

# **Guidelines for the Safety Assessment of Foods Derived from Genetically Engineered Plants**



Indian Council of Medical Research,  
New Delhi

2008

## TABLE OF CONTENTS

### Foreword

1	Introduction.....	1
2	Concept of Safety Assessment.....	2
3	Framework for Safety Assessment .....	3
4	Scope.....	5
5	Definitions.....	5
6	General Considerations .....	6
6.1	Description of GE Plant .....	6
6.2	Description of the Non-Transgenic Host Plant and its Use as Food.....	6
6.2.1	History of Safe Use and Dietary Exposure .....	7
6.3	Description of the Donor Organisms.....	7
6.4	Description of the Genetic Modification(s).....	8
6.5	Characterization of the Genetic Modification(s).....	9
7	Safety Assessment .....	10
7.1	Assessment of Possible Toxicity.....	10
7.2	Assessment of Possible Allergenicity (Proteins).....	11
7.2.1	Assessment Strategy.....	12
7.2.2	Source of the Protein.....	13
7.2.3	Amino Acid Sequence Homology .....	13
7.2.4	Pepsin Resistance.....	14
7.2.5	Specific Serum Screening .....	14
7.2.6	Other Considerations.....	14
7.3	Compositional Analyses of Key Components.....	15
7.4	Intended Nutritional Modifications .....	18
7.5	Unintended Effects .....	19
8	References.....	20
9	Composition of the Drafting Committee .....	22
10	Appendix I: Dossier Preparation Checklists .....	24
11	Appendix II: Codex Alimentarius Principles for the Risk Analysis of Foods Derived from Modern Biotechnology.....	28

## 1 INTRODUCTION

Modern biotechnology, involving the use of recombinant DNA (rDNA) technologies, also known as genetic engineering, has emerged as a powerful tool with many potential applications in healthcare and agriculture. New plant varieties developed using rDNA techniques, commonly referred to as genetically engineered (GE), genetically modified (GM) or transgenic plants, have been and are being developed with the aim of: enhancing productivity; decreasing dependence on the use of agricultural chemicals; modifying the inherent properties of crops; and improving the nutritional value of foods and livestock feeds. As more GE plants are released and the resultant food products are commercially available and are traded across various countries, concerns have been expressed about their safety. With this increased awareness, the concept of food safety assurance (*i.e.*, that a food is safe for human consumption according to its intended use) has assumed importance as with any method of genetic manipulation, including genetic engineering of plants, there is a possibility of introducing unintended changes along with the intended changes, which may in turn have an impact on the nutritional status or health of the consumer.

To address the human health safety of foods derived from GE plants, there is a need to adopt a systematic and structured approach to their risk analysis. Risk analysis is a science based process comprised of risk assessment, risk management and risk communication and is an analytical tool to systematically evaluate safety concerns addressing human health safety of GM foods within a framework for decision making. It also provides further basis for reviewing the safety evaluation parameters as and when further information becomes available.

In India, the manufacture, import, use, research and release of genetically modified organisms (GMOs) as well as products made by the use of such organisms are governed by the rules notified by Ministry of Environment and Forests (MoEF), Government of India on December 5, 1989 under the Environmental (Protection) Act 1986 (EPA). These rules and regulations, commonly referred to as Rules 1989, cover the areas of research as well as large-scale applications of GMOs and products made therefrom throughout India (MoEF 1989). The regulatory agencies responsible for implementation of the Rules 1989 are MoEF and the Department of Biotechnology (DBT), Government of India, through six competent authorities:

- Recombinant DNA Advisory Committee (RDAC);
- Review Committee on Genetic Manipulation (RCGM);
- Genetic Engineering Approval Committee (GEAC);
- Institutional Biosafety Committees (IBSC);
- State Biotechnology Coordination Committees (SBCC);
- District Level Committees (DLC).

The Ministry of Health and Family Welfare (MoHFW) is primarily responsible with ensuring the availability of food that is safe. In 2006, the Food Standards and Safety Act,

2006<sup>1</sup> was promulgated. This Act will be implemented by the Food Safety and Standards Authority and includes genetically modified foods within the definition of food under the Act<sup>2</sup>.

Other government departments have also undertaken steps to address the safety assessment of foods derived from GE plants and recombinant microorganisms. In 1990, DBT issued rDNA guidelines covering research in biotechnology, field trials and commercial applications (DBT, 1990). DBT also brought out separate guidelines for research in transgenic plants in 1998 (DBT, 1998). The Bureau of Indian Standards (BIS) has also initiated a program to develop draft Indian standards for GM foods.

There is a need for comprehensive guidance for the safety assessment of foods derived from GE plants, particularly with respect to impact on human health. This has assumed importance in view of the many GE food crops under field trial in India, as well as increased global trade in foods derived from GE crops approved for cultivation in other countries.

The Indian Council of Medical Research (ICMR), in its capacity as the scientific and technical advisory body to MoHFW, has formulated these guidelines to establish the safety assessment procedures for foods derived from GE plants taking into consideration the international *Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants* (CAC 2003b).

## 2 CONCEPT OF SAFETY ASSESSMENT

Detecting any potential adverse effects and relating these conclusively to an individual characteristic can be extremely difficult in the safety assessment process. In practice very few foods consumed today are subjected to any systematic safety assessment process, yet they are generally accepted as safe to eat. In view of the difficulties of applying traditional toxicological testing and risk assessment procedures to food as a whole, an alternative approach has been adopted in developing the framework for the safety assessment of GM foods. This approach acknowledges that the goal of the assessment is not establishing absolute safety but to consider whether the GM food is as safe as its traditional counterpart, where such a counterpart exists.

---

<sup>1</sup> The Food Standards and Safety Act, 2006 “consolidates the laws relating to food and to establish the Food Safety and Standards Authority of India for laying down science based standards for articles of food and to regulate their manufacture, storage, distribution, sale and import, to ensure availability of safe and wholesome food for human consumption and for matters connected therewith or incidental thereto.” Source: The Food Safety and Standards Act, 2006. Ministry of Law and Justice, Government of India. The Gazette of India Extraordinary, Part II, Sec. I, pp. 46., 2006.

<sup>2</sup> “Food means any substance whether processed, partially processed or unprocessed, which is intended for human consumption and includes primary food to the extent defined in clause (zk), genetically modified or engineered food or food containing such ingredients, infant food, packaged drinking water, alcoholic drink, chewing gum, and any substance, including water used into the food during its manufacture, preparation or treatment but does not include any animal feed, live animals unless they are prepared or processed for placing on the market for human consumption, plants prior to harvesting, drugs and medicinal products, cosmetic, narcotic or psychotropic substance.” Source: The Food Safety and Standards Act, 2006. Ministry of Law and Justice, Government of India. The Gazette of India Extraordinary, Part II, Sec. I, pp. 46.

This comparative approach, embodied in the concept of substantial equivalence, is not a safety assessment in itself. Rather, it represents the starting point which is used to structure the safety assessment of a new food relative to its counterpart. This concept is used to identify similarities and differences between the new food and its conventional counterpart and is considered the most appropriate strategy to date for safety assessment of foods derived from GE plants (CAC, 2003a-c; FAO/WHO 1996, 2000; OECD, 1998, 2002; WHO 1994, 2005).

