SOUTH ASIA
BIOSAFETY PROGRAM

Towards a Harmonised Approach to Food Safety Assessment of Genetically Engineered Plants in South Asia

EXPERT WORKING GROUP REPORT

Agriculture & Food Systems Institute

BCIL

Prepared by the Expert Working Group (EWG) on Harmonisation of Safety Assessment of Foods with members from Bangladesh, Bhutan, India, and Sri Lanka.

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Introduction

The foods that are derived from modern biotechnology, including ones that are produced locally or imported, are subject to a pre-market safety assessment as per national regulations. Harmonisation of these regulatory requirements is important for advancing research and development, smooth regional trade, and providing access to international markets. Discussions about harmonisation of safety assessment requirements for genetically engineered foods have progressed at multiple fora, most notably by the Codex Alimentarius Commission.

In South Asia, similar discussions on harmonisation of food safety assessment for foods derived from rDNA plants began in 2014 in the form of peripheral informal consultations during the South Asia Biosafety Conference. The need for harmonisation of GE food safety standards and the potential benefits of doing so are well recognized by Bangladesh, Bhutan, India, and Sri Lanka, all of which have participated in regional consultations and workshops on this topic, including efforts organized by the South Asia Biosafety Programme (SABP) and the SAARC Agricultural Center.

The harmonisation initiative in South Asia was formally undertaken in 2020 by the Agriculture & Food Systems Institute (AFSI), as part of SABP and in partnership with Biotech Consortium India Limited (BCIL), by convening an Expert Working Group (EWG). The EWG constituted senior experts and regulators, identified from agencies from the aforementioned countries, that are relevant to safety assessment of foods derived from rDNA plants.

This report was systematically drafted by the EWG with experts from Bangladesh, Bhutan, India, and Sri Lanka, with support from SABP. All experts participated in the meetings and the process for drafting the report in their individual capacity. The names and affiliations of the experts who constituted the EWG are listed below:

- **Bangladesh**
  - Dr. Anima Rani Nath, Additional Secretary, Safe Food Section, Ministry of Food
  - Dr. Md. Abdur Rouf, Additional Secretary, Policy Planning & Coordination Wing, Ministry of Agriculture (Sep 2020–Jan 5, 2021)
  - Dr. Md. Ruhul Amin Talukder, Additional Secretary, Policy Planning & Coordination Wing, Ministry of Agriculture (Jan 27, 2021 onwards)
- **Bhutan**
  - Mr. Jambay Dorji, Senior Regulatory and Quarantine Officer, Bhutan Agriculture and Food Regulatory Authority (BAFRA), Ministry of Agriculture and Forests
  - Ms. Dechen Wangmo, Deputy Chief Laboratory Officer/Officer In-Charge, National Food Testing Laboratory, BAFRA, Ministry of Agriculture and Forests
- **India**
  - Mr. Sunil Bakshi, Head (Regulations/Codex/International Cooperation), Food Safety and Standards Authority of India (FSSAI)
  - Dr. Lalitha Gowda, Former Chief Scientist, CSIR- Central Food Technological Institute, Mysore, Member, Panel on Genetically Modified Organisms and Foods, FSSAI, and Member, Genetic Engineering Appraisal Committee
- **Sri Lanka**
  - Dr. T.B. Ananda Jayalal, Deputy Director General (DS), Ministry of Health
  - Dr. D.M.J.B. Senanayake, Director, Rice Research and Development Institute, Department of Agriculture

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Consensus Statement on Safety Assessment of Foods Derived from Genetically Engineered Plants in South Asia

Overview

1. Foods derived from modern biotechnology, whether produced locally or imported, are subject to safety assessment as per national regulations.
2. While countries may differ in statutory and non-statutory approaches to regulating foods derived from genetically engineered (GE) plants, the criteria used to assess the safety of these products is generally consistent from one country to another. This is because concerted efforts that have been made internationally to harmonize the risk assessment of foods derived from modern biotechnology and develop science-based international approaches and methodologies.
3. The *Codex Alimentarius Commission* (*CAC*), established under the Joint FAO/WHO programme to develop food standards, has contributed significantly to the development of internationally accepted approaches to assessing the safety of foods derived from modern biotechnology, as articulated in "Principles for the Risk Analysis of Foods Derived from Modern Biotechnology"[1] (hereinafter referred to as "Codex Principles") and "Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants"[2] (hereinafter referred to as "Codex Guideline") with two additional annexures[3], which were adopted in 2008.
4. The Codex Principles and Codex Guideline generally form the basis of safety assessment of foods derived from GE plants in countries that have a regulatory system for regulating products of modern biotechnology, including in South Asia. Despite being non-binding, the guidelines have been adopted voluntarily by these countries.
5. Continuous efforts are being made to make safety regulations for foods derived from GE plants consistent and compatible between the countries and at the global level through multiple approaches, including:
   - Presentations and trainings based on the Codex Guidelines at various international fora.
   - Use of a Codex compliant safety assessment at national levels.
   - Transparency and sharing of safety assessment (or even regulatory decisions) between jurisdictions.
6. Globally, regulators have accumulated a wealth of experience in evaluating the safety of foods derived from GE plants in several countries. The same GE event has been assessed multiple times, and there have been no different opinions. It is expected that harmonisation of approaches and sharing of safety assessment can reduce duplication of efforts.
7. The South Asian region, with a population of almost 1.8 billion people representing more than 22% of the global population on just 3.3% of the world's land, requires robust mechanisms for regional cooperation and trade, and large-scale adoption of innovative technologies, including biotechnologies for the establishment of sustainable and efficient food systems.

[1] CAC/GL 44-2003

[2] CAC/GL 45-2003

[3] Annex 2: Food Safety Assessment of Foods derived from Recombinant-DNA Plants modified for Nutritional or Health Benefits and Annex 3: Food Safety Assessment in Situations of Low-Level Presence of Recombinant-DNA Plant Material in Food.

8. In South Asia, India, Bangladesh, and Pakistan are cultivating a limited number of GE plants, as well as importing food and feed derived from GE plants. As more GE plants are approved and enter the food and feed supply chains globally and in the region, differences in national regulatory systems that lead to asynchronous approvals may result in trade disruptions.

9. The need for harmonisation of safety assessment for foods derived from GE plants and the potential benefits of doing so have been well recognized by South Asian countries, including Bangladesh, Bhutan, India, and Sri Lanka, all of whom have participated in regional consultations and workshops on this topic from time to time.

10. In continuation with the above efforts, an Expert Working Group (EWG) was convened with experts identified from Bangladesh, Bhutan, India, and Sri Lanka, to work towards a consensus statement on safety assessment of foods derived from GE plants.

11. The EWG agreed to the following consensus statement, after series of meetings, review of documents and exchange of information, with an objective to promote regional harmonisation in safety assessment of foods derived from GE plants.[4]

12. This consensus statement reflects the EWG's assessment of scientific knowledge available at the time the statement was written.

Text of the Consensus Statement on Safety Assessment of Foods Derived from GE Plants

The countries in South Asia, including Bangladesh, Bhutan, India, and Sri Lanka, are members of Codex Alimentarius Commission. These four countries have integrated the science-based framework outlined in the Codex Principles and Codex Guideline into their national guidance document for regulation of foods derived from GE plants. The EWG members recognize that this offers an opportunity to strengthen and harmonize the process for safety assessment of foods derived from GE plants by regulatory authorities in the region. It is agreed that a regional approach to assess safety of foods derived from GE plants, based on Codex Guideline, may be adopted.

The regional harmonized approach can be operationalized through adoption of common

- Information recommended for safety assessment of foods derived from GE plants (Appendix 1)
- Format for application (Appendix 2)
- Recommended format for a risk assessment summary (Appendix 3)

Use of common formats would enable developers to prepare and submit a single dossier for consideration by the regulatory authorities, encourage parallel review of application dossiers by the regulatory agencies, and facilitate synchronous approvals.

Countries in the region are encouraged to engage in collaborative safety assessments/joint reviews and to work toward mutual recognition of Codex compliant safety assessments done by other regulatory authorities. This would be beneficial to reduce regulatory resource burden and help in promoting innovation and adoption of novel technologies.

Implementing a harmonized approach will result in increased trust, judicious use of intellectual and monetary resources, along with increased transparency among countries in the South Asian region.

[4] The process followed for developing the consensus statement and additional documents has been described in Appendix 4.

List of Appendices

Appendices 1-6 are supporting documents for the Consensus Statement.

Appendix 1: Information Recommended for the Safety Assessment of Foods Derived from Genetically Engineered Plants

Introduction

The information elements, based on the guidelines of the four countries and Codex are summarised. This information will facilitate the preparation of dossiers for seeking approvals of foods derived from GE plants in the four countries, *viz.*, Bangladesh, Bhutan, India, and Sri Lanka.

The objective of this Appendix is to provide a comprehensive list of information elements that are generally associated with the safety assessment 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 with new knowledge and experiences. Regulators in each country may request additional information on a case-by-case basis.

Information Elements

Description of the GE Plant

A description of the GE plant being presented for safety assessment is to be provided. This description should identify the plant, the transformation event to be reviewed, a pedigree map of each transformation event, and the type and purpose of the modification, including the intended use of the product. The information should be provided in sufficient detail to help in understanding the GE plant or food product being submitted for safety assessment.

Description of the Host Plant and Its Use as Food or Feed

A comprehensive description of the unmodified host plant (also referred to as non-GE counterpart) is required to facilitate comparative assessment. The necessary data and information should generally include:

a. Common or usual name, scientific name, and taxonomic classification;
b. History of cultivation, including geographical location(s) and development through breeding, in particular identifying traits that may adversely impact human or animal health;
c. Information on the host plant's genotype and phenotype relevant to its safety, including any known toxicity or allergenicity;
d. History of safe use for consumption as food: 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 for consumption, 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 vulnerable subgroups of the population, and what important macro- or micro-nutrients it contributes to the diet).

