein;
- the expression level of the expressed protein;
- the availability of any required cofactor in the gastrointestinal tract; and,
- the human or animal use of the antibiotic, taking into account those populations that consume the food product.

6.3 Gene transfer from genetically modified microorganisms

The Consultation noted that there are well-known mechanisms of transfer of genetic material between microorganisms, such as transduction and conjugation. Transformation of naked DNA into microorganisms in the GI tract has not been conclusively demonstrated.

The probability of gene transfer in the GI tract has to be assessed in the light of the nature of the genetically modified organism and the characteristics of the gene construct. Possible consequences of a transfer event should be assessed based on the function and specificity of the transgene. The likelihood of maintenance of the transferred gene in a recipient microorganism increases if the gene confers to the microorganism a selective advantage. Factors that may enhance the selective advantage over other organisms or the colonization ability include: phage resistance, virulence, adherence, substrate utilization or production of bacterial antibiotics.

If the transferred gene is not expected to enhance any of the survival characteristics of the recipient gastrointestinal microorganism, no further safety assessment concerning these

characteristics would be required. If the function of the gene suggests that survival of the recipient organism would be enhanced, the possible health consequences need to be assessed, based on the function and specificity of the gene. The Consultation affirmed the recommendations from the 1990 FAO/WHO joint consultation (1) regarding genetically modified microorganism including: 1) that vectors should be modified so as to minimize the likelihood of transfer to other microbes; and, 2) selectable marker genes that encode resistance to clinically useful antibiotics should not be used in microbes intended to be present as living organisms in food. Food components obtained from microbes that encode such antibiotic resistance marker genes should be demonstrated to be free of viable cells and genetic material that could encode resistance to antibiotics.

The Consultation was not aware of any reports of transfer of genes from animal, plant or microbial origin into epithelial cells except for genes from infectious agents, such as viral DNA. However, even if such transfer were to occur, the transformed epithelial cells would not be maintained in the GI tract due to continuous replacement of these cells.

6.4 Pathogenicity of microorganisms

The Consultation reviewed the 1990 report (1) discussion of the issue of pathogenicity related to genetically modified microorganisms, and agreed that no new issues have arisen since that consultation. To summarize, microorganisms intended for use as food or in food processing should be derived from organisms that are known, or have been shown by appropriate tests in animals, to be free of traits that confer pathogenicity. Furthermore it was stated that assessment of viable genetically modified organisms as part of a food must also take into consideration characteristics that determine their survival, growth and colonizing potential in the GI tract, including the capability to undergo transformation, transduction and conjugation, and to exchange plasmids and phages. In this regard, a general principle was elaborated that design should be directed towards minimizing intrinsic traits in microbes that allow them to transfer genetic information to other microorganisms.

6.5 Genetically modified animals

The 1990 consultation (1) reviewed the safety assessment of genetically modified animals and foods derived from them and concluded *inter alia* that:

> "Mammals are important indicators of their own safety, since adverse consequences of introduced genetic material will generally be reflected in the growth, development and reproductive capacity of the animal. The principle that healthy mammals only should enter the food supply is of itself a method of ensuring the safety of foods derived from animals. Primarily because some fish and invertebrates are known to produce toxins, the healthy animal principle does not provide the same degree of assurance that food derived from such animals is safe and should be used with caution in determining the need for additional safety assessment".

The OECD report on "Safety Evaluation of Foods Derived by Modern Biotechnology: Concepts and Principles" (3), focused its attention on new foods of terrestrial origin and

concluded that, "In general, foods from new strains of mammals and birds that appear to be in good health have proven to be as safe as the animal breeds from which they were derived."

Subsequently OECD convened a workshop on "Aquatic Biotechnology and Food Safety" at which was discussed the notion that when a (domestic) animal appears healthy, this is an indication that the animal is safe to eat (14). It was recognized that the apparent good health of aquatic food organisms *per se* is not a useful indicator of food safety, because many such species are known to contain either exogenously or endogenously derived compounds that are toxic to humans. Individuals of such species frequently appear to be in good health because they are resistant, in some degree, to these toxins. However, if the notion of healthy appearance is applied in this sense, and if it is applied in conjunction with other attributes to assess safety, then it can still have utility when applied to food and food components derived from aquatic animals.