Accordingly the safety assessment of foods derived from GE plants in these guidelines is based on the evaluation of these foods relative to their conventional counterparts that have a history of safe use. This takes into account both intended and unintended effects.

While the objective is to determine if the GM food presents any new or greater risks in comparison with its traditional counterpart, or whether it can be used interchangeably with its traditional counterpart without affecting the health or nutritional status of consumers, the inherent objective is to establish the relative safety of the new product such that there is a reasonable certainty that no harm will result from intended uses under the anticipated conditions of processing and consumption. If a new or altered hazard, nutritional or other food safety concern is identified by the safety assessment, it is further evaluated to determine its relevance to human health. Following the safety assessment and, if necessary, further risk analysis, the food or component of food may be subjected to risk management options before it is considered for commercial distribution. Where no conventional counterpart exists for comparison, the safety of a GM food must be evaluated from data derived directly from historical experience or experimental studies with the food.

### **3 FRAMEWORK FOR SAFETY ASSESSMENT**

Safety assessment is designed to identify whether a hazard, nutritional or other safety concern is present and if present, to collect and analyse information on its nature and severity following a structured and integrated approach performed on a case-by-case basis. The safety assessment of foods derived from GE plants follows a stepwise process aided by a series of structured questions. Factors taken into account in the safety assessment include:

- Identity;
- Source;
- Composition;
- Effects of processing/cooking
- Transformation process;
- The recombinant DNA (*e.g.*, stability of insertion, potential for gene transfer);

- Expression product of the novel DNA;
  - Effects on function;
  - Potential toxicity;
  - Potential allergenicity;
- Possible secondary effects from gene expression or the disruption of the host DNA or metabolic pathways, including composition of critical macro-, micro-nutrients, anti-nutrients, endogenous toxicants, allergens, and physiologically active substances; and,
- Potential intake and dietary impact of the introduction of the GM food.

With a wide range of foods available, the amount of information necessary for assessment may vary from case to case. Therefore, in order to provide guidance for applicants, these guidelines describe the types of information generally required to assess the safety of foods derived from GE plants. All requirements may not be relevant in every case and the explanations and interpretations are also subject to change as new knowledge and experience are gained.

Making available scientific data is the responsibility of the developer. In addition to the scientific data generated through experiments, the same needs to be supplemented from a variety of sources such as scientific literature, general technical information, independent scientists, regulatory agencies, international bodies and other interested parties. Data should be evaluated using appropriate science-based risk assessment methods.

Experiments intended to generate data to demonstrate the safety of foods derived from GE plants need to be designed and conducted in accordance with sound scientific concepts and principles, as well as, where applicable, Good Laboratory Practices. Primary data should be made available to regulatory authorities upon request. Data needs to be obtained using sound scientific methods and analysed using appropriate statistical techniques, where applicable. The sensitivity of all analytical methods should be documented and references to analytical methods made available. Prior to making a submission, applicants are encouraged to consult with the concerned regulatory authorities for submission requirements for the primary whole food product derived from a GE plant.

## 4 SCOPE

This document applies to all whole foods, food products, and foods used as ingredients that are derived from GE plant sources.

These guidelines are intended to provide guidance to both applicants and reviewers for regulatory purposes. They are not intended to explicitly define all the data that might be required in the course of a safety assessment as further data requirements may be identified during the safety assessment process. Information and data submitted will be for the parts of the plant used as a food source as identified in 6.2.1

## 5 DEFINITIONS

**Antinutrient** means a substance that interferes with the utilization of one or more nutrients by the body (*e.g.*, oxalate and phytate, which prevent calcium absorption).

**Conventional counterpart** means the related non-genetically engineered plant variety, its components and/or products for which there is experience of established safety based on common use as food.

**Donor organism** means the organism from which genetic material is obtained for transfer to the recipient organism.

**Genetically engineered food** means both the food and food ingredients composed of or containing genetically engineered organisms/plants obtained through modern biotechnology, or food and food ingredients produced from but not containing genetically engineered organisms/plants obtained through modern biotechnology.

**Genetically engineered plant** (GE plant) means a plant in which the genetic material has been changed through *in vitro* nucleic acid techniques, including recombinant deoxyribonucleic acid (DNA) and direct injection of nucleic acid into cells or organelles. Also referred to as a genetically modified (GM) or recombinant DNA (rDNA) or transgenic plant.

**Hazard** means a biological, chemical or physical agent in, or condition of, food with the potential to cause an adverse health effect subject to exposure.

**Modern biotechnology** means the application of:

- i. *In vitro* nucleic acid techniques, including recombinant deoxyribonucleic acid (DNA) and direct injection of nucleic acid into cells or organelles, of plants/crops OR

- ii. Fusion of cells beyond the taxonomic family, that overcome natural physiological reproductive or recombinant barriers and that are not techniques used in traditional breeding and selection of plants/crops.

**Risk**, in relation to any article of food, means the probability of an adverse effect on the health of consumers of such food and the severity of that effect, consequential to a food hazard.

**Risk analysis**, in relation to any article of food, means a process consisting of three components, *i.e.*, risk assessment, risk management and risk communication.

**Risk assessment** means a scientifically-based process consisting of the following steps: i) hazard identification; ii) hazard characterization; iii) exposure assessment; and iv) risk characterization.

**Transgenic plant** means a plant in which a transgene has been integrated into its genome.

**Transformation** means the unique DNA recombination event that took place through the integration of a transgene(s) in one plant cell for genetic modification, which was then used to generate entire transgenic plants.

## **6 GENERAL CONSIDERATIONS**

### **6.1 DESCRIPTION OF GE PLANT**

A description of the GE plant being presented for safety assessment needs to be provided. This description should identify the crop, the transformation event(s) to be reviewed, a pedigree map of each transformation event, and the type and purpose of the modification, sufficient to aid in understanding the food being submitted for safety assessment.

### **6.2 DESCRIPTION OF THE NON-TRANSGENIC HOST PLANT AND ITS USE AS FOOD**

A comprehensive description of the non-transgenic host plant needs to be provided. The necessary data and information should include, but need not be restricted to:

1. Common or usual name; botanical name; and, taxonomic classification;
2. Centre of origin, history of cultivation and development through breeding, in particular identifying traits that may adversely impact on human health;
3. Information on the host plant's genotype and phenotype relevant to its safety, including any known toxicity or allergenicity; and



#### 4. History of safe use for consumption as food.

##### *6.2.1 History of Safe Use and Dietary Exposure*

A food may be considered to have a history of safe use if it has been commonly used in the diet for a number of generations in a large, genetically diverse human population where it has been used in ways and at levels that are similar to those expected or intended in India. The fact that a product has had a history of use according to the above definition in a jurisdiction with a similar food safety system would increase the level of confidence in the evidence presented.

The history of safe use may include information on how the plant is typically cultivated, transported and stored, whether special processing is required to make the plant safe to eat, and the plant's normal role in the diet (*e.g.*, which part of the plant is used as a food source, whether its consumption is important in particular subgroups of the population, what important macro- or micro-nutrients it contributes to the diet).

The submission needs to include reliable information from referenced sources. Anecdotal evidence will be given less weight than scientifically derived data. Information on the history of human exposure will be particularly important where there is traditional handling, storing or cooking requirements for processing the food.