The submitted information must be reliable and 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. Information on the status of approval in other geographies/countries may be submitted to facilitate the risk assessment.

The guidelines in the region also include information about centre of origin, which is generally relevant for environmental risk assessment.

Description of the Donor Organisms

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

a. Common name;
b. Scientific name;
c. Taxonomic classification;
d. Information about the natural history of the organism as concerns to human or animal health;
e. Information on naturally occurring toxins, antinutrients and allergens, as applicable);
f. for microorganisms, additional information on human pathogenicity and the relationship to known human pathogens; and
g. Information on the past and present use, if any, in the food supply and exposure routes other than intended food use (e.g., possible presence as contaminants).

Description of the Genetic Modification

Method of Genetic Modification

a. Describe and provide references for the method used for genetic modification (e.g., *Agrobacterium*-mediated transformation or direct transformation by methods such as particle bombardment).
b. If applicable, for direct transformation methods, describe the nature and source of any carrier DNA used, and describe how the transforming DNA was isolated and purified (e.g., if the transforming DNA was a plasmid vector-derived restriction fragment).
c. Describe any manipulations or modifications to introduced DNA sequences (e.g., resynthesis of genes to incorporate plant-preferred codons, introduction or deletion of post-translational modification sites, and any changes that would affect the amino acid sequence of the expressed product).

Potentially Introduced Genetic Material

Provide a list with a detailed description of all the genetic elements contained in the potentially introduced genetic material, including both coding and non-coding regions of known function. For each genetic element, include:

a. Name of the gene sequence or regulatory element;
b. The portion and size of the sequence;
c. The location, order, and orientation of the sequence in the vector or transforming DNA;
d. The function in the plant;
e. Provide references from the scientific literature, including, if applicable, sequence accession numbers from nucleotide sequence databases;
f. The source (scientific and common name of the donor organism for each element);
g. Indicate whether the genetic component is responsible for disease or injury to plants or other organisms, or if it encodes a known toxicant, allergen, pathogenicity factor, or irritant;
h. Indicate whether the donor organism is a known source of significant toxins, allergens, or irritants;
i. Indicate whether there is any history of safe use of the introduced genetic element(s), including whether it is present in other GE plants authorised for use in food, feed, or processing.

A detailed map of the plasmid vector or transforming DNA, with the location and orientation of all the sequences described above, is required. The map should also indicate the cleavage sites of any restriction endonucleases used in subsequent analyses of the inserted DNA, including any regions used as hybridization probes.

The nucleotide sequence of the entire potentially introduced DNA/genetic construct should be provided.

Molecular Characterization of the GE Plant

The molecular characterization of the GE plant should be sufficient to demonstrate that the introduced DNA has been stably incorporated into the plant's genetic material (whether it is the nuclear genome or a plastid genome) and that the introduced DNA (or trait) is inherited over multiple/several generations in a predictable manner consistent with the laws of inheritance.

Information required for a comprehensive molecular and biochemical characterization of the GE plant are as follows:

DNA Insertions Into the Plant Genome

- the characterization and description of the inserted genetic materials;
- the number of insertion sites;
- the organization of the inserted genetic material at each insertion site, including copy number at each insertion site and sequence data of the inserted material and of the surrounding region, sufficient to identify any substances expressed as a consequence of the inserted material, or, where more appropriate, other information such as analysis of transcripts or expression products to identify any new substances that may be present in the food; and
- 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.

Expressed Substances in the GE plant:

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

Additional Information:

- to demonstrate whether the arrangement of the genetic material used for insertion has been conserved or whether significant rearrangements have occurred upon integration;
- 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;
- to demonstrate whether 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. 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;
- 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;
- to indicate whether there is any evidence to suggest that one gene (or several genes) in the host plant has been affected by the transformation process; and
- to confirm the identity and expression pattern of any new fusion proteins.

For demonstrating stable inheritance of the inserted gene, one of the following methods may be used. The methods used may not be limited to:

a. Southern blot hybridisation of genomic plant DNA digested with one, or more, restriction endonucleases and probed with DNA sequences complementary to different genetic elements contained on the transforming DNA;
b. Polymerase chain reaction (PCR) analysis using primers designed to amplify different regions of the introduced DNA;
c. Protein-based methods [e.g., Enzyme Linked Immunosorbent Assay (ELISA), Western blotting], or biological assay to demonstrate stable inheritance of the introduced DNA (or trait) over multiple generations;
d. The use of methods, such as those described above, to demonstrate segregation of the introduced DNA (or trait) within a segregating generation.

On a case-by-case basis, and if warranted by observations of biologically significant unintended phenotypic characteristics, other more elaborate methods of molecular characterization may be required to explain these phenomena.

For any introduced sequences intended to result in the expression of a new protein product, information should be provided on:

a. The level of expression of the protein in relevant plant tissues that may be used in food or for livestock feed (e.g., seed or grain, above ground vegetative tissue);
b. The levels of affected plant metabolites in cases where the protein is intended, or anticipated, to affect plant metabolic pathways or alter the levels of plant metabolites;
c. The molecular size of the protein (e.g., via Western blotting) to confirm that it is as expected (in the case of any significant deviations from the anticipated size, additional data explaining the discrepancy may be required);
d. In cases where deliberate changes were introduced into the amino acid sequence (e.g., changes affecting post-translational modification or affecting sites critical for structure or function), data should be provided to demonstrate the effectiveness of these changes;
e. If protein expression is inducible, either in response to a stage of plant development, a biotic or abiotic stress, or some external agent, then levels of expression in relevant plant tissues before and after induction should be reported; and
f. If the protein is intended to alter endogenous gene expression (e.g., transcription factor) then levels of gene expression should be compared with that of the unmodified host plant.

In cases where the genetic modification is not intended to result in the expression of a new protein (e.g., expression of a non-translatable mRNA, truncated sense constructs, antisense constructs, small interfering RNAs, or ribozymes), data should be provided to demonstrate that the intended effect has been achieved.

In any case where the intent of the genetic modification is to alter the regulation of endogenous genes, the characteristics and level of gene expression should be compared with that of the unmodified host.

Assessment of Potential Toxicity

In cases where the intended genetic modification results in the expression of a substance that has, or is closely related to a substance that has, a history of safe (dietary) exposure to humans and animals, further toxicological testing is not necessary. Otherwise, the use of conventional toxicology studies on the new substance is necessary.

- Where possible, these studies should be performed on the new substance as expressed in the GE plant; however, where this is not feasible because of the amounts required, alternative sources may be used. In this case, studies demonstrating that the material isolated from the alternative source is biochemically and functionally equivalent to the plant-expressed form are required.
- For proteins, the assessment of possible toxicity is based on a weight-of-evidence that considers the following parameters:
  a. In the case of proteins, the assessment of potential toxicity should 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.
  b. Appropriate oral toxicity studies may need to be carried out in cases where the protein present in the food is not similar to proteins that have previously been consumed safely in food and taking into account its biological function in the plant where known.
- Proteins are not normally considered to have any potential mutagenic, teratogenic, or carcinogenic activity, nor are there any data to indicate that proteins are capable of interactions with DNA that would give rise to mutagenic effects; hence, it is generally not necessary to test proteins for these toxicological endpoints.
- Different types of *in vivo* or *in vitro* studies would be needed to conduct the toxicological assessment of introduced substances that are not proteins, and these should be determined on a case-by-case basis in direct consultation with the competent national authority.

Assessment of Potential Allergenicity

All newly expressed proteins in the GE plant that could be present in the final food, and do not have a history of consumption in the context of that food, need to be assessed for their potential to cause allergic reactions. This should include 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 (i.e., sensitize certain individuals).

At present, there is no single definitive test that can be relied on to predict the allergenic potential of a protein, and the recommended approach is one that takes into account a weight-of-evidence from different types of information in an integrated, stepwise, and case-by-case manner. The following types of information are considered:

a. **The source of the introduced gene**. Genes derived from known allergenic sources should be assumed to encode an allergen unless scientific evidence demonstrates otherwise. Allergenic sources would be defined as those organisms for which reasonable evidence of IgE-mediated oral, respiratory, or dermal allergy is available. Information should be provided on any substantiated reports of allergenicity associated with the donor organism.
b. **Amino acid sequence similarity with known allergens.** Sequence comparisons should be conducted against peer-reviewed allergen databases using appropriate search algorithms.
c. **Pepsin resistance.** Typically, most food allergens tend to be stable to the peptic and acidic conditions of the digestive system to reach and pass through the intestinal mucosa to elicit an allergic response. *In vitro* digestibility of proteins in the presence of pepsin at acid pH (pH 1.2–pH 2.0) has shown a good correlation between resistance to degradation and allergenic potential. Investigation of proteins that have been tested suggest a strong positive predictive value that food allergens causing systemic reactions are relatively stable in the assay, while non-allergenic food proteins are typically digested relatively quickly. Although the pepsin resistance protocol is strongly recommended, it is recognized that other digestibility protocols exist, and alternative protocols may be used where adequate justification is provided.

In cases where the newly expressed protein exhibits significant sequence similarity to a known allergen, or where the gene is derived from a known allergenic source, additional testing in immunological assays is required.

In any situation where the assessment of potential allergenicity is not straightforward, the applicant is encouraged to consult with the competent national authority in advance of submitting the application.

Compositional Analysis

For GE plants without intentionally altered nutritional properties, the nutritional evaluation is part of the weight-of-evidence approach for evaluating whether there were any unanticipated consequences of the genetic modification. Data should be provided on the levels of key nutrients and antinutrients present in the edible portions of the plant (e.g., seed or grain), including other plant parts (e.g., forage) that may be used as feed for livestock animals. The compounds chosen for testing should be those recognized as key nutrients and antinutrients for the plant species (e.g., those identified in international consensus documents on nutrient properties, where applicable).