In general, the OECD workshop on Aquatic Biotechnology and Food Safety (14) considered it unlikely that techniques of modern biotechnology will increase the risk to human health if applied to aquatic organisms containing toxins. It is possible that modern breeding techniques could affect the metabolism and properties of such toxins, perhaps in ways that modify their effects. In such circumstances, however, the safety assessment of such organisms will depend on knowledge of, and on techniques to detect, toxins. Consequently, the fact that some aquatic food organisms might contain compounds toxic to humans does not reduce the value of the application of the concept of substantial equivalence. The OECD workshop also concluded that no issue could be identified which reduced or invalidated the application of the principle of substantial equivalence to food or food components derived from modern aquatic biotechnology. However, it was recognized that in some instances there may be a lack of appropriate data from the conventional species. This lack of data could lead to difficulties when making comparisons with the new food or food component. This problem arises, in part, because there is less familiarity with most aquatic organisms in food production when compared with terrestrial food animals and plants.

If animals are genetically modified to improve their resistance to bacteria and viruses that also represent a human health concern, appropriate hygiene measures should be taken to ensure that there are no food safety risks to consumers of the animal products.

Issues arising from the use of genetically modified animals for the production of pharmaceuticals and industrial chemicals are discussed in section 6.6.

6.6 Food organisms expressing pharmaceuticals or industrial chemicals

Genetic modification has considerable potential to enable the production of pharmaceuticals or industrial chemicals in varieties of organisms (plants, animals and microorganisms), that are also used as sources of food. The Consultation recognised that, generally, the genetically modified organism would not be used as food without prior removal of the pharmaceutical or industrial chemical.

The Consultation agreed that the safety assessment of pharmaceuticals and industrial chemicals, as such, was outside its remit. In situations in which the genetically modified organism or its products are used in food (usually after removal of the pharmaceutical or chemical), the Consultation agreed that the concept of substantial equivalence, as developed elsewhere in this report (see Section 5), could be used for the safety assessment of the food. Some such foods could be substantially equivalent to existing foods, apart from well defined differences whilst others (including meat from animals modified to express chemicals only in their milk) might be substantially equivalent to their conventional counterparts. There might also be situations in which the food would not be substantially equivalent to an existing counterpart.

In addition to concerns about food safety, the Consultation recognised that the genetic modification of food organisms to produce pharmaceuticals or industrial chemicals may raise ethical and control issues that were outside its remit because the issues were unrelated to food safety. The ethical issues relate to the scope for administering treatments to consumers without their knowledge. The Consultation agreed that this issue should be brought to the attention of FAO and WHO.

6.7 Databases

To facilitate the compositional comparisons necessary to establish substantial equivalence, it may be useful to use and even generate international databases containing validated data on the nutrient, allergen and, especially, toxicant composition of commonly used food organisms. If the genetically modified organism is being compared directly to its parent then the data will be developed when the modified organism and the parental organism are grown and analyzed under a limited number of selected environments that are representative of the conditions under which the modified organism will be used commercially.

Comparison of genetically modified plants with other commercial varieties will typically focus on data generated within these varieties grown within similar geographical regions and in which the new variety is intended to be grown commercially. Where compositional analyses of key nutrients and toxicants are required for the registration of a new plant variety, these data would be updated periodically for current commercial varieties. The published literature on these parameters would also serve as a source for this information. It is important that the reference ranges represent reasonably current information since the ranges will probably change over time.

In the case of plants, relevant information could be obtained from the international centres of the Consultative Group on International Agricultural Research (CGIAR), which holds the world-wide mandate for the conservation and use of genetic resources. These include the Centres for Genetic Resources Conservation and Breeding Research on specific crops; e.g. the International Maize and Wheat Improvement Centre (CIMMYT) (wheat and corn), the International Rice Research Institute (IRRI) (rice), the International Potato Centre (CIP) (potato and sweet potato) and the International Plant Genetic Resources Institute

(IPGRI). The FAO and the World Food Programme provide other sources of information on food composition.

Databases on microorganisms, mainly in the form of type culture collections, are in existence but not all are suited for the purpose of establishment of substantial equivalence.