### **6.3 DESCRIPTION OF THE DONOR ORGANISMS**

Information has to be provided on the donor organism(s) and, when appropriate, on other related species. It is particularly important to determine if the donor organism(s) or other closely related members of the family naturally exhibit characteristics of human pathogenicity or toxin production, or have other traits that affect human health (*e.g.* presence of antinutrients). The description of the donor organism(s) should include:

1. Common name;
2. Scientific name;
3. Taxonomic classification;
4. Information about the natural history of the organism as concerns human health;
5. Information on naturally occurring toxins, anti-nutrients and allergens; for microorganisms, additional information on human pathogenicity and the relationship to known human pathogens; and
6. Information on the past and present use, if any, in the food supply and exposure route(s) other than intended food use (*e.g.* possible presence as contaminants).

#### **6.4 DESCRIPTION OF THE GENETIC MODIFICATION(S)**

Detailed information is required on the genetic modification to allow for the identification of all genetic material potentially delivered to the host plant and to provide all relevant information required for the analysis of the data supporting the characterization of the DNA inserted in the plant.

The description of the genetic modification needs to include:

1. Information on the specific method used for the modification (*e.g. Agrobacterium* mediated transformation or direct transformation by methods such as particle bombardment or electroporation, etc.);
2. Description and characterization of all genetic material used to modify the plant, including the source (*e.g. plant, microbial, viral, synthetic*), identity and expected function in the plant;
3. Details of modifications to be introduced, intermediate and recipient genetic material (*e.g., changes in amino acid sequence that may affect expression of the expressed protein*);

A summary diagram of all genetic components, which comprise the vector including coding regions, and non-coding sequences of known function needs to be provided. For each genetic component a citation where these functional sequences are characterized (publicly available database citations are acceptable) is required and also indicate:

1. The portion and size of the sequence inserted.
2. The location, order, and orientation in the vector.
3. The function in the plant.
4. The source (common and scientific and/or trade name, of the donor organism).
5. If the genetic component is responsible for disease or injury to plants or other organisms, and is a known toxicant, allergen, pathogenicity factor, or irritant, if any.
6. If the donor organism responsible for any disease or injury to plants or other organisms, produces toxicants, allergens or irritants or whether closely related to organisms that do.
7. History of safe use of the donor organism or components thereof, if available.

## **6.5 CHARACTERIZATION OF THE GENETIC MODIFICATION(S)**

In order to provide clear understanding of the impact on the composition and safety of foods derived from GE plants, a comprehensive molecular and biochemical characterization of the genetic modification needs to be carried out.

Information is required on the DNA insertions into the plant genome and should include:

1. The characterization and description of the inserted genetic materials;
2. The number of insertion sites;
3. The organisation of the inserted genetic material at each insertion site including copy number and data to demonstrate if complete or partial copies were inserted, and if the arrangement of the genetic material was conserved or if significant rearrangements have occurred upon integration;
4. Sequence data of the inserted material and of the flanking regions bordering the site of insertion;
5. Identification of any open reading frames within the inserted DNA or created by the insertions with contiguous plant genomic DNA including those that could result in fusion proteins;

Information needs to be provided on any expressed substances in the GE plant including:

1. The gene product(s) (*e.g.*, a protein or an untranslated RNA);
2. The gene product(s)' function;
3. The phenotypic description of the new trait(s);
4. The level and site of expression of the expressed gene product(s) in the plant, and the levels of its metabolites in the edible portions; and
5. The amount of the target gene product(s), where possible, if the function of the expressed sequence(s)/gene(s) is to alter the accumulation of a specific endogenous mRNA or protein.

In addition, information is also required:

1. To demonstrate whether deliberate modifications made to the amino acid sequence of the expressed protein result in changes in its post-translational modification or affect sites critical for its structure or function;
2. To demonstrate whether the intended effect of the modification has been achieved and that all expected traits are expressed and inherited in a manner that is stable through several generations consistent with laws of inheritance. It may be necessary to examine the inheritance of the DNA insert itself or the expression of

the corresponding RNA if the phenotypic characteristics cannot be measured directly;

3. To demonstrate whether the newly expressed trait(s) are expressed as expected in the appropriate tissues in a manner and at levels that are consistent with the associated regulatory sequences driving the expression of the corresponding gene;
4. To indicate whether there is any evidence to suggest that one or several genes in the host plant has been affected by the transformation process; and
5. To confirm the identity and expression pattern of any new fusion proteins.

## **7 SAFETY ASSESSMENT**

### **7.1 ASSESSMENT OF POSSIBLE TOXICITY**

Toxicological testing is required for substances of unknown safety that are introduced to the food supply. *In vitro* nucleic acid techniques enable the introduction of DNA that can result in the synthesis of new substances in plants. These include the protein expression product and other substances, which may be generated as a result of enzymatic activity of the protein expression product. The new substances can be conventional components of plant foods such as proteins, fats, carbohydrates, vitamins, which are novel in the context of that GE plant.

The safety assessment has to take into account the following:

1. The chemical nature and function of the newly expressed substance;
2. The concentration of the substance in the edible parts of the GE plant, including variations and mean values;
3. Current dietary exposure and possible effects on population sub-groups, if applicable.
4. Information, if any, that genes coding for known toxins or anti-nutrients present in the donor organisms are not transferred to GE plants that do not normally express those toxin or anti-nutrient characteristics.

This assurance is particularly important in cases where the GE plant is processed differently from a donor plant, since conventional food processing techniques associated with the donor organisms may deactivate, degrade or eliminate anti-nutrients or toxicants.

Toxicology studies are not considered necessary where the substance or a closely related substance has been consumed safely in food at equivalent intakes or where the new

substance is not present in the food. Otherwise, the use of conventional toxicology studies on the new substance will be necessary. This may require the isolation of the new substance from the GE plant, or the production of the substance from an alternative source, in which case, the material has to be shown to be biochemically and functionally equivalent to that produced in the GE plant.

In the case of proteins, the assessment of potential toxicity needs to focus on amino acid sequence similarity between the protein and known protein toxins and anti-nutrients (*e.g.* protease inhibitors, lectins) as well as stability to heat or processing and to degradation in appropriate representative gastric and intestinal model systems.

Proteins that are enzymes have never been shown to be direct-acting carcinogens, mutagens, teratogens or reproductive toxicants (Pariza and Foster, 1983). Hence, it is generally not necessary to test proteins for these toxicological endpoints when exposure occurs by the oral route. Protein toxins act through acute mechanisms after the administration of a single dose at doses in the nanogram to milligram per kilogram body weight. Therefore, acute oral toxicity studies using gram per kilogram body weight doses of the novel protein are appropriate for assessing the potential toxicity of proteins. A negative result using doses in the gram/kg body weight range together with evidence that the protein is digested to small peptides and amino acids would provide assurance that the protein is not a toxin and is digested to nutrients as are the vast majority of dietary proteins.

Potential toxicity of non-protein substances that have not been safely consumed in food should be assessed on a case-by-case basis depending on the identity and biological function in the plant of the substance and dietary exposure. The type of studies to be performed may include studies on metabolism, toxicokinetics, sub-chronic toxicity, chronic toxicity/carcinogenicity, reproduction and development toxicity according to the traditional toxicological approach.