Material/GE plants subjected to compositional analysis should be obtained from confined field trials conducted in a range of environmental conditions representative of the intended area of commercial cultivation. Comparisons should be made between the GE plant and an appropriate counterpart (e.g., near-isogenic line or parental line) and considering the normal range of variation for the nutrient in other cultivated varieties of the plant (e.g., comparisons with data from the published scientific literature or nutrient databases). The focus should be on identifying and discussing any biologically significant differences in nutrient composition.

Existing data on the compositional analysis of the GE plant and its counterparts developed outside may be accepted for the assessment of compositional equivalence.

Consideration should also be given to whether the introduced trait is likely to result in changes in consumption patterns for the crop, and whether there may be differential impacts on vulnerable subgroups of the population (e.g., children, infants, elderly, ethnic groups, etc.) due to varying exposure.

Compositional analyses should normally include the following (the applicant may provide valid scientific rationale to exclude items or include additional items):

a. Proximates (i.e., ash, moisture, protein, fat, fiber, and carbohydrate)
b. Amino acid composition
c. Fatty acid profile
d. Vitamins
e. Minerals
f. Naturally occurring antinutrients (e.g., phytates, protease inhibitors, lectins, alpha-galactosides, cyanogens, glucosinolates, saponins, etc.)
g. Predictable secondary metabolites or other physiologically active substances normally associated with the plant species.

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. Annex-II to the Codex Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants can be referred to for additional information.

Appendix 2: Application for the Safety Assessment of Foods Derived from Genetically Engineered Plants

- The application form will be supported by the full submission dossier, including supporting studies,that contain the complete set of data required for the safety assessment.
- For any information not included, please provide a rationale as to why the information is not relevant or necessary for the food safety assessment of the GE plant, or what information is being provided in its place, if applicable.

Section 1: Administrative Requirements

1.1 Applicant Details

Name:	
Organisation:	
Address:	
Telephone:	
E-mail:	

1.2 Authorized Signatory, if any

Name:	
Organisation:	
Address:	
Telephone:	
E-mail:	

1.3 General Information of the GE Plant

Name of the GE plant	
Description of the introduced trait (e.g., drought tolerance, insect resistance)	
OECD Unique Identifier (if applicable)	
Intended use (e.g., food, feed, cultivation)	
Status of authorization in other countries • For cultivation • For food and feed use	

Please mention countries and date of authorisation and attach copies of relevant permits/authorisation letters

Type of Authorisation	Competent National Authority	Date of Authorisation	Permit or Authorisation No.	Official Authorisation Documentation Attached (Yes/No)

Section 2: Technical Information

2.1 Description of Events in the GE plant

Name of the transformation event(s)	
Pedigree map for each transformation event	
Purpose of the modification	

2.2 Description of the Host/Recipient Plant

Common or usual name, scientific name, and taxonomic classification	
History of cultivation and development through breeding, in particular information on: • Traits that may adversely impact human or animal health • Any known toxicants or antinutrients • Any known allergens	
History of safe use for consumption as food. Please provide a summary covering: • How the plant is typically cultivated, transported, and stored • Any special processing required to make the plant safe for consumption • The plant's normal role in the diet • Part of the plant that is used as a food source • If consumption of the plant is important in any vulnerable subgroups of the population • Important macro- or micro-nutrients it contributes to the diet	

2.3 Description of the Donor Organism

Common or usual name, scientific name, and taxonomic classification	
Information about: • the natural history of the organism as concerns human or animal health • 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).	

2.4 Description of the Genetic Modification

2.4.1 Method of Modification

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, or 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)	

2.4.2 Potentially Introduced Genetic Material

Provide a detailed description of all genetic elements of the vector, including coding regions and non-coding sequences of known function. For each genetic element, 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))

Provide a detailed map of the plasmid vector or transforming DNA with the location and orientation of all the sequences described above.

2.4.3 Molecular Characterization

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	Copy number and sequence 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.

Describe how genetic stability of the introduced trait over multiple generations was demonstrated

Describe how segregation of the introduced trait within a generation was demonstrated.

2.4.4 Expressed Substances in the GE Plant:

Information about each of the gene products (e.g., a protein or an untranslated RNA)				
The gene product(s)	Function	Level and site of expression of the expressed gene product(s) in the plant	Levels of its metabolites in the edible portions	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.

2.4.5 Any other information:

2.5 Potential Toxicity Assessment

Describe the safety studies undertaken to demonstrate lack of potential toxicity of any newly expressed proteins in the GE plant that do not have a history of safe consumption				
Protein*	Amino acid sequence similarity with known toxins? If yes, provide details	Rapidly digested via *in vitro* pepsin digestibility assay? If yes, provide details.	Activity is stable to heat or processing? If yes, provide details.	Acute oral toxicity testing? If yes, provide details.

* 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.

Provide additional details as necessary:

2.6 Potential Allergenicity Assessment

Describe the safety studies undertaken to demonstrate lack of potential allergenicity of any newly expressed proteins in the GE plant that do not have a history of safe consumption				
Protein	Donor organism a known source of significant allergens? If yes, provide details	Amino acid sequence similarity with known allergens? If yes, provide details	Rapidly digested via *in vitro* pepsin digestibility assay? If yes, provide details.	Stable to heat or processing? If yes, provide details

Provide additional details as necessary:

2.7 Compositional Analysis

Describe the results of compositional analyses. Data should be provided on the levels of key nutrients and antinutrients present in the edible portions of the plant (e.g., seed or grain), including other plant parts (e.g., forage) that may be used as animal feed		
Plant part	Used as food or animal feed	Differences observed if any in the levels of key nutrients and antinutrients

Section 3: Procedural Information

3.1 Describe any specific instructions and/or recommendations for use, storage, and handling

3.2 Describe any proposed packaging and labelling requirements

3.3 Briefly describe the event-specific detection method for the GE plant event

3.4 Any other specific information

Signature of applicant **Date**

By my signature, above, I attest that the information contained herein is accurate and complete to the best of my knowledge and belief, and that this application includes all relevant data and information upon which to base a decision, including all data and information that are unfavorable to the application.

Appendix 3: Risk Assessment Summary Report

About This Document

At the final conclusion of a risk assessment, assessors (including expert committee members or professional staff) need to report the results of their assessment to decision-makers and the public. Importantly for efforts at harmonisation, the risk assessment summary may also be used by other interested governments. This document is intended to provide a suggested format for preparing uniform risk assessment summaries that will make them easy to use for each of these stakeholder groups.

Throughout the document, recommended headings will be suggested. Following the headings, text describing the purpose of the section will be included. This will be followed by sample text that can be used to help assessors adopt more uniform language. Because risk assessments are conducted on a case-by-case basis, assessors may need to adopt appropriate language for each specific case. In some cases, assessors may address additional information or aspects of the assessment in the summary or find that some of the items listed below are not relevant.

Outline for Risk Assessment Summary

I. Risk Conclusion
II. Risk Assessment Summary
    a. Summary Description of the Plant Subject to the Assessment
        i. Species
        ii. Genetic Modification Method
        iii. Resulting Trait
        iv. Intended Use
    b. Results of the Molecular Characterization
    c. Results of the Toxicity Assessment
    d. Results of the Allergenicity Assessment
    e. Results of the Compositional Analysis

Risk Conclusion

The conclusions of the risk assessment should be stated clearly and simply at the beginning of the document. This includes the overall conclusion regarding the risk, an indication of who has reached the conclusion, and any associated recommendations.

Example Risk Conclusion Text

Positive Result:

> *Following a safety assessment in accordance with [national guidelines], [committee or agency] has concluded that the genetically modified plant [species/plant type, unique identifier] is as safe as the conventional counterpart for use in food and feed.*

Negative Result:

> *Following a safety assessment in accordance with [national guidelines], [committee or agency] has concluded that the genetically modified plant [species/plant type, unique identifier] presents unique food safety risks when compared to the conventional counterpart.*

Risk Assessment Summary

Summary Description of the Plant

This should include a short summary describing the identity of the plant. It should include the species of the plant, the source, and a brief description of introduced genetic elements that are expressed in the plant, and any pertinent information about the intended use of the plant as food. This includes any relevant processing.

Disclaimer: *Examples provided below are for illustrative purposes and are not intended to be an endorsement or recommendation regarding the safety of any particular GM plant.*

Example Summary Description of the Plant

> *The genetically modified plant MON531 is a cotton plant (*Gossypium hirsutum*) that has been modified to impart insect resistance to lepidopteran insects. It contains three introduced genes: one to confer insect resistance and two selectable markers to assist in plant breeding and selection. The* Cry1AC *gene from the bacteria* Bacillus thuringiensis *confers resistance to certain lepidopteran insects. The* nptII *gene and the* aad *gene are derived from the bacterium* Escherichia coli *and impart resistance to antibiotics used in laboratory selection.*
>
> *Cotton is used primarily for the production of fiber. However, cotton seeds may be used in the production of oil and cellulose for food and for animal feed. Cottonseed oil is highly processed and typically contains no trace of DNA or protein. Both unprocessed cotton seeds and the leftover meal and hulls following oil production may be used in animal feed. Linters, the fibers remaining on cotton seed following fiber harvesting, are removed and processed using alkaline pH and high temperatures into cellulose, which may be used in food. No other parts of the cotton plant are used in food or feed due to the presence of antinutrient and toxicant compounds, including gossypol.*

Results of the Molecular Characterization

This section should highlight the results of the molecular characterization. It is not important to detail all of the experiments or the data that have been presented in the dossier. Instead, the summary should focus on the conclusions regarding the nature of the plant under assessment. This typically includes the stable inheritance of the trait, the nature of the integration into the genome, and the expression pattern of any resulting gene product.