The Consultation acknowledged that molecular databases (e.g. University of Wisconsin Database) are available and commonly used to identify genes/proteins of similar structure and/or function. These databases are also used to compare amino acid sequence homology of an encoded protein to known protein toxins or allergens. These databases should continue to expand as new genes/proteins are isolated and characterized.

The Consultation pointed to the need to develop and expand databases with valid data on the content and ranges of nutrients, toxicants and allergens in food organisms used throughout the world.

6.8 The application of rDNA technology in developing countries

Recombinant DNA technology has broad application in developing countries and has the potential for very positive impact on their economies, which are frequently agriculturally based. In this context the view has been expressed that rDNA technology might be of greater importance for developing countries than for industrialized countries. In particular, developing countries look on rDNA technology as a means of addressing the need to produce sufficient quantities of nutritionally adequate and safe food for their growing populations. The benefits of this technology are likely to impact directly on people at the production level as this technology is extremely easy to transfer, being "packaged in a seed". However, in order for the entire global population to fully benefit from rDNA technology, the safety assessment of food derived from genetically modified organisms requires trained manpower, up-to-date legislation and a food control system for its enforcement. This applies equally in all the countries of the world. Food safety issues, as outlined in Section 4, are not bound by national borders, and it is therefore important that countries that have inadequate resources for assessing rDNA technology and products derived from it, make special efforts to obtain these resources. Moreover, since globalization interconnects raw material production to processing and consumers of all regions of the world, it is imperative that proper safety assessment of foods and food components produced by genetic modification, be practised world wide.

7. CONCLUSIONS

1. Food safety considerations regarding organisms produced by techniques that change the heritable traits of an organism, such as rDNA technology, are basically of the same nature as those that might arise from other ways of altering the genome of an organism, such as conventional breeding.

2. Application of the concept of substantial equivalence is a basic tool in the assessment used to establish the safety of food products derived from genetically modified

organisms. It is not a safety assessment in itself, but is a dynamic, analytical exercise in the assessment of the safety of a new food or food component relative to an existing food/component.

3. The reference characteristics for substantial equivalence comparison need to be flexible and will change over time in accordance with changing needs of processors and consumers and with experience gained.

4. Substantial equivalence is established by a demonstration that the characteristics assessed for the genetically modified organism, or the specific food product derived therefrom, are equivalent to the same characteristics of the conventional comparator (conventional foods or food components already available in the food supply), within the natural variation for such characteristics, based upon an appropriate analysis of data.

5. The determination of substantial equivalence entails a consideration of the molecular characterization of the genetically modified organism, its phenotypic characteristics, and the key nutrients and toxicants for the food source in question. Analyzing a broader spectrum of components is in general unnecessary, but should be considered if there is an indication from other traits that there may be an unintended effect of the genetic modification.

6. While there may be limitations to the application of the substantial equivalence approach to safety assessment, this approach provides equal or increased assurance of the safety of food products derived from genetically modified organisms as compared to foods or food components derived by conventional methods.

7. When substantial equivalence is established for an organism or food product, the food is regarded to be as safe as its conventional counterpart and no further safety consideration is needed.

8. When substantial equivalence apart from certain defined differences is established, further safety assessment should focus on those defined differences. The Consultation established a sequential approach focusing on the new gene product(s) and the(ir) structure, function, specificity and history of use. If these indicate a potential safety concern, additional *in vitro* and/or *in vivo* studies may be appropriate.

9. When substantial equivalence cannot be established, it does not necessarily mean that the food product is unsafe. Not all such products will necessarily require extensive safety testing. The Consultation advised designing any testing program on a case-by-case basis taking into account the reference characteristics of the food or food component. The objectives should be clear and care should be taken in experimental design. Human nutritional studies may be required, especially when the new food is intended to replace a significant part of the diet.

10. Food allergies afflict a small percentage, but significant number, of consumers. Some of these consumers will experience life-threatening reactions upon exposure to foods to

which they are allergic. Thus, a rational scientific approach to the assessment of the allergenicity of genetically modified organisms can and should be undertaken.

11. The Consultation considered the possibility of horizontal gene transfer from genetically modified plants to be vanishingly small. Thus, data on gene transfer is only necessary when the nature of the marker gene is such that, if transfer were to occur, it would give rise to a human health concern. In assessing any such health concerns, the human and animal use of the antibiotic and the prevalence of resistance to the same antibiotic in the gastrointestinal microflora should be considered.