## **7.2 ASSESSMENT OF POSSIBLE ALLERGENICITY (PROTEINS)**

The primary consideration in allergenicity assessment of a newly expressed novel protein in a food derived from GE plant is the prevention of unexpected exposure of sensitized individuals to food allergens. This includes the assessment of the potential for foods containing such novel proteins to cross-react with known food allergens or to lead to the development of *de novo* hypersensitivity. In addition, the potential of increasing the allergenic potential of foods already containing allergens as an unintended result of genetic modification needs to be assessed. The newly expressed proteins in foods derived from GE plants should be evaluated for any possible role in the elicitation of gluten-sensitive enteropathy, if the introduced genetic material is obtained from wheat, rye, barley, oats, or related cereal grains.

All newly expressed proteins in GE plants that could be present in the final food need to be assessed for their potential to cause allergic reactions. This requires consideration of whether a newly expressed protein is one to which certain individuals may already be sensitive as well as whether a protein new to the food supply is likely to induce allergic reactions in some individuals.

At present, there is no definitive test that can be relied upon to predict allergic response in humans to a newly expressed protein, therefore, it is recommended that a case by case weight of evidence approach as described below, be used in the assessment of possible allergenicity of newly expressed proteins. This approach takes into account the preponderance of evidence derived from several types of information and data since no single criterion is sufficiently predictive. The endpoint of the assessment is a conclusion as to the likelihood of the protein being a food allergen.

#### 7.2.1 Assessment Strategy

Genes derived from known allergenic sources should be assumed to encode an allergen unless scientific evidence demonstrates otherwise.

The initial steps in assessing possible allergenicity of any newly expressed proteins are the determination of:

1. The source of the introduced protein;
2. Any significant similarity between the amino acid sequence of the protein and that of known allergens. As there is no single test that can predict the likely human IgE response to oral exposure, the first step to characterize newly expressed proteins should be the comparison of the amino acid sequence and certain physicochemical characteristics of the newly expressed protein with those of established allergens in a weight of evidence approach.
3. Its structural properties, including but not limited to, its susceptibility to enzymatic degradation, heat stability and/or, acid and enzymatic treatment.
4. Isolation of any newly expressed proteins from the GE plant, or the synthesis or production of the substance from an alternative source, in which case the material should be shown to be structurally, functionally and biochemically equivalent to that produced in the GE plant.
5. The choice of the expression host, since post-translational modifications allowed by different hosts (*i.e.*, eukaryotic *vs.* prokaryotic systems) may have an impact on the allergenic potential of the protein.

### 7.2.2 Source of the Protein

Allergenic sources of genes are defined as those organisms for which reasonable evidence of IgE mediated oral, respiratory or contact allergy is available. Knowledge of the source of the introduced protein allows the identification of tools and relevant data to be considered in the allergenicity assessment, these include:

1. The availability of sera for screening purposes;
2. Documented type, severity and frequency of allergic reactions;
3. Structural characteristics and amino acid sequence;
4. Physicochemical and immunological properties (when available) of known allergenic proteins from that source.

### 7.2.3 Amino Acid Sequence Homology

Amino acid sequence homology comparisons need to be used to assess the extent to which a newly expressed protein is similar in structure to known allergens to determine whether that protein has allergenic or cross-reactivity potential. Sequence homology searches comparing the structure of all newly expressed proteins with all known allergens are required to be undertaken. Searches should be conducted using various algorithms such as FASTA or BLASTP to predict overall structural similarities.

Sequence homology searches have certain limitations. In particular, comparisons are limited to the sequences of known allergens in publicly available databases and the scientific literature. There are also limitations in the ability of such comparisons to detect non-contiguous epitopes capable of binding themselves specifically with IgE antibodies.

Strategies such as stepwise contiguous identical amino acid segment searches may also be performed for identifying sequences that may represent linear epitopes. The size of the contiguous amino acid search should be based on a scientifically justified rationale in order to minimize the potential for false negative or false positive results<sup>3</sup>. Validated search and evaluation procedures should be used in order to produce biologically meaningful results.

IgE cross-reactivity between the newly expressed protein and a known allergen should be considered a possibility when there is more than 35% identity in a segment of 80 or more amino acids (FAO/WHO, 2001). All the information resulting from the sequence homology comparison between the newly expressed protein and known allergens should

---

<sup>3</sup> It is recognized that the 2001 FAO/WHO consultation suggested moving from 8 to 6 identical amino acid segment searches. The smaller the peptide sequence used in the stepwise comparison, the greater the likelihood of identifying false positives; inversely, the larger the peptide sequence used, the greater the likelihood of false negatives, thereby reducing the utility of the comparison.

be reported to allow a case-by-case scientifically based evaluation. A positive sequence homology result using the above criteria indicates that the newly expressed protein is likely to be allergenic. If the product is to be considered further, it should be assessed using serum from individuals sensitized to the identified allergenic source.

A negative sequence homology result indicates that a newly expressed protein is not a known allergen and is unlikely to be cross-reactive to known allergens. A result indicating absence of significant sequence homology needs to be considered along with the other data outlined below in assessing the allergenic potential of newly expressed proteins.

#### 7.2.4 Pepsin Resistance

Resistance to pepsin digestion has been observed in several food allergens; thus a correlation exists between resistance to digestion by pepsin and allergenic potential<sup>4</sup>. The resistance of a protein to degradation in the presence of pepsin under appropriate conditions indicates that further analysis has to be conducted to determine the likelihood of the newly expressed protein being allergenic. A consistent and well-validated pepsin degradation protocol may enhance the utility of this method and is strongly recommended. However, it is recognized that other enzyme susceptibility protocols also exist and these may be used with adequate justification.

#### 7.2.5 Specific Serum Screening

For those proteins that originate from a source known to be allergenic, or have sequence homology with a known allergen, testing in immunological assays need to be performed where sera are available. Sera from individuals with a clinically validated allergy to the source of the protein can be used to test the specific binding to IgE class antibodies of the protein *in vitro* assays. A critical issue for testing will be the availability of human sera from sufficient numbers of individuals<sup>5</sup>. The quality of the sera and the assay procedure need to be standardized to produce a valid test result.

In the case of a newly expressed protein derived from a known allergenic source, a negative result in *in vitro* immunoassays may not be considered sufficient, but should prompt additional testing, such as the possible use of skin test and *ex vivo* protocols. A positive result in such tests would indicate a potential allergen.

#### 7.2.6 Other Considerations

The absolute exposure to the newly expressed protein and the effects of relevant food processing will contribute toward an overall conclusion about the potential for human

---

<sup>4</sup> The method outlined in the U.S. Pharmacopoeia (1995) was used in the establishment of the correlation (Astwood *et al.* 1996).

<sup>5</sup> According to the Joint Report of the FAO/WHO Expert Consultation on Allergenicity of Foods Derived from Biotechnology (22-25 January 2001, Rome, Italy) a minimum of 8 relevant sera is required to achieve a 99% certainty that the new protein is not an allergen in the case of a major allergen. Similarly, a minimum of 24 relevant sera is required to achieve the same level of certainty in the case of a minor allergen. It is recognized that these quantities of sera may not be available for testing purposes.



health risk. In this regard, the nature of the food product intended for consumption should be taken into consideration in determining the types of processing which would be applied and its effects on the presence of the protein in the final food product.

As scientific knowledge and technology evolves, other methods and tools may be considered in assessing the allergenicity potential of newly expressed proteins as part of the assessment strategy. These include:

1. Targeted serum screening (*i.e.* the assessment of binding to IgE in sera of individuals with clinically validated allergic responses to broadly-related categories of foods);
2. Development of international serum banks;
3. Use of animal models;
4. Examination of newly expressed proteins for T-cell epitopes and structural motifs associated with allergens.