Example Results of the Molecular Assessment

> *Molecular characterization data was reviewed as part of the food safety assessment. The data indicates that the inserted transgene is stably integrated into the genome. A single copy [or multiple copies] are inserted into the genome. Expression of the transgenic protein was confirmed and found to be present in leaves and stems, as expected, and absent in roots and pollen.*

Results of the Toxicity Assessment

When a novel substance is introduced and expressed in the plant, then a toxicity assessment may be required. The toxicity assessment results will depend on what experiments were considered necessary to inform the assessment. For example, proteins with a long history of safe use in food may not require specific toxicity testing. Novel proteins or proteins that are known to be toxic to one or more species are likely to be subject to *in vitro* or *in vivo* experiments. The results reported

in the risk assessment summary should address the results of the assessment and the information that was considered when formulating the conclusions. Descriptions of the test parameters and other scientific methodology are not likely to be useful here.

Example Results of the Toxicity Assessment (non-toxic protein derived from a food plant)

> *The introduced gene* ZmPsy1 *encodes for the phytoene synthase enzyme derived from the plant* Zea mays *(colloquially known as maize or corn). Maize has a long history of safe use and is not known to contain any endogenous toxins. The ZmPSY1 protein was shown to be rapidly digested in pepsin digestion assays, and to be heat labile. Based on this weight of evidence, additional toxicity testing was considered unnecessary, and [committee or agency] concluded that this protein does not pose any meaningful risk of toxicity when used in food.*

Example Results of the Toxicity Assessment (non-toxic protein)

> *The protein EPSPS is found in plants, fungi and bacteria and is a common component of food. The introduced protein CP4EPSPS, is sourced from Agrobacterium strain CP4. A bioinformatic comparison of the protein sequence for the modified CP4EPSPS protein expressed in this plant [revealed no sequence homology to known toxins]. [A bacterially produced protein of the same sequence was found to be readily digestible in pepsin digestibility assays. Based on this weight of evidence and considering the use of the same protein in other genetically modified plants, [committee or agency] concluded that [plant] [does not pose a risk of toxicity when used in food or feed].*

Example Results of the Toxicity Assessment (protein with known species-specific toxicity)

> *The introduced protein Vip3A is derived from the bacteria* Bacillus thuringiensis *and is known to possess toxicity to certain lepidopteran insects. Sequence comparisons show no similarity to known mammalian or human toxins. In addition, the protein is rapidly digested in pepsin digestion assays. Further, acute mammalian oral toxicity studies showed no adverse effects at concentrations up to 1,250 mg/Kg body weight. Based on the weight of the above evidence, [the committee or agency] concludes that Vip3A does not pose any risk of toxicity when incorporated into [subject plant] for use in food.*

Results of the Allergenicity Assessment

The allergenicity assessment always relies on the weight of evidence approach because there is no single, definitive test for allergenicity. In part this is because allergenicity is a combination of the allergen, but also the individual. Individuals may respond very differently when exposed to the same protein. This section should summarize the key pieces of information that form the basis of the conclusion of the assessor. Specific technical details about testing parameters and their interpretation are likely not helpful.

Example Results of the Allergenicity Assessment

> *The allergenic potential of the Cry1AB protein was considered. The* Bacillus thuringiensis *bacteria, from which the protein is derived, is not a known source of allergens. Sequence comparisons with known allergens showed [no homology greater than 35% identity over a segment of 80 amino acids with any known allergens]. The Cry1AB protein was digested rapidly in pepsin digestion assays, and the protein does not show any evidence for glycosylation. Taken together, this evidence supports a conclusion that Cry1AB protein is not likely to be an allergen when found in foods derived from [plant].*

Results of the Compositional Assessment

There are two ostensible reasons for the conduct of a compositional assessment. First, compositional information can provide direct evidence for a nutritional equivalence assessment. In this case, important nutritional components are considered and compared to a range of conventional comparators. The second reason is that compositional assessments contribute to a weight of evidence assessment of unintended effects of the genetic modification. The summary should address both purposes for compositional assessment.

Key Questions for Compositional Assessment

- Are any key nutritional components consistently different than the conventional comparator?
- For any identified differences
  - Is there a pattern that would indicate a substantial metabolic difference from the conventional comparator, or is it an isolated difference that would be expected from random variation?
  - Do differences fall within the range of values observed across conventional varieties?
  - Would any identified differences alter the nutritional value of foods derived from the plant?

Key Things to Avoid

- Do not list statistically significant differences in composition without providing context to allow readers to understand your conclusions about whether these differences pose a risk.

Example Results of the Compositional Assessment

> *The composition of [subject plant] was assessed in comparison to a conventional counterpart. Parameters for compositional assessment included proximate analysis, assessment of levels of key nutrients [mention nutrients] and antinutrients (if any), as well as assessment of toxicants [cite a source document for the key nutrients and analytes that are relevant for the plant, if available]. The [subject plant] demonstrated a composition similar to the conventional comparator. While [x] number of compositional differences were determined to be statistically significant, none of these differences were determined to be biologically significant. The absolute value of measured components fell within reported ranges for conventional varieties of [plant]. Taken together, the composition of [subject plant] showed no differences suggestive of any metabolic or nutritional differences from conventional varieties.*

Appendix 4: Process Followed for Drafting the Consensus Statement on Safety Assessment of Foods Derived from Genetically Engineered Plants and the Supporting Appendices

The Consensus Statement on Safety Assessment of Foods derived from GE Plants and the supporting Appendices have been prepared by an Expert Working Group (EWG) convened as part of the project on **"Regional Harmonisation for the Safety Assessment of Foods Derived from Genetically Modified Plants"** being implemented by the Agriculture & Food Systems Institute and Biotech Consortium India Limited under the aegis of the South Asia Biosafety Program.

Members of EWG included senior experts and regulators from four participating countries, *viz.*, Bangladesh, Bhutan, India, and Sri Lanka.

This document outlines the process that was followed in convening the EWG to draft a consensus statement on safety assessment of foods derived from GE plants with an objective to harmonize the safety assessment. The statement has six supporting appendices.

The EWG was convened virtually over the course of 2020 and 2021. The deliberations took place with experts from all four participating countries at the EWG meetings. Nine meetings of the EWG were held that involved discussions on all technical aspects concerning safety assessments of foods derived from GE plants (Table 1). In addition, discussion sessions were conducted on topics relevant to safety assessment. These sessions involved interactive discussions between members of the EWG and regulators and technical experts from various countries (Table 2).

In the initial meeting, members from each participating country shared information about the status of biosafety regulations in their respective countries. This was followed by detailed discussions on the commonalities of the national guidelines (of the four participating countries) on GE food safety assessment. This established the groundwork for drafting the Consensus Statement and supporting Appendices. All documents were drafted collaboratively. The preparation of each document followed an iterative process, which involved comments from all members, with subsequent editing until a consensus on the content was reached. Each document was finalized upon agreement by all members of the EWG.

Table 1: Schedule of EWG Meetings and Overview of Activities

Meetings of the EWG	Activities
1st (30.09.2020)	Overview of the project and proposed activities Brief presentations by each EWG member to share information specific to the respective country's situation
2nd (11.11.2020)	Summary of the status of GM food safety guidance and its implementation in participating countries Possibilities of harmonisation of GM food safety assessment in South Asia: needs and gaps
3rd (05.01.2021)	Draft text of the consensus statement on harmonisation of safety assessment of foods derived from GE plants

4th (27.01.2021)	Comparison of information requirements in the guidelines for GM food safety assessment of Bangladesh, Bhutan, India, and Sri Lanka Proposed structure for Information Requirements
5th (24.02.2021)	Information Elements for the Safety Assessment of Foods Derived from GE Plants
6th (20.04.2021)	Introduction and discussion on Structure of the Common Application Format
7th (07.07.2021)	Discussion on Common Application Format Risk Assessment Summary - Context and Overview
8th (18.08.2021)	Feedback on Common Application Format Proposed format for Risk Assessment Summary
9th (22.09.2021)	Feedback on Risk Assessment Summary Overview of the Process Followed for Drafting of All Documents

Table 2: Details of Discussion Sessions

Discussion Sessions	Topic	Presentations by
1st (21.10.2020)	International Guidance on Regulation of Foods Derived from Modern Biotechnology	Dr. Janet Gorst (Retired), Food Standards Australia and New Zealand (FSANZ)
	Status of OECD GLP Program in South Asia	Dr. (Mrs.) Ekta Kapoor, Scientist 'E', National GLP Compliance Monitoring Authority, Department of Science and Technology, Government of India
2nd (03.12.2020)	Regulatory Harmonisation for Food Safety in South Asia	Dr. Syed Humayun Kabir, Former Director General, South Asian Regional Standards Organization (SARSO), Bangladesh
	Agricultural Trade in South Asia and Potential Impacts on Products of Modern Biotechnology	Dr. Devesh Roy, Senior Research Fellow, International Food Policy Research Institute (IFPRI), India
3rd (24.03.2021)	OECD Work on the Safety Assessment of GE Organisms and Derived Foods and Feeds – Towards Harmonised Risk/Safety Assessment	Dr. Bertrand Dagallier, Principal Administrator, Biosafety and Novel Foods & Feeds Safety, Chemical Accidents, OECD Environment, Health and Safety Division (ENV/EHS)
	OECD Consensus Documents on Compositional Considerations	Mr. Jason Dietz, Senior Policy Analyst-Biotechnology Coordinator, Office of Food Additive Safety, Center for Food Safety and Applied Nutrition, US Food and Drug Administration
4th (05.05.2021)	FSANZ-Health Canada Collaboration on GM Food Safety Assessment	Dr. Lisa Kelley, Team Leader, Microbiology and Biotechnology Section, Food Standards Australia New Zealand (FSANZ)
	Paraguay's Path Towards the Simplification of Procedures in the Approval of GE Crops	Prof. Danilo Fernández Ríos, National University of Asunción, Faculty of Exact and Natural Sciences, Paraguay

Appendix 5: Codex 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[1] as well as the Codex Working Principles for Risk Analysis[2].

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[3].

[1] 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).