12. With respect to the genetic modification of animals, the Consultation endorsed the conclusions reached by the first FAO/WHO consultation (1) and by OECD (3), and in particular:

    - the concept of substantial equivalence is applicable to the safety assessment of animals and animal products including foods of aquatic origin.

    - in respect of safety assessment, mammals are important indicators of their own safety.

    - if animals are genetically modified to improve their resistance to bacteria and viruses that also represent a human health concern, appropriate hygiene measures should be taken to ensure that there are no food safety risks to consumers of the animal products.

13. Accessible databases on reference characteristics of plants, microorganisms and animals are of utmost importance for the establishment of substantial equivalence.

14. Recombinant DNA technology is of particular importance to developing countries as it can help to address the need to produce sufficient quantities of nutritionally adequate and safe food for their growing populations.

15. Since globalization interconnects raw material production to processing and consumers of all regions of the world, it is imperative that proper safety assessments be made of food produced by rDNA technology, world wide.

8. RECOMMENDATIONS

General recommendations

1. The Consultation affirmed the general recommendations made by the first FAO/WHO consultation (1), which are attached as Annex 2. In doing so, the Consultation emphasized the first recommendation of that consultation, that comprehensive and well-enforced food regulations are important in protecting consumer health, and that all national governments should ensure that such regulations keep pace with developing technology.

Specific recommendations

The Consultation RECOMMENDED that:

Substantial equivalence

2. Safety assessment based upon the concept of substantial equivalence, as described in this report, be applied in establishing the safety of foods and food components derived from genetically modified organisms.

Allergenicity

3. The transfer of genes from commonly allergenic foods should be discouraged unless it can be documented that the gene transferred does not code for an allergen.

4. Foods found to contain an allergen transferred from the organism which provided the DNA should not be considered for marketing approval unless such products can be clearly identified in the marketplace and this identity will not be lost through distribution and processing. Further, that labelling approaches may not be practical in these situations, and that particular problems exist for consumers who cannot read, or who may not be provided with labels.

5. Involved organizations should consider the appropriateness of, and/or actions to take, in respect to foods containing new protein(s) that are determined to have the characteristics of an allergen, even though no patient population is known to exist which has an allergy to this gene product.

6. The identification of food allergens and the characteristics of these allergens that define their immunogenicity be encouraged.

Gene transfer from genetically modified plants

7. FAO/WHO convene a workshop of experts to consider if there are conditions or circumstances and, if so, what those conditions or circumstances would be, that certain antibiotic resistant marker genes should be precluded from commercial food crops.

8. The Consultation affirmed the specific recommendations regarding genetically modified microorganisms of the 1990 FAO/WHO consultation (1) (see Annex 3).

Food organisms expressing pharmaceuticals or industrial chemicals

9. The Consultation recognized that the genetic modification of food organisms to produce pharmaceutical or industrial chemicals may raise ethical and control issues, outlined elsewhere in this report, that are outside its remit and recommended that these should be brought to the attention of FAO and WHO.

Databases

10. The Consultation stressed the need for the development, maintenance and accessibility of databases regarding food plants, food microorganisms and food animals for the purpose of the establishment of substantial equivalence. Of particular interest are databases on:

    - the nutrient, toxicant and allergen content of foods;
    - the amino acid sequence of protein toxins and allergens found in food.

Method development

11. The Consultation recognized that in certain areas, method development would be beneficial in order to improve the ability to complete a safety assessment of genetically modified organisms. The following was recommended in the area of method development:

    - Estimation of the potential for unintended effects may be improved through the application of methods which allow a comparison of the chemical composition of new food sources or products to existing food sources or products. Tests which might be considered include mRNA analysis, metabolic profiling, genotoxicity and cytotoxicity. Validation of these methods both from the context of the methodology and its application in prediction of critical changes is necessary.
    - Animal test methods for safety assessment of complex new food products should be improved and research focused on the identification of sensitive parameters which are predictive of specific toxicological endpoints like immunotoxicity, neurotoxicity, carcinogenicity or reproductive toxicity in relation to the testing of complex food matrices.
    - Development of animal models that would be predictive of the allergenicity of proteins in humans when presented by the oral route.