### **7.3 COMPOSITIONAL ANALYSES OF KEY COMPONENTS**

Analyses of concentrations of key components of the GE plant and, especially those typical of the food, need to be compared with an equivalent analysis of a conventional counterpart grown and harvested under the same conditions:

1. Key nutrients or key anti-nutrients of those components in a particular food that may have a substantial impact in the overall diet.
2. Major constituents (fats, proteins, carbohydrates as nutrients or enzyme inhibitors as anti-nutrients)
3. Minor compounds (minerals, vitamins).
4. Key toxicants or toxicologically significant compounds known to be inherently present in the plant, whose toxic potency and level may be significant to health (*e.g.* solanine in potatoes if the level is increased, selenium in wheat) and allergens.
5. A comparison with the GE plant grown under its expected agronomic conditions may need to be considered (*e.g.* application of an herbicide) in some cases. The statistical significance of any observed differences should be assessed in the context of the range of natural variations for that parameter to determine its

biological significance. The comparator(s) used in this assessment need to be ideally the near isogenic parental line. In practice, this may not be feasible at all times, in which case a line as close as possible should be chosen.

6. Literature from a range of standard cultivars that are in commercial production for the same purposes and grown in the same geographical areas as those typically found in the Indian market may also be provided for assessing the nutritional relevance of any unintended effect. The purpose of this comparison, in conjunction with an exposure assessment as necessary, is to establish that substances that are nutritionally important or that can affect the safety of the food have not been altered in a manner that would have an adverse impact on human health.
7. Trial sites:
  - a. The location of trial sites needs to be representative of the range of environmental conditions under which the plant varieties would be expected to be grown.
  - b. The number of trial sites need to be sufficient to allow accurate assessment of compositional characteristics over this range. Trials have to be conducted over a sufficient number of generations to allow adequate exposure to the variety of conditions met in nature.
  - c. Each trial site is required to be replicated to minimise environmental effects, and to reduce any effect from naturally occurring genotypic variation within a crop variety,
  - d. Sampling of adequate number of plants and the methods of analysis need to be sufficiently sensitive and specific to detect variations in key components.

In the context of these study guidelines, the following components of foods have to be analysed. Where not all are analysed, the applicant needs to provide the criteria used to select the nutrients analysed and the rationale for the exclusion from analysis of any nutrients and other substances listed below. Appropriate analyses must be performed on all the parts of the plant that may be used as food in India. For example, if the intended uses of a transgenic corn event include the oil and the meal, samples of both corn oil and cornmeal should be analysed for the appropriate nutrients.

1. Proximate composition *e.g.*, ash, moisture content, crude protein, crude fat, crude carbohydrate;

2. Content of true protein, non-protein nitrogenous material (*e.g.*, nucleic acids and aminoglycosides), amino acid profile [unusual amino acids should be determined if their presence is suspected (*e.g.*, d-amino acids from bacterial proteins)];
3. Quantitative and qualitative composition of total lipids, *i.e.*, saponifiable and nonsaponifiable components, complete fatty acid profile, phospholipids, sterols, cyclic fatty acids and known toxic fatty acids;
4. Composition of the carbohydrate fraction *e.g.*, sugars, starches, chitin, tannins, non-starch polysaccharides and lignin;
5. Qualitative and quantitative composition of micronutrients, *i.e.*, significant vitamin and mineral analysis;
6. Presence of naturally occurring or adventitious anti-nutritional factors *e.g.*, phytates, trypsin inhibitors, etc.;
7. Predictable secondary metabolites, physiologically active (bioactive) substances, other detected substances.

Characterization of the product by such techniques as HPLC, GC-MS, and conventional analytical methods is considered appropriate.

The statistical significance of any observed differences will be assessed in the context of the range of natural variations for that parameter to determine its biological significance. If the composition of the GM food is judged not to be nutritionally equivalent to that of its parent and commercial varieties, *i.e.*, significant differences (statistical and biological) exist in the nutrient data, additional nutritional data may be required on a case-by-case basis.

All aspects of nutritional quality will be evaluated based on modern nutritional principles, standards and guidelines aimed at meeting human nutritional needs. The bases of evaluation include:

1. Nutrient intake recommendations;
2. The role of the food in the diet of the population;
3. The role of diet and nutrition in reducing the risk of developing a diet-related disease and health promotion.

Detection of a major change due to an unintended nutritional effect may not preclude the marketing of the product. However, such changes may require limits on the use of the food in food products or a requirement for labelling that goes beyond basic provisions.

The first phase of nutritional evaluation will be based on the nutrient composition data. If there is a finding of unusual or unanticipated components or levels of nutrients or nutritive substances, the food may need to be subjected to further analysis and assessment.

The safety of a major increase in the level of a nutrient or other bioactive component would need to be assessed in a similar way to the safety assessment of an intended nutritional change.

#### **7.4 INTENDED NUTRITIONAL MODIFICATIONS**

Foods derived from GE plants that have undergone modification to intentionally alter nutritional quality or functionality need to be subjected to additional nutritional assessment to assess the consequences of the changes and whether the nutrient intakes are likely to be altered by the introduction of such foods into the food supply.

Information about the known patterns of use and consumption of a food, and its derivatives should be used to estimate the likely intake of the food derived from the GE plant. The expected intake of the food should be used to assess the nutritional implications of the altered nutrient profile both at customary and maximal levels of consumption. Basing the estimate on the highest likely consumption provides assurance that the potential for any undesirable nutritional effects will be detected. Attention needs to be paid to the particular physiological characteristics and metabolic requirements of specific population groups such as infants, children, pregnant and lactating women, the elderly and those with chronic diseases or compromised immune systems. Based on the analysis of nutritional impacts and the dietary needs of specific population subgroups, additional nutritional assessments may be necessary. It is also important to ascertain to what extent the modified nutrient is bioavailable and remains stable with time, processing and storage.

The use of plant breeding, including *in vitro* nucleic acid techniques, to change nutrient levels in crops can result in broad changes to the nutrient profile in two ways. The intended modification in plant constituents could change the overall nutrient profile of the plant product and this change could affect the nutritional status of individuals consuming the food. Unexpected alterations in nutrients could have the same effect.

Although the GE plant components may be individually assessed as safe, the impact of the change on the overall nutrient profile needs to be determined.

When the modification results in a food product, such as vegetable oil, with a composition that is significantly different from its conventional counterpart, it may be appropriate to use additional conventional foods or food components whose nutritional composition is closer to that of the food derived from the GE plant.

Nutritional changes to a specific food may have a greater impact in some geographical areas or in some cultural population than in others due to variations in food consumption patterns. The nutrient and the populations affected need to be identified.

Some foods require additional testing. For example, animal feeding studies may be warranted for foods derived from GE plants if changes in the bioavailability of nutrients are expected or if the composition is not comparable to conventional foods. Also, foods designed for health benefits may require specific nutritional, toxicological or other appropriate studies. If the characterization of the food indicates that the available data are insufficient for a thorough safety assessment, properly designed animal studies could be requested on the whole food.