[2] "Working Principles for Risk Analysis for Application in the Framework of the Codex Alimentarius" (adopted by the 26th Session of the Codex Alimentarius Commission, 2003; Codex Alimentarius Commission Procedural Manual; Thirteenth edition)

[3] This document does not address animal feed and animals fed such feed except insofar as these animals have been developed by using modern biotechnology.

Adopted in 2003. Amendments 2008, 2011

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
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[4].

"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[5].

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[6].

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.

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[4] This definition is taken from the Cartagena Biosafety Protocol under the Convention on Biological Diversity.

[5] It is recognized that for the foreseeable future, foods derived from modern biotechnology will not be used as conventional counterparts.

[6] Reference is made to the Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants (CAC/GL 45-2003), the Guideline for the Conduct of Food Safety Assessment of Foods Produced using Recombinant- DNA Microorganisms (CAC/GL 46-2003) and the Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Animals (CAC/GL 68-2008).

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 the Codex Alimentarius Commission[7] 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[8] 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[9] 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 biotechnology. This should include consistency of data requirements, assessment frameworks, the acceptable level of risk, communication and consultation mechanisms and timely decision processes.

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7 See footnote 1.

8 Reference is made to the *Compilation of Codex Texts Relevant to Labelling of Foods Derived from Modern Biotechnology* (CAC/GL 76-2011).

9 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 was considered by the Codex Committee on Food Import and Export Inspection and Certification Systems, see CAC/GL 60-2006: *Principles for Traceability/Product Tracing as a Tool within a Food Inspection and Certification System*.

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 recognised 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[10].

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.

[10] Reference is made to technical assistance of provisions in Article 9 of the SPS Agreement and Article 11 of the TBT Agreement.

Appendix 6: Codex Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants (CAC/GL 45-2003)

Section 1 - Scope

1. This Guideline supports the Principles for the Risk Analysis of Foods Derived from Modern Biotechnology. It addresses safety and nutritional aspects of foods consisting of, or derived from, plants that have a history of safe use as sources of food, and that have been modified by modern biotechnology to exhibit new or altered expression of traits.

2. This document does not address animal feed or animals fed with the feed. This document also does not address environmental risks.

3. The Codex principles of risk analysis, particularly those for risk assessment, are primarily intended to apply to discrete chemical entities such as food additives and pesticide residues, or a specific chemical or microbial contaminant that have identifiable hazards and risks; they are not intended to apply to whole foods as such. Indeed, few foods have been assessed scientifically in a manner that would fully characterise all risks associated with the food. Further, many foods contain substances that would likely be found harmful if subjected to conventional approaches to safety testing. Thus, a more focused approach is required where the safety of a whole food is being considered.

4. This approach is based on the principle that the safety of foods derived from new plant varieties, including recombinant-DNA plants, is assessed relative to the conventional counterpart having a history of safe use, taking into account both intended and unintended effects. Rather than trying to identify every hazard associated with a particular food, the intention is to identify new or altered hazards relative to the conventional counterpart.

5. This safety assessment approach falls within the risk assessment framework as discussed in Section 3 of the Principles for the Risk Analysis of Foods Derived from Modern Biotechnology. If a new or altered hazard, nutritional or other food safety concern is identified by the safety assessment, the risk associated with it would first be assessed to determine its relevance to human health. Following the safety assessment and if necessary further risk assessment, the food would be subjected to risk management considerations in accordance with the Principles for the Risk Analysis of Foods Derived from Modern Biotechnology before it is considered for commercial distribution.

6. Risk management measures such as post-market monitoring of consumer health effects may assist the risk assessment process. These are discussed in paragraph 20 of the Principles for the Risk Analysis of Foods derived from Modern Biotechnology.

7. The Guideline describes the recommended approach to making safety assessments of foods derived from recombinant-DNA plants where a conventional counterpart exists, and identifies the data and information that are generally applicable to making such assessments. While this Guideline is designed for foods derived from recombinant- DNA plants, the approach described could, in general, be applied to foods derived from plants that have been altered by other techniques.

Adopted in 2003, Annexes II and III adopted in 2008.

Section 2 - Definitions

8. The definitions below apply to this Guideline:

"Recombinant-DNA 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.

"Conventional Counterpart" - means a related plant variety, its components and/or products for which there is experience of establishing safety based on common use as food[1].

Section 3 - Introduction to Food Safety Assessment

9. Traditionally, new varieties of food plants have not been systematically subjected to extensive chemical, toxicological, or nutritional evaluation prior to marketing, with the exception of foods for specific groups, such as infants, where the food may constitute a substantial portion of the diet. Thus, new varieties of corn, soya, potatoes and other common food plants are evaluated by breeders for agronomic and phenotypic characteristics, but generally, foods derived from such new plant varieties are not subjected to the rigorous and extensive food safety testing procedures, including studies in animals, that are typical of chemicals such as food additives or pesticide residues that may be present in food.

10. The use of animal models for assessing toxicological endpoints is a major element in the risk assessment of many compounds such as pesticides. In most cases, however, the substance to be tested is well characterised, of known purity, of no particular nutritional value, and, human exposure to it is generally low. It is therefore relatively straightforward to feed such compounds to animals at a range of doses some several orders of magnitude greater than the expected human exposure levels, in order to identify any potential adverse health effects of importance to humans. In this way, it is possible, in most cases, to estimate levels of exposure at which adverse effects are not observed and to set safe intake levels by the application of appropriate safety factors.

11. Animal studies cannot readily be applied to testing the risks associated with whole foods, which are complex mixtures of compounds, often characterised by a wide variation in composition and nutritional value. Due to their bulk and effect on satiety, they can usually only be fed to animals at low multiples of the amounts that might be present in the human diet. In addition, a key factor to consider in conducting animal studies on foods is the nutritional value and balance of the diets used, in order to avoid the induction of adverse effects which are not related directly to the material itself. Detecting any potential adverse effects and relating these conclusively to an individual characteristic of the food can therefore be extremely difficult. 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 foods. Another consideration in deciding the need for animal studies is whether it is appropriate to subject experimental animals to such a study if it is unlikely to give rise to meaningful information.

12. Due to the difficulties of applying traditional toxicological testing and risk assessment procedures to whole foods, a more focused approach is required for the safety assessment of foods derived from food plants, including recombinant-DNA plants. This has been addressed by the development of a multidisciplinary approach for assessing safety which takes into account both intended and unintended changes that may occur in the plant or in the foods derived from it, using the concept of substantial equivalence.

13. The concept of substantial equivalence is a key step in the safety assessment process. However, it 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 conventional counterpart. This concept is used to identify similarities and differences between the new food and its conventional counterpart[2]. It aids in the identification of potential safety and nutritional issues and is considered the most appropriate strategy to date for safety assessment of foods derived from recombinant-DNA plants. The safety assessment carried out in this way does not imply absolute safety of the new product; rather, it focuses on assessing the safety of any identified differences so that the safety of the new product can be considered relative to its conventional counterpart.

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[1] It is recognized that for the foreseeable future, foods derived from modern biotechnology will not be used as conventional counterparts.

[2] The concept of *substantial equivalence* as described in the report of the 2000 joint FAO /WHO expert consultations (Document WHO/SDE/PHE/FOS/00.6, WHO, Geneva, 2000).

Unintended Effects

14. In achieving the objective of conferring a specific target trait (intended effect) to a plant by the insertion of defined DNA sequences, additional traits could, in some cases, be acquired or existing traits could be lost or modified (unintended effects). The potential occurrence of unintended effects is not restricted to the use of *in vitro* nucleic acid techniques. Rather, it is an inherent and general phenomenon that can also occur in conventional breeding. Unintended effects may be deleterious, beneficial, or neutral with respect to the health of the plant or the safety of foods derived from the plant. Unintended effects in recombinant-DNA plants may also arise through the insertion of DNA sequences and/or they may arise through subsequent conventional breeding of the recombinant-DNA plant. Safety assessment should include data and information to reduce the possibility that a food derived from a recombinant-DNA plant would have an unexpected, adverse effect on human health.

15. 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. For example, the expression of enzymes at high levels may give rise to secondary biochemical effects or changes in the regulation of metabolic pathways and/or altered levels of metabolites.

16. Unintended effects due to genetic modification may be subdivided into two groups: those that are "predictable" and those that are “unexpected”. Many unintended effects are largely predictable based on knowledge of the inserted trait and its metabolic connections or of the site of insertion. Due to the expanding information on plant genome and the increased specificity in terms of genetic materials introduced through recombinant-DNA techniques compared with other forms of plant breeding, it may become easier to predict unintended effects of a particular modification. Molecular biological and biochemical techniques can also be used to analyse potential changes at the level of gene transcription and message translation that could lead to unintended effects.

17. The safety assessment of foods derived from recombinant-DNA plants involves methods to identify and detect such unintended effects and procedures to evaluate their biological relevance and potential impact on food safety. A variety of data and information are necessary to assess unintended effects because no individual test can detect all possible unintended effects or identify, with certainty, those relevant to human health. These data and information, when considered in total, provide assurance that the food is unlikely to have an adverse effect on human health. 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. These observations by breeders provide a first screen for plants that exhibit unintended traits. New varieties that pass this screen are subjected to safety assessment as described in Sections 4 and 5.

Framework of Food Safety Assessment

18. The safety assessment of a food derived from a recombinant-DNA plant follows a stepwise process of addressing relevant factors that include:

A) Description of the recombinant-DNA plant;
B) Description of the host plant and its use as food;
C) Description of the donor organism(s);
D) Description of the genetic modification(s);
E) Characterization of the genetic modification(s);
F) Safety assessment:
   a) expressed substances (non-nucleic acid substances);
   b) compositional analyses of key components;
   c) evaluation of metabolites ;
   d) food processing;
   e) nutritional modification; and
G) Other considerations.

19. In certain cases, the characteristics of the product may necessitate development of additional data and information to address issues that are unique to the product under review.