Developing countries

12. Developing countries should be provided with assistance and education regarding approaches to the safety assessment of foods and food components produced by genetic modification.

9. REFERENCES

Literature cited

1. WHO. 1991. *Strategies for assessing the safety of foods produced by biotechnology*. Report of a Joint FAO/WHO Consultation. World Health Organization, Geneva.

2. FAO/WHO. 1995. Unpublished Codex Document ALINORM 97/13, Appendix II. Report of the 28th Session of the Codex Committee on Food Hygiene. FAO, Rome.

3. OECD (Organisation for Economic Cooperation and Development). 1993. *Safety evaluation of foods produced by modern biotechnology: Concepts and principles*. OECD, Paris.

4. WHO. 1995. *Application of the principles of substantial equivalence to the safety evaluation of foods or food components from plants derived by modern biotechnology*. Report of a WHO Workshop. World Health Organization, Geneva. WHO/FNU/FOS/95.1

5. Pariza, M.W. and E.M. Foster. 1983. *Determining the safety of enzymes used in food processing*. J. of Food Protection 46:453-468.

6. Jaffe, W.G.. 1973. *Toxicants occurring naturally in foods*. National Academy of Sciences, Washington D.C. 106-128.

7. USP. 1990. The United States Pharmacopeia, Vol. XXII, NFXVII. United States Pharmacopeial Convention, Inc. Rockville, MD.

8. Voelker, T.A. et al. 1992. *Fatty acid biosynthesis redirected to medium chains in transgenic oilseed plants*. Science 257:72.

9. FAO. 1995. *Report of the FAO Technical Consultation on Food Allergies*. Food and Agriculture Organization, Rome.

10. Metcalfe, D.D., J.D. Astwood, R. Townsend, H.A. Sampson, S.L. Taylor and R.L. Fuchs. *Assessment of the allergenic potential of foods derived from genetically engineered crop plants*. Crit. Rev. In Food Science and Nutrition, in press.

11. Astwood, J.D. and R.L. Fuchs. 1996. *Food biotechnology and genetic engineering*. In: Food Allergy: Adverse reactions to Foods and Food Additives, 2nd edition, edited by D.D. Metcalfe, H.A. Sampson and R.A. Simon. Blackwell Scientific Publications, Boston, MA, 65-92.

12. Metcalfe, D.D.. 1996. *Allergic gastrointestinal diseases*. In: Clinical Immunology: Principles and Practice, 1st edition, edited by R.R. Rich, T.A. Feisher, B.D. Schwartz, W.T. Shearer and W. Strober. Mosby-Year Book Inc. St. Louis, MO 966-975.

13. WHO. 1993. *Health aspects of marker genes in genetically modified plants*. Report of a WHO Workshop. World Health Organization, Geneva. WHO/FNU/FOS/93.6

14. OECD. 1994. *Aquatic biotechnology and food safety*. OECD, Paris.

Other reading

IFBC (International Food Biotechnology Council). 1990. *Biotechnologies and food: Assuring the safety of foods produced by genetic modification*. Regul. Toxicol. Pharmacol. 12:S1-S196.

ACNFP (Advisory Committee on Novel Foods and Processes). 1991. *Department of Health Report on health and social subjects No. 38. Guidelines on the assessment of novel foods and processes*. London (HMSO).

Nordic Working Group on Food Toxicology and Risk Evaluation. 1991. *Food and new biotechnology - novelty, safety and control aspects of foods made by new biotechnology*. Nordic Council, Copenhagen. Nord 1991:18.

Food and Drug Administration. 1992. *Statement of policy: Foods derived from new plant varieties*: Notice. Federal Register 57:104 22984-23005.

Health Council of the Netherlands. 1992. *Safety of food produced by new biotechnology*. Publication No. 92/03E. The Hague.

Health Protection Branch. 1994. *Guidelines for the safety assessment of novel foods*. Vol I and II. Health Canada, Ottawa.

ILSI (International Life Sciences Institute). 1995. *The safety assessment of novel foods*. ILSI Europe, Brussels.