#### **7.5 UNINTENDED EFFECTS**

Unintended effects can result from the random insertion of DNA sequences into the plant genome which may cause disruption or silencing of existing genes, activation of silent genes, or modifications in the expression of existing genes. Unintended effects may also result in the formation of new or changed patterns of metabolites.

The assessment for unintended effects takes into account the agronomic/phenotypic characteristics of the plant that are typically observed by breeders in selecting new varieties for commercialization.

## 8 REFERENCES

- CAC. 2003a. Principles for the Risk Analysis of Foods Derived from Modern Biotechnology CAC/GL 44-2003. Codex Alimentarius Commission, Geneva.
- CAC. 2003b. Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants, CAC/GL 45-2003. Codex Alimentarius Commission, Geneva.
- CAC. 2003c. Guideline for the Conduct of Food Safety Assessment of Foods Produced Using Recombinant-DNA Microorganisms, CAC/GL 46-2003. Codex Alimentarius Commission, Geneva.
- DBT. 1990. Recombinant DNA safety guidelines, 1990. Department of Biotechnology, Government of India.
- DBT. 1998. Revised guidelines for research in transgenic plants & guidelines for toxicity and allergenicity evaluation of transgenic seeds, plants and plant parts. Department of Biotechnology, Government of India.
- FAO/WHO. 2001. Allergenicity of genetically modified foods, a joint FAO/WHO consultation on foods derived from biotechnology. Food and Agriculture Organization (FAO), Rome.
- FAO/WHO. 2000. Safety aspects of genetically modified foods of plant origin, a joint FAO/WHO consultation on foods derived from biotechnology, Food and Agriculture Organization (FAO), Rome.
- FAO/WHO. 1996. Biotechnology and food safety. Report of a Joint FAO/WHO Consultation, Rome, Italy, 30 September-4 October 1996. FAO Food and Nutrition Paper No. 61. Food and Agriculture Organization (FAO), Rome.
- MoEF. 1989. Rules For The Manufacture, Use/Import/Export And Storage Of Hazardous Microorganisms/Genetically Engineered Organisms or Cells notified under Environment Protection Act (1986 ),. Ministry of Environment and Forests, Government of India.
- OECD. 2002. Report of the OECD Workshop on the Nutritional Assessment of Novel Foods and Feeds. Organization of Economic Cooperation and Development (OECD), Paris.
- OECD. 1998. Report of the OECD Workshop on the Toxicological and Nutritional Testing of Novel Foods. Organization of Economic Cooperation and Development (OECD), Paris.
- Pariza, M.W. and Foster, E.M. 1983. Determining the safety of enzymes used in food processing. Journal of Food Protection 46: 453-468.

WHO. 1994. 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, Copenhagen, Denmark, 31 October-4 November 1994. World Health Organization (WHO), Geneva.

WHO. 2005. Modern food biotechnology, human health and development: an evidence based study. World Health Organization (WHO), Geneva.

## **9 COMPOSITION OF THE DRAFTING COMMITTEE**

### **CHAIR**

Dr. S.D. Seth  
Chair in Clinical Pharmacology  
Indian Council of Medical Research, New Delhi

### **MEMBERS**

Dr. Vasantha Muthuswamy  
Senior Deputy Director General  
Indian Council of Medical Research, New Delhi  
Tel: 011-26589791; 26963980, 26962794  
Fax: 011-26589791; 26868662, 26856713  
Email: muthuswamyv@icmr.org.in

Dr. B. Sesikaran  
Director, National Institute of Nutrition, Hyderabad  
Tel: 040-27018083; 9849081993;  
Email: sesikaran@gmail.com

Dr Pawan S Chauhan  
Formerly, Emeritus Med Scientist and Head,  
Cell Biology Division, BARC  
Tel: 9892301221; 022 27700210  
Email: drchauhan@vsnl.com

Shri A.K. Shrivastav  
Deputy Assistant Director General (PFA), Directorate General of Health Services,  
Ministry of Health and Family Welfare, New Delhi  
Tel: 011-23063030; Fax: 011-23061968  
Email: dadgpfa@nb.nic.in

Dr. O.P. Agarwal  
Emeritus Scientist, CSIR  
Indian Council of Medical Research, New Delhi  
Tel: 011-26589791  
Email: op\_agarwal@yahoo.com

Dr. Vijay Kumar  
Deputy Director General, Division of Basic Medical Sciences  
Indian Council of Medical Research, New Delhi  
Tel: 011-26589272; Fax: 011- 26589791  
Email: kumarv@icmr.org.in

### **CONVENORS:**

Dr. Vibha Ahuja  
Deputy General Manager  
Biotech Consortium India Limited, New Delhi  
Tel. No. 011-23219064-67 (PBX); 23219059 (D); Fax No. 011-23219063



Email: [biotechdelhi@vsnl.com](mailto:biotechdelhi@vsnl.com); [bcildelhi@vsnl.com](mailto:bcildelhi@vsnl.com)

Dr. Geeta Jotwani  
Senior Research Officer, Division of Basic Medical Sciences  
Indian Council of Medical Research, New Delhi  
Tel: 011-26589272; 9810146975; Fax: 011- 26589791  
Email: [jotwanig@icmr.org.in](mailto:jotwanig@icmr.org.in)

## 10 APPENDIX I: DOSSIER PREPARATION CHECKLISTS

The following checklists are provided to assist applicants prepare their dossiers for submission to GEAC. The checklists are an aid and are not a replacement for reading Sections 5 and 6 which provide essential details.

### Checklist 1: Description of the GE Plant

- Identification of the crop
- Name of the transformation event(s)
- Pedigree map for each transformation event
- Purpose of the modification, sufficient to aid in understanding the nature of the food being submitted for safety assessment.

### Checklist 2: Description of the Non-Transgenic Host Plant and its Use as Food

- Common or usual name; botanical name; and, taxonomic classification;
- History of cultivation and development through breeding, in particular identifying traits that may adversely impact on human health;
- Information on the host plant's genotype and phenotype relevant to its safety, including any known toxicity or allergenicity; and
- History of safe use for consumption as food.

### Checklist 3: History of Safe Use and Dietary Exposure

- Information on how the plant is typically cultivated, transported and stored
- Information on special processing required to make the plant safe to eat
- The plant's normal role in the diet
- Part of the plant is used as a food source
- Is consumption of the plant important in particular subgroups of the population What important macro- or micro-nutrients does the food contribute to the diet

### Checklist 4: Description of the Donor Organisms

For each donor organism, provide the following:

- Common name
- Scientific name
- Taxonomic classification
- Information about the natural history of the organism as concerns human health
- Information on naturally occurring toxins, anti-nutrients and allergens
- For donor microorganisms, additional information on human pathogenicity and the relationship to known human pathogens
- Information on the past and present use, if any, in the food supply and exposure route(s) other than intended food use (e.g. possible presence as contaminants).

### Checklist 5: Description of the Genetic Modification(s)

Provide:

- Information on the specific method used for the modification
- Description and characterization of all genetic material used to modify the plant, including the source (e.g., plant, microbial, viral, synthetic), identity and expected function in the plant

- Details of modifications to introduced, intermediate and recipient genetic material (e.g., changes in amino acid sequence that may affect expression of the expressed protein)

Provide a summary diagram of all genetic components of the vector, including coding regions, and non-coding sequences of known function and for each genetic component include:

- A citation where these functional sequences are characterized.
- Indicate the portion and size of the sequence inserted.
- Indicate the location, order, and orientation in the vector.
- Indicate the function in the plant.
- Indicate the source (common and scientific and/or trade name, of the donor organism).
- Indicate if the genetic component is responsible for disease or injury to plants or other organisms and is a known toxicant, allergen, pathogenicity factor, or irritant.
- Indicate if the donor organism is responsible for any disease or injury to plants or other organisms, produces toxicants, allergens or irritants or whether closely related to organisms that do.
- Indicate if there is a history of safe use of the donor organism or components thereof, if available.