20. Experiments intended to develop data for safety assessments should be designed and conducted in accordance with sound scientific concepts and principles, as well as, where appropriate, Good Laboratory Practice. Primary data should be made available to regulatory authorities at request. Data should be obtained using sound scientific methods and analysed using appropriate statistical techniques. The sensitivity of all analytical methods should be documented.

21. The goal of each safety assessment is to provide assurance, in the light of the best available scientific knowledge, that the food does not cause harm when prepared, used and/or eaten according to its intended use. The expected endpoint of such an assessment will be a conclusion regarding whether the new food is as safe as the conventional counterpart taking into account dietary impact of any changes in nutritional content or value. In essence, therefore, the outcome of the safety assessment process is to define the product under consideration in such a way as to enable risk managers to determine whether any measures are needed and if so to make well-informed and appropriate decisions.

Section 4 - General Considerations

Description of the Recombinant-DNA Plant

22. A description of the recombinant-DNA plant being presented for safety assessment should be provided. This description should identify the crop, the transformation event(s) to be reviewed and the type and purpose of the modification. This description should be sufficient to aid in understanding the nature of the food being submitted for safety assessment.

Description of the Host Plant and Its Use As Food

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

A) common or usual name; scientific name; and, taxonomic classification;
B) history of cultivation and development through breeding, in particular identifying traits that may adversely impact on human health ;
C) information on the host plant's genotype and phenotype relevant to its safety, including any known toxicity or allergenicity; and
D) history of safe use for consumption as food.

24. Relevant phenotypic information should be provided not only for the host plant, but also for related species and for plants that have made or may make a significant contribution to the genetic background of the host plant.

25. The history of 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).

Description of the Donor Organism(s)

26. Information should 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 pathogenicity or toxin production, or have other traits that affect human health (e.g. presence of anti-nutrients). The description of the donor organism(s) should include:

A) its usual or common name;
B) scientific name;
C) taxonomic classification;
D) information about the natural history as concerns food safety;
E) information on naturally occurring toxins, anti-nutrients and allergens; for microorganisms, additional information on pathogenicity and the relationship to known pathogens; and
F) 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).

Description of the Genetic Modification(s)

27. Sufficient information should be provided on the genetic modification to allow for the identification of all genetic material potentially delivered to the host plant and to provide the necessary information for the analysis of the data supporting the characterization of the DNA inserted in the plant.

28. The description of the transformation process should include:

A) information on the specific method used for the transformation (e.g. Agrobacterium-mediated transformation);
B) information, if applicable, on the DNA used to modify the plant (e.g. helper plasmids), including the source (e.g. plant, microbial, viral, synthetic), identity and expected function in the plant; and
C) intermediate host organisms including the organisms (e.g. bacteria) used to produce or process DNA for transformation of the host organism.

29. Information should be provided on the DNA to be introduced, including:

A) the characterization of all the genetic components including marker genes, regulatory and other elements affecting the function of the DNA;
B) the size and identity;
C) the location and orientation of the sequence in the final vector/construct; and
D) the function.

Characterization of the Genetic Modification(s)

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

31. Information should be provided on the DNA insertions into the plant genome; this should include:

A) the characterization and description of the inserted genetic materials;
B) the number of insertion sites;
C) the organisation of the inserted genetic material at each insertion site including copy number and sequence data of the inserted material and of the surrounding region, sufficient to identify any substances expressed as a consequence of the inserted material, or, where more appropriate, other information such as analysis of transcripts or expression products to identify any new substances that may be present in the food; and
D) 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.

32. Information should be provided on any expressed substances in the recombinant-DNA plant; this should include:

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

33. In addition, information should be provided:

A) to demonstrate whether the arrangement of the genetic material used for insertion has been conserved or whether significant rearrangements have occurred upon integration;
B) 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;
C) to demonstrate whether 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.

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;

D) 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;

E) 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

F) to confirm the identity and expression pattern of any new fusion proteins.

Safety Assessment

Expressed Substances (non-nucleic acid substances)

Assessment of Possible Toxicity

34. *In vitro* nucleic acid techniques enable the introduction of DNA that can result in the synthesis of new substances in plants. The new substances can be conventional components of plant foods such as proteins, fats, carbohydrates, vitamins which are novel in the context of that recombinant-DNA plant. New substances might also include new metabolites resulting from the activity of enzymes generated by the expression of the introduced DNA.

35. The safety assessment should take into account the chemical nature and function of the newly expressed substance and identify the concentration of the substance in the edible parts of the recombinant-DNA plant, including variations and mean values. Current dietary exposure and possible effects on population sub-groups should also be considered.

36. Information should be provided to ensure that genes coding for known toxins or anti-nutrients present in the donor organisms are not transferred to recombinant-DNA plants that do not normally express those toxic or anti-nutritious characteristics. This assurance is particularly important in cases where a recombinant-DNA 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.

37. For the reasons described in Section 3, conventional toxicology studies may not be considered necessary where the substance or a closely related substance has, taking into account its function and exposure, been consumed safely in food. In other cases, the use of appropriate conventional toxicology or other studies on the new substance may be necessary.

38. In the case of proteins, the assessment of potential toxicity should 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. Appropriate oral toxicity studies[3] may need to be carried out in cases where the protein present in the food is not similar to proteins that have previously been consumed safely in food, and taking into account its biological function in the plant where known.

39. 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.

40. This may require the isolation of the new substance from the recombinant-DNA plant, or the synthesis or production of the substance from an alternative source, in which case, the material should be shown to be biochemically, structurally, and functionally equivalent to that produced in the recombinant-DNA plant.

Assessment of Possible Allergenicity (Proteins)

41. When the protein(s) resulting from the inserted gene is present in the food, it should be assessed for potential allergenicity in all cases. An integrated, stepwise, case-by-case approach used in the assessment of the potential allergenicity of the newly-expressed protein(s) should rely upon various criteria used in combination (since no single criterion is sufficiently

[3] Guidelines for oral toxicity studies have been developed in international fora, for example, the OECD Guidelines for the Testing of Chemicals.

predictive on either allergenicity or non-allergenicity). As noted in paragraph 20, the data should be obtained using sound scientific methods. A detailed presentation of issues to be considered can be found in Annex 1 to this document[4].

42. The newly expressed proteins in foods derived from recombinant-DNA 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.

43. The transfer of genes from commonly allergenic foods and from foods known to elicit gluten-sensitive enteropathy in sensitive individuals should be avoided unless it is documented that the transferred gene does not code for an allergen or for a protein involved in gluten-sensitive enteropathy.

Compositional Analyses of Key Components

44. Analyses of concentrations of key components[5] of the recombinant-DNA plant and, especially those typical of the food, should be compared with an equivalent analysis of a conventional counterpart grown and harvested under the same conditions. In some cases, a further comparison with the recombinant-DNA plant grown under its expected agronomic conditions may need to be considered (e.g. application of an herbicide). 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 should ideally be 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. 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.

45. The location of trial sites should be representative of the range of environmental conditions under which the plant varieties would be expected to be grown. The number of trial sites should be sufficient to allow accurate assessment of compositional characteristics over this range. Similarly, trials should be conducted over a sufficient number of generations to allow adequate exposure to the variety of conditions met in nature. To minimise environmental effects, and to reduce any effect from naturally occurring genotypic variation within a crop variety, each trial site should be replicated. An adequate number of plants should be sampled and the methods of analysis should be sufficiently sensitive and specific to detect variations in key components.

Evaluation of Metabolites

46. Some recombinant-DNA plants may have been modified in a manner that could result in new or altered levels of various metabolites in the food. Consideration should be given to the potential for the accumulation of metabolites in the food that would adversely affect human health. Safety assessment of such plants requires investigation of residue and metabolite levels in the food and assessment of any alterations in nutrient profile. Where altered residue or metabolite levels are identified in foods, consideration should be given to the potential impacts on human health using conventional procedures for establishing the safety of such metabolites (e.g. procedures for assessing the human safety of chemicals in foods).

Food Processing

47. The potential effects of food processing, including home preparation, on foods derived from recombinant-DNA plants should also be considered. For example, alterations could occur in the heat stability of an endogenous toxicant or the bioavailability of an important nutrient after processing. Information should therefore be provided describing the processing conditions used in the production of a food ingredient from the plant. For example, in the case of vegetable oil, information should be provided on the extraction process and any subsequent refining steps.

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[4] The FAO/WHO expert consultation 2001 report, which includes reference to several decision trees, was used in developing Annex 1 to these guidelines.

[5] Key nutrients or key anti-nutrients are those components in a particular food that may have a substantial impact in the overall diet. They may be major constituents (fats, proteins, carbohydrates as nutrients or enzyme inhibitors as anti-nutrients) or minor compounds (minerals, vitamins). Key toxicants are those toxicologically significant compounds known to be inherently present in the plant, 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) and allergens.

Nutritional Modification

48. The assessment of possible compositional changes to key nutrients, which should be conducted for all recombinant-DNA plants, has already been addressed under 'Compositional analyses of key components'. However, foods derived from recombinant-DNA plants that have undergone modification to intentionally alter nutritional quality or functionality should 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. A detailed presentation of issues to be considered can be found in Annex 2 to this document.

49. 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 recombinant-DNA 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 should 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.

50. 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 recombinant-DNA plant components may be individually assessed as safe, the impact of the change on the overall nutrient profile should be determined.

51. 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 (i.e. foods or food components whose nutritional composition is closer to that of the food derived from recombinant-DNA plant) as appropriate comparators to assess the nutritional impact of the food.

52. Because of geographical and cultural variation in food consumption patterns, nutritional changes to a specific food may have a greater impact in some geographical areas or in some cultural population than in others. Some food plants serve as the major source of a particular nutrient in some populations. The nutrient and the populations affected should be identified.

53. Some foods may require additional testing. For example, animal feeding studies may be warranted for foods derived from recombinant-DNA 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 foods.