EEC Workshop. 1995. *Risk evaluation of genetically modified microorganisms in relation to human health*. Microbial Ecology in Health and Disease: vol 8, suppl 1, London.

OECD. 1996. *OECD Documents: Food safety evaluation*. OECD, Paris.

Kärenlampi, S. 1996. *Health effects of marker genes in genetically engineered food plants*. Nordic Council, Copenhagen. TemaNord 1996:530.

ANNEX 1

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ANNEX 2

GENERAL RECOMMENDATIONS[4]

1. Comprehensive, well enforced food regulations are important in protecting consumer health and all national governments should ensure that such regulations keep pace with developing technology.

2. National regulatory agencies should adopt the strategies identified in this report for evaluating the safety of foods derived from biotechnology.

3. To facilitate the evaluation of foods produced by biotechnology, databases should be established on:

   - the nutrient and toxicant content of foods;
   - the molecular analysis of organisms used in food production;
   - the molecular, nutritional and toxicant content of genetically modified organisms intended for use in food production.

4. Consumers should be provided with sound, scientifically based information on the application of biotechnology in food production and processing and on the safety issues.

5. FAO and WHO, in cooperation with other international organizations, should take the initiative in ensuring a harmonized approach on the part of national governments to the safety assessment of foods produced by biotechnology.

6. FAO and WHO should ensure that timely expert advise on the impact of biotechnology on the safety assessment of foods is provided to Member States, the Codex Alimentarius Commission, the Joint FAO/WHO Expert Committee on Food Additives and the Joint FAO/WHO Meeting on Pesticide Residues.

7. FAO and WHO should convene further consultations at an appropriate time to review the Consultation's advice in the light of scientific and technical progress.

[4] Taken from Section 7.2 of "Strategies for Assessing the Safety of Foods Produced by Biotechnology", Report of a Joint FAO/WHO Consultation, World Health Organization, Geneva, 1991.

ANNEX 3

SPECIFIC RECOMMENDATIONS SAFETY ASSESSMENT OF GENETICALLY MODIFIED MICROORGANISMS AND FOODS PRODUCED BY THEM[5]

1. Because of the diversity of foods and food ingredients derived from microorganisms, a large number of factors must be considered in assessing any potential risks in the light of the intended use of the substance in food.

2. The safety assessment should be based on sound scientific principles and data and should be flexible so as to be able to accommodate scientific advances.

3. The approach to safety assessment should rely to the extent possible on the use of molecular, microbial, genetic and chemical data and information in the evaluation of potential risks and the choice of appropriate safety tests.

4. General requirements in the safety assessment of food and food ingredients derived from microorganisms include the following:

   a. the production organism and any organisms that contribute genetic material to it should be identified taxonomically and genotypically;

   b. all introduced genetic material should be well characterized and should not encode any harmful substances; the modified organism should be genetically stable;

   c. vectors should be modified so as to minimize the likelihood of transfer to other microbes;

   d. selectable marker genes that encode resistance to clinically useful antibiotics should not be used in microbes intended to be present as living organisms in food. Food ingredients obtained from microbes that encode such antibiotic-resistance marker genes should be demonstrated to be free of viable cells and genetic material that could encode resistance to antibiotics;

   e. pathogenic organisms should not be introduced into food. The modified production organism used to produce food ingredients should not produce substances that are toxic at the levels found in the finished product;

   f. the safety of the modified production organism should be assessed with respect to the safety of the product of the introduced genes (including allergenic effects when appropriate), the ability to alter adversely the nutritional composition of the food, and any appropriate biological containment.

5. When molecular, microbial, genetic and chemical data establish that the food or food ingredient is sufficiently similar to its conventional counterpart, only minimal toxicological testing will generally be required.

6. The safety of foods and food ingredients derived from microorganisms depends on all the stages involved - strain development, production, processing and purification. Each case must be evaluated in order to identify critical points and establish appropriate controls that will ensure safety and quality. Any change in the process should be evaluated in the light of these considerations. The maintenance of good manufacturing practices must be a fundamental part of any process.

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[5] Taken from Section 6.3.1 of "Strategies for Assessing the Safety of Foods Produced by Biotechnology", Report of a Joint FAO/WHO Consultation, World Health Organization, Geneva, 1991.