#### **Checklist 6: Characterization of the Genetic Modification(s)**

Information about the DNA insertion(s) into the plant genome is required, including:

- Characterization and description of the inserted genetic material.
- Number of insertion sites.
- Organisation of the inserted genetic material at each insertion site including copy number and data to demonstrate if complete or partial copies were inserted, and if the arrangement of the genetic material was conserved or if significant rearrangements have occurred upon integration.
- Sequence data of the inserted material and of the flanking regions bordering the site of insertion.
- Identification of any open reading frames within the inserted DNA or created by the insertions with contiguous plant genomic DNA including those that could result in fusion proteins.

For any expressed substances in the GE plant provide:

- The gene product(s) (e.g. a protein or an untranslated RNA);
- The gene product(s)' function;
- The phenotypic description of the new trait(s);
- The level and site of expression of the expressed gene product(s) in the plant, and the levels of its metabolites in the edible portions; and
- The amount of the target gene product(s), where possible, if the function of the expressed sequence(s)/gene(s) is to alter the accumulation of a specific endogenous mRNA or protein.

Information is required to demonstrate each of the following (where applicable):

- Deliberate modifications made to the amino acid sequence of the expressed protein result in changes in its post-translational modification or affect sites critical for its structure or function.
- The intended effect of the modification has been achieved and that all expressed traits are expressed and inherited in a manner that is stable through several generations consistent with laws of inheritance.

- The newly expressed trait(s) are expressed as expected in the appropriate tissues in a manner and at levels that are consistent with the associated regulatory sequences driving the expression of the corresponding gene.
- Evidence to suggest that one or several genes in the host plant has been affected by the transformation process.
- Confirm the identity and expression pattern of any new fusion proteins.

**Checklist 7: Assessment of Possible Toxicity**

- Indicate if the donor organism(s) is a known source of toxins.
- Amino acid sequence homology comparison of the newly expressed protein and known protein toxins and anti-nutrients.
- Demonstrate the susceptibility of each newly expressed protein to pepsin digestion.
- Where a host other than the transgenic plant is used to produce sufficient quantities of the newly expressed protein for toxicological analyses, demonstrate the structural, functional and biochemical equivalence of the non-plant expressed protein with the plant expressed protein.
- Acute oral toxicity study completed for newly expressed proteins.

**Checklist 8: Assessment of Possible Allergenicity (Proteins)**

- Indicate if the donor organism(s) is a known source of allergens (defined as those organisms for which reasonable evidence of IgE mediated oral, respiratory or contact allergy is available).
- Amino acid sequence homology comparison of the newly expressed protein and known allergens.
- Demonstrate the susceptibility of each newly expressed protein to pepsin digestion.
- Where a host other than the transgenic plant is used to produce sufficient quantities of the newly expressed protein for toxicological analyses, demonstrate the structural, functional and biochemical equivalence of the non-plant expressed protein with the plant expressed protein.
- For those proteins that originate from a source known to be allergenic, or have sequence homology with a known allergen, testing in immunological assays is to be performed where sera are available.

**Checklist 9: Compositional Analyses of Key Components**

For all parts of the GE plant and its conventional counterpart that may be used as food in India, provide the following:

- Proximate composition e.g., ash, moisture content, crude protein, crude fat, crude carbohydrate;
- Content of true protein, non-protein nitrogenous material (e.g., nucleic acids and aminoglycosides), amino acid profile [unusual amino acids should be determined if their presence is suspected (e.g., d-amino acids from bacterial proteins)];
- Quantitative and qualitative composition of total lipids, i.e., saponifiable and nonsaponifiable components, complete fatty acid profile, phospholipids, sterols, cyclic fatty acids and known toxic fatty acids;
- Composition of the carbohydrate fraction e.g., sugars, starches, chitin, tannins, non-starch polysaccharides and lignin;
- Qualitative and quantitative composition of micronutrients, i.e., significant vitamin and mineral analysis;

- Presence of naturally occurring or adventitious anti-nutritional factors e.g., phytates, trypsin inhibitors, etc.;
- Predictable secondary metabolites, physiologically active (bioactive) substances, other detected substances.

## 11 APPENDIX II: CODEX ALIMENTARIUS PRINCIPLES FOR THE RISK ANALYSIS OF FOODS DERIVED FROM MODERN BIOTECHNOLOGY

---

*Foods derived from Biotechnology*

*Codex Alimentarius*

---

### PRINCIPLES FOR THE RISK ANALYSIS OF FOODS DERIVED FROM MODERN BIOTECHNOLOGY

*CAC/GL 44-2003*

#### SECTION 1 - INTRODUCTION

1. For many foods, the level of food safety generally accepted by the society reflects the history of their safe consumption by humans. It is recognised that in many cases the knowledge required to manage the risks associated with foods has been acquired in the course of their long history of use. Foods are generally considered safe, provided that care is taken during development, primary production, processing, storage, handling and preparation.
2. The hazards associated with foods are subjected to the risk analysis process of the Codex Alimentarius Commission to assess potential risks and, if necessary, to develop approaches to manage these risks. The conduct of risk analysis is guided by general decisions of the Codex Alimentarius Commission (CAC)<sup>6</sup> as well as the Codex Working Principles for Risk Analysis<sup>7</sup>.
3. While risk analysis has been used over a long period of time to address chemical hazards (e.g. residues of pesticides, contaminants, food additives and processing aids), and it is being increasingly used to address microbiological hazards and nutritional factors, the principles were not elaborated specifically for whole foods.
4. The risk analysis approach can, in general terms, be applied to foods including foods derived from modern biotechnology. However, it is recognised that this approach must be modified when applied to a whole food rather than to a discrete hazard that may be present in food.
5. The principles presented in this document should be read in conjunction with the Codex Working Principles for Risk Analysis to which these principles are supplemental.
6. Where appropriate, the results of a risk assessment undertaken by other regulatory authorities may be used to assist in the risk analysis and avoid duplication of work.

#### SECTION 2 – SCOPE AND DEFINITIONS

7. The purpose of these Principles is to provide a framework for undertaking risk analysis on the safety and nutritional aspects of foods derived from modern biotechnology. This document does not address environmental, ethical, moral and socio-economic aspects of the research, development, production and marketing of these foods<sup>8</sup>.
8. The definitions below apply to these Principles:  
“**Modern Biotechnology**” means the application of:
  - (i) *In vitro* nucleic acid techniques, including recombinant deoxyribonucleic acid (DNA) and direct injection of nucleic acid into cells or organelles, or

---

<sup>6</sup> These decisions include the Statements of principle concerning the role of science in the Codex decision-making process and the extent to which other factors are taken into account and the Statements of principle relating to the role of food safety risk assessment (Codex Alimentarius Commission Procedural Manual; Thirteenth edition).