Section 5 - Other Considerations

Potential Accumulation of Substances Significant to Human Health

54. Some recombinant-DNA plants may exhibit traits (e.g., herbicide tolerance) which may indirectly result in the potential for accumulation of pesticide residues, altered metabolites of such residues, toxic metabolites, contaminants, or other substances which may be relevant to human health. The safety assessment should take this potential for accumulation into account. Conventional procedures for establishing the safety of such compounds (e.g., procedures for assessing the human safety of chemicals) should be applied.

Use of Antibiotic Resistance Marker Genes

55. Alternative transformation technologies that do not result in antibiotic resistance marker genes in foods should be used in the future development of recombinant-DNA plants, where such technologies are available and demonstrated to be safe.

56. Gene transfer from plants and their food products to gut microorganisms or human cells is considered a rare possibility because of the many complex and unlikely events that would need to occur consecutively. Nevertheless, the possibility of such events cannot be completely discounted[6].

57. In assessing safety of foods containing antibiotic resistance marker genes, the following factors should be considered:

A) the clinical and veterinary use and importance of the antibiotic in question;

(Certain antibiotics are the only drug available to treat some clinical conditions (e.g. vancomycin for use in treating certain staphylococcal infections). Marker genes encoding resistance to such antibiotics should not be used in recombinant-DNA plants.)

B) whether the presence in food of the enzyme or protein encoded by the antibiotic resistance marker gene would compromise the therapeutic efficacy of the orally administered antibiotic; and

(This assessment should provide an estimate of the amount of orally ingested antibiotic that could be degraded by the presence of the enzyme in food, taking into account factors such as dosage of the antibiotic, amount of enzyme likely to remain in food following exposure to digestive conditions, including neutral or alkaline stomach conditions and the need for enzyme cofactors (e.g. ATP) for enzymatic activity and estimated concentration of such factors in food.)

C) safety of the gene product, as would be the case for any other expressed gene product.

58. If evaluation of the data and information suggests that the presence of the antibiotic resistance marker gene or gene product presents risks to human health, the marker gene or gene product should not be present in the food. Antibiotic resistance genes used in food production that encode resistance to clinically used antibiotics should not be present in foods.

Review of Safety Assessments

59. The goal of the safety assessment is a conclusion as to whether the new food is as safe as the conventional counterpart taking into account dietary impact of any changes in nutritional content or value. Nevertheless, the safety assessment should be reviewed in the light of new scientific information that calls into question the conclusions of the original safety assessment.

[6] In cases where there are high levels of naturally occurring bacteria which are resistant to the antibiotic, the likelihood of such bacteria transferring this resistance to other bacteria will be orders of magnitude higher than the likelihood of transfer between ingested foods and bacteria.

Annex 1: Assessment of Possible Allergenicity

Section 1 – Introduction

1. All newly expressed proteins[7] in recombinant-DNA plants that could be present in the final food should be assessed for their potential to cause allergic reactions. This should include 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.

2. 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 an integrated, stepwise, case by case approach, as described below, be used in the assessment of possible allergenicity of newly expressed proteins. This approach takes into account the evidence derived from several types of information and data since no single criterion is sufficiently predictive.

3. The endpoint of the assessment is a conclusion as to the likelihood of the protein being a food allergen.

Section 2 – Assessment Strategy

4. The initial steps in assessing possible allergenicity of any newly expressed proteins are the determination of: the source of the introduced protein; any significant similarity between the amino acid sequence of the protein and that of known allergens; and its structural properties, including but not limited to, its susceptibility to enzymatic degradation, heat stability and/or, acid and enzymatic treatment.

5. 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. This will require the isolation of any newly expressed proteins from the recombinant-DNA 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 recombinant-DNA plant. Particular attention should be given to 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.

6. It is important to establish whether the source is known to cause allergic reactions. Genes derived from known allergenic sources should be assumed to encode an allergen unless scientific evidence demonstrates otherwise.

Section 3 – Initial Assessment

Section 3.1 – Source of the Protein

7. As part of the data supporting the safety of foods derived from recombinant-DNA plants, information should describe any reports of allergenicity associated with the donor organism. Allergenic sources of genes would be 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: the availability of sera for screening purposes; documented type, severity and frequency of allergic reactions; structural characteristics and amino acid sequence; physicochemical and immunological properties (when available) of known allergenic proteins from that source.

Section 3.1 – Amino Acid Sequence Homology

8. The purpose of a sequence homology comparison is to assess the extent to which a newly expressed protein is similar in structure to a known allergen. This information may suggest whether that protein has an allergenic potential. Sequence homology searches comparing the structure of all newly expressed proteins with all known allergens should be done. Searches should be conducted using various algorithms such as FASTA or BLASTP to predict overall structural

[7] This assessment strategy is not applicable for assessing whether newly expressed proteins are capable of inducing gluten- sensitive or other enteropathies. The issue of enteropathies is already addressed in Assessment of possible allergenicity (proteins), paragraph 42 of the Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant- DNA Plants. In addition, the strategy is not applicable to the evaluation of foods where gene products are down regulated for hypoallergenic purposes.

similarities. 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[8]. Validated search and evaluation procedures should be used in order to produce biologically meaningful results.

9. 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) or other scientifically justified criteria. All the information resulting from the sequence homology comparison between the newly expressed protein and known allergens should be reported to allow a case-by-case scientifically based evaluation.

10. 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.

11. 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 should be considered along with the other data outlined under this strategy in assessing the allergenic potential of newly expressed proteins. Further studies should be conducted as appropriate (see also sections 4 and 5). A positive sequence homology result 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.

Section 3.1 – Pepsin Resistance

12. Resistance to pepsin digestion has been observed in several food allergens; thus a correlation exists between resistance to digestion by pepsin and allergenic potential[9]. Therefore, the resistance of a protein to degradation in the presence of pepsin under appropriate conditions indicates that further analysis should be conducted to determine the likelihood of the newly expressed protein being allergenic. The establishment of a consistent and well-validated pepsin degradation protocol may enhance the utility of this method. However, it should be taken into account that a lack of resistance to pepsin does not exclude that the newly expressed protein can be a relevant allergen.

13. Although the pepsin resistance protocol is strongly recommended, it is recognized that other enzyme susceptibility protocols exist. Alternative protocols may be used where adequate justification is provided[10].

Section 4 – Specific Serum Screening

14. For those proteins that originate from a source known to be allergenic, or have sequence homology with a known allergen, testing in immunological assays should 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 *in vitro* assays. A critical issue for testing will be the availability of human sera from sufficient numbers of individuals[11]. In addition, the quality of the sera and the assay procedure need to be standardized to produce a valid test result. For proteins from sources not known to be allergenic, and which do not exhibit sequence homology to a known allergen, targeted serum screening may be considered where such tests are available as described in paragraph 17.

15. 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[12]. A positive result in such tests would indicate a potential allergen.

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[8] It is recognized that the 2001 FAO/WHO consultation suggested moving from 8 to 6 identical amino acid segments in 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.

[9] The method outlined in the U.S. Pharmacopoeia (1995) was used in the establishment of the correlation (Astwood *et al.* 1996)

[10] Report of Joint FAO/WHO Expert Consultation on Allergenicity of Foods Derived from Biotechnology (2001): Section "6.4 Pepsin Resistance".

[11] 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.

[12] *Ex vivo* procedure is described as the testing for allergenicity using cells or tissue culture from allergic human subjects (Report of Joint FAO/WHO Expert Consultation on Allergenicity of Foods derived from Biotechnology).

Section 5 – Other Considerations

16. 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 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.

17. 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 methods should be scientifically sound and may include 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); the development of international serum banks; use of animal models; and examination of newly expressed proteins for T-cell epitopes and structural motifs associated with allergens.

Annex 2: Food Safety Assessment of Foods Derived from Recombinant-DNA Plants Modified for Nutritional or Health Benefits

Section 1 – Introduction

1. General guidance for the safety assessment of foods derived from recombinant-DNA plants is provided in the Codex Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants (CAC/GL 45-2003) (Codex Plant Guideline). This Annex provides additional considerations that are specific to foods modified for nutritional or health benefits. The document does not extend beyond a safety assessment and therefore, it does not cover assessment of the benefits themselves or any corresponding health claims, or risk-management measures[13].

2. The following factors determine whether a recombinant-DNA plant is a recombinant-DNA Plant Modified for Nutritional or Health Benefits, and as such within the scope of this Annex:

(a) the recombinant-DNA plant exhibits a particular trait in portion(s) of the plant intended for food use, and;
(b) The trait is a result of i) introduction of a new nutrient(s) or related substance(s), or ii) alteration of either the quantity or bioavailability of a nutrient(s) or related substance(s), iii) removal or reduction of undesirable substance(s) (e.g. allergens or toxicants), or iv) alteration of the interaction(s) of nutritional or health relevance of these substances.

Section 2 – Definition

3. The definition below applies to this Annex:

"Nutrient"[14] - means any substance normally consumed as a constituent of food:

(a) which provides energy; or
(b) which is needed for growth and development and maintenance of healthy life; or
(c) a deficit of which will cause characteristic biochemical or physiological changes to occur.

4. This Annex draws, where appropriate, on the definitions of key nutritional concepts to be found or to be developed in relevant Codex texts, especially those elaborated by the Codex Committee on Nutrition and Foods for Special Dietary Uses.

Section 3 – Food Safety Assessment

5. The Codex General Principles for the Addition of Essential Nutrients to Foods (CAC/GL 09-1987) are generally applicable to the assessment of food derived from a plant which is modified by increasing the amount of a nutrient(s) or related substance(s) available for absorption and metabolism. The Food Safety Framework outlined within the Codex Plant Guideline[15] applies to the overall safety assessment of a food derived from a recombinant-DNA plant modified for nutritional or health benefits. This Annex presents additional considerations regarding the food safety assessment of those foods.