<sup>7</sup> Adopted by the 26th Session of the Codex Alimentarius Commission, 2003

<sup>8</sup> This document does not address animal feed and animals fed such feed except insofar as these animals have been developed by using modern biotechnology.

- (ii) Fusion of cells beyond the taxonomic family, that overcome natural physiological reproductive or recombinant barriers and that are not techniques used in traditional breeding and selection<sup>9</sup>.

“**Conventional Counterpart**” means a related organism/variety, its components and/or products for which there is experience of establishing safety based on common use as food<sup>10</sup>.

### ***SECTION 3 – PRINCIPLES***

- 9. The risk analysis process for foods derived from modern biotechnology should be consistent with the Codex Working Principles for Risk Analysis.

#### ***RISK ASSESSMENT***

- 10. Risk assessment includes a safety assessment, which is designed to identify whether a hazard, nutritional or other safety concern is present, and if present, to gather information on its nature and severity. The safety assessment should include a comparison between the food derived from modern biotechnology and its conventional counterpart focusing on determination of similarities and differences. If a new or altered hazard, nutritional or other safety concern is identified by the safety assessment, the risk associated with it should be characterized to determine its relevance to human health.
- 11. A safety assessment is characterized by an assessment of a whole food or a component thereof relative to the appropriate conventional counterpart:
  - a) taking into account both intended and unintended effects;
  - b) identifying new or altered hazards;
  - c) identifying changes, relevant to human health, in key nutrients.
- 12. A pre-market safety assessment should be undertaken following a structured and integrated approach and be performed on a case-by-case basis. The data and information, based on sound science, obtained using appropriate methods and analysed using appropriate statistical techniques, should be of a quality and, as appropriate, of quantity that would withstand scientific peer review.
- 13. Risk assessment should apply to all relevant aspects of foods derived from modern biotechnology. The risk assessment approach for these foods is based on a consideration of science-based multidisciplinary data and information taking into account the factors mentioned in the accompanying Guidelines<sup>11</sup>.
- 14. Scientific data for risk assessment are generally obtained from a variety of sources, such as the developer of the product, scientific literature, general technical information, independent scientists, regulatory agencies, international bodies and other interested parties. Data should be assessed using appropriate science-based risk assessment methods.
- 15. Risk assessment should take into account all available scientific data and information derived from different testing procedures, provided that the procedures are scientifically sound and the parameters being measured are comparable.

#### ***RISK MANAGEMENT***

- 16. Risk management measures for foods derived from modern biotechnology should be proportional to the risk, based on the outcome of the risk assessment and, where relevant, taking into account other legitimate factors in accordance with the general decisions of

---

<sup>9</sup> This definition is taken from the Cartagena Biosafety Protocol under the Convention on Biological Diversity.

<sup>10</sup> It is recognized that for the foreseeable future, foods derived from modern biotechnology will not be used as conventional counterparts

<sup>11</sup> Reference is made to the Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants and the Guideline for the Conduct of Food Safety Assessment of Foods Produced using Recombinant-DNA Microorganisms.

the Codex Alimentarius Commission (CAC)<sup>12</sup> as well as the Codex Working Principles for Risk Analysis.

17. It should be recognised that different risk management measures may be capable of achieving the same level of protection with regard to the management of risks associated with safety and nutritional impacts on human health, and therefore would be equivalent.
18. Risk managers should take into account the uncertainties identified in the risk assessment and implement appropriate measures to manage these uncertainties.
19. Risk management measures may include, as appropriate, food labelling<sup>13</sup>, conditions for marketing approvals and post-market monitoring.
20. Post-market monitoring may be an appropriate risk management measure in specific circumstances. Its need and utility should be considered, on a case-by-case basis, during risk assessment and its practicability should be considered during risk management. Post-market monitoring may be undertaken for the purpose of:
  - A) verifying conclusions about the absence or the possible occurrence, impact and significance of potential consumer health effects; and
  - B) monitoring changes in nutrient intake levels, associated with the introduction of foods likely to significantly alter nutritional status, to determine their human health impact.
21. Specific tools may be needed to facilitate the implementation and enforcement of risk management measures. These may include appropriate analytical methods; reference materials; and, the tracing of products<sup>14</sup> for the purpose of facilitating withdrawal from the market when a risk to human health has been identified or to support post-market monitoring in circumstances as indicated in paragraph 20.

### ***RISK COMMUNICATION***

22. Effective risk communication is essential at all phases of risk assessment and risk management. It is an interactive process involving all interested parties, including government, industry, academia, media and consumers.
23. Risk communication should include transparent safety assessment and risk management decision making processes. These processes should be fully documented at all stages and open to public scrutiny, whilst respecting legitimate concerns to safeguard the confidentiality of commercial and industrial information. In particular, reports prepared on the safety assessments and other aspects of the decision-making process should be made available to all interested parties.
24. Effective risk communication should include responsive consultation processes. Consultation processes should be interactive. The views of all interested parties should be sought and relevant food safety and nutritional issues that are raised during consultation should be addressed during the risk analysis process.

### ***CONSISTENCY***

25. A consistent approach should be adopted to characterise and manage safety and nutritional risks associated with foods derived from modern biotechnology. Unjustified differences in the level of risks presented to consumers between these foods and similar conventional foods should be avoided.
26. A transparent and well-defined regulatory framework should be provided in characterising and managing the risks associated with foods derived from modern

---

<sup>12</sup> See footnote 1.

<sup>13</sup> Reference is made to the Codex Committee on Food Labelling in relation to the Proposed Draft Guidelines for the Labelling of Foods and Food Ingredients obtained through certain techniques of genetic modification/genetic engineering at Step 3 of the procedures.

<sup>14</sup> It is recognised that there are other applications of product tracing. These applications should be consistent with the provisions of the SPS and TBT Agreements. The application of product tracing to the areas covered by both Agreements is under consideration within Codex on the basis of decisions of 49<sup>th</sup> Session of Executive Committee.



biotechnology. This should include consistency of data requirements, assessment frameworks, acceptable level of risk, communication and consultation mechanisms and timely decision processes.

#### ***CAPACITY BUILDING AND INFORMATION EXCHANGE***

27. Efforts should be made to improve the capability of regulatory authorities, particularly those of developing countries, to assess, manage and communicate risks, including enforcement, associated with foods derived from modern biotechnology or to interpret assessments undertaken by other authorities or recognized expert bodies, including access to analytical technology. In addition capacity building for developing countries either through bilateral arrangements or with assistance of international organizations should be directed toward effective application of these principles<sup>15</sup>.
28. Regulatory authorities, international organisations and expert bodies and industry should facilitate through appropriate contact points including but not limited to Codex Contact Points and other appropriate means, the exchange of information including the information on analytical methods.

#### ***REVIEW PROCESSES***

29. Risk analysis methodology and its application should be consistent with new scientific knowledge and other information relevant to risk analysis.30. Recognizing the rapid pace of development in the field of biotechnology, the approach to safety assessments of foods derived from modern biotechnology should be reviewed when necessary to ensure that emerging scientific information is incorporated into the risk analysis. When new scientific information relevant to a risk assessment becomes available the assessment should be reviewed to incorporate that information and, if necessary, risk management measures adapted accordingly.

---

<sup>15</sup> Reference is made to technical assistance of provisions in Article 9 of the SPS Agreement and Article 11 of the TBT Agreement.