6. Foods derived from recombinant-DNA plants modified for nutritional or health benefits may benefit certain populations/sub populations, while other populations/sub populations may be at risk from the same food[16].

7. Rather than trying to identify every hazard associated with a particular food, the intention of a safety assessment of food derived from recombinant-DNA plants is the identification of new or altered hazards relative to the conventional counterpart[17]. Since recombinant-DNA plants modified for nutritional or health benefits result in food products with a composition that may be significantly different from their conventional counterparts, the choice of an appropriate

[13] Principles for the Risk Analysis of Foods Derived from Modern Biotechnology (CAC/GL 44-2003, paragraph 19)

[14] General Principles for the Addition of Essential Nutrients to Foods (CAC/GL 09-1987)

[15] Paragraphs 18-21 (Safety Framework) and 48-53 (Nutrition Modification

[16] Further guidance for susceptible and high-risk population groups is provided in paragraph 49 of the Codex Plant Guideline.

[17] Codex Plant Guideline, paragraph 4

comparator[18] is of great importance for the safety assessment addressed in this Annex. Those alterations identified in a plant modified to obtain nutritional or health benefits are the subject of this safety assessment.

8. Upper levels of intake for many nutrients that have been set out by some national, regional and international bodies[19] may be considered, as appropriate. The basis for their derivation should also be considered in order to assess the public health implications of exceeding these levels.

9. The safety assessment of related substances should follow a case-by-case approach taking into account upper levels as well as other values, where appropriate.

10. Although it is preferable to use a scientifically-determined upper level of intake of a specific nutrient or related substance, when no such value has been determined, consideration may be given to an established history of safe use for nutrients or related substances that are consumed in the diet if the expected or foreseeable exposure would be consistent with those historical safe levels.

11. With conventional fortification of food, typically a nutrient or a related substance is added at controlled concentrations and its chemical form is characterized. Levels of plant nutrients or related substances may vary in both conventionally bred and recombinant-DNA plants due to growing conditions. In addition, more than one chemical form of the nutrient might be expressed in the food as a result of the modification and these may not be characterized from a nutrition perspective. Where appropriate, information may be needed on the different chemical forms of the nutrient(s) or related substance(s) expressed in the portion of the plant intended for food use and their respective levels .

12. Bioavailability of the nutrient(s), related substance(s), or undesirable substance(s) in the food that were the subject of the modification in the recombinant-DNA plant should be established, where appropriate. If more than one chemical form of the nutrient(s) or related substance(s) is present, their combined bioavailability should be established, where appropriate.

13. Bioavailability will vary for different nutrients, and methods of testing for bioavailability should be relevant to the nutrient, and the food containing the nutrient, as well as the health, nutritional status and dietary practices of the specific populations consuming the food. *In vitro* and *in vivo* methods to determine bioavailability exist, the latter conducted in animals and in humans. *In vitro* methods can provide information to assess extent of release of a substance from plant tissues during the digestive process. *In vivo* studies in animals are of limited value in assessing nutritional value or nutrient bioavailability for humans and would require careful design in order to be relevant. *In vivo* studies, in particular, human studies may provide more relevant information about whether and to what extent the nutrient or related substance is bioavailable.

14. Guidance on dietary exposure assessment of foods derived from recombinant-DNA plants with nutritional modifications is provided in paragraph 49 of the Codex Plant Guideline. In the context of this Annex, dietary exposure assessment is the estimation of the concentration of the nutrient(s) or related substance(s) in a food, the expected or foreseeable consumption of that food, and any known factors that influence bioavailability. Exposure to a nutrient(s) or related substance(s) should be evaluated in the context of the total diet and the assessment should be carried out based on the customary dietary consumption, by the relevant population(s), of the corresponding food that is likely to be displaced. When evaluating the exposure, it is appropriate to consider information on whether the consumption of the modified food could lead to adverse nutritional effects as compared to consumption of the food that it is intended to replace. Most, if not all, aspects of exposure assessment are not unique to recombinant-DNA plants modified for nutritional or health benefits[20].

15. The first step of an exposure assessment is determining the level(s) of the substance(s) in question in the portion of the plant intended for food use. Guidance on determining changes in levels of these substances is provided in the Codex Plant Guideline[21].

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[18] Codex Plant Guideline, paragraph 51

[19] Where such guidance is not provided by Codex, information provided by the FAO/WHO may be preferably considered.

[20] Additional applicable guidance on dietary exposure assessment of nutrients and related substances is provided in the Report of a Joint FAO/WHO Technical Workshop on Nutrient Risk Assessment. WHO Headquarters, Geneva, Switzerland, 2-6 May 2005.

[21] Paragraphs 44 and 45

16. Consumption patterns will vary from country to country depending on the importance of the food in the diet(s) of a given population(s). Therefore, it is recommended that consumption estimates are based on national or regional food consumption data when available, using existing guidance on estimation of exposure in a given population(s)[22]. When national or regional food consumption data is unavailable, food availability data may provide a useful resource[23].

17. To assess the safety of a food derived from a recombinant-DNA plant modified for a nutritional or health benefit, the estimated intake of the nutrient or related substance in the population(s) is compared with the nutritional or toxicological reference values, such as upper levels of intake, ADIs for that nutrient or related substance, where these values exist. This may involve assessments of different consumption scenarios against the relevant nutritional reference value, taking into account possible changes in bioavailability, or extend to probabilistic methods that characterise the distribution of exposures within the relevant population(s).

[22] A Model for Establishing Upper Levels of Intake for Nutrients and Related Substances. Report of a Joint FAO/WHO Technical Workshop on Nutrient Risk Assessment. WHO Headquarters, Geneva, Switzerland, 2-6 May 2005.

[23] Data on staple food products may also be supplemented by information from FAO Food Balance Sheets.

Annex 3: Food Safety Assessment in Situations of Low-Level Presence of Recombinant-DNA Plant Material in Food

Section 1 – Preamble

1. An increasing number of recombinant–DNA plants are being authorized for commercialization. However, they are authorized at different rates in different countries. As a consequence of these asymmetric authorizations, low levels of recombinant DNA plant materials that have passed a food safety assessment according to the Codex Guideline for the conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants (CAC/GL 45-2003) (Codex Plant Guideline) in one or more countries may on occasion be present in food in importing countries in which the food safety of the relevant recombinant-DNA plants has not been determined.

2. This Annex describes the recommended approach to the food safety assessment in such situations of low-level presence of recombinant-DNA plant material or in advance preparation for such potential circumstances[24].

3. This Annex also describes data and information sharing mechanisms to facilitate utilization of the Annex and to determine whether it should apply.

4. This Annex can be applied in two different dietary exposure situations:

(a) That involving commodities, such as grains, beans or oil seeds, in which exposure to food from a variety not authorized in the importing country would likely be to dilute low level amounts at any one time. This would likely be the more common situation of low-level presence of recombinant-DNA plant material. Because any food serving of grains, beans or oil seeds would almost necessarily come from multiple plants, and because of how these types of commodities generally are sourced from multiple farms, are commingled in grain elevators, are further commingled in export shipments, at import and when used in processed foods, any inadvertently commingled material derived from recombinant-DNA plant varieties would be present only at a low level in any individual serving of food.

(b) That involving foods that are commonly consumed whole and undiluted, such as some fruits and vegetables like potatoes, tomatoes, and papaya, in which exposure would be rare but could be to an undiluted form of the unauthorized recombinant-DNA plant material. While the likelihood of consuming material from such an unauthorized variety would be low and the likelihood of repeated consumption would be much lower, any such consumption might be of an entire unauthorized fruit or vegetable.

5. In both cases, the dietary exposure will be significantly lower than would be considered in a food safety assessment of the recombinant-DNA plant according to the Codex Plant Guideline. As a result, only certain elements of the Codex Plant Guideline will be relevant and therefore are included in this Annex.

6. This Annex does not:

- address risk management measures; national authorities will determine when a recombinant-DNA plant material is present at a level low enough for this Annex to be appropriate;
- preclude national authorities from conducting a safety assessment according to the Codex Plant Guideline; countries can decide when and how to use the Annex within the context of their regulatory systems; or
- eliminate the responsibility of industries, exporters and, when applicable, national competent authorities to continue to meet countries' relevant import requirements, including in relation to unauthorized recombinant-DNA plant material.

[24] This guidance is not intended for a recombinant-DNA plant that was not authorized in an importing country as a result of that country's food safety assessment.

Section 2 – General and Other Considerations

7. For the food safety assessment in situations of low-level presence of recombinant DNA plant materials in food, sections 4 and 5 of the Codex Plant Guideline apply as amended as follows. The applicable paragraphs are specifically indicated. Those paragraphs of the Codex Plant Guidelines that are not listed can be omitted from consideration.

Description of the Recombinant-DNA Plant

8. Paragraph 22 of the Codex Plant Guideline applies.

Description of the Host Plant and Its Use As A Food

9. Paragraphs 23, 24 and 25 of the Codex Plant Guideline apply.

Description of the Donor Organism(s)

10. Information should 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 pathogenicity or toxin production, or have other traits that affect human health. The description of the donor organism(s) should include:

(a) its usual or common name;
(b) scientific name;
(c) taxonomic classification;
(d) information about the natural history as concerns food safety;
(e) information on naturally occurring toxins and allergens; for microorganisms, additional information on pathogenicity and the relationship to known pathogens; and,
(f) information on 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)[25].

Description of the Genetic Modification(s)

11. Paragraphs 27, 28 and 29 of the Codex Plant Guideline apply.

Characterization of the Genetic Modification(s)

12. Paragraphs 30 and 31 of the Codex Plant Guideline apply.

13. Information should be provided on any expressed substances in the recombinant-DNA plant; this should include:

(a) the gene product(s) (e.g. a protein or an untranslated RNA);
(b) the gene product(s)' function;
(c) the phenotypic description of the new trait(s);
(d) the level and site of expression in the plant of the expressed gene product(s), and the levels of its metabolites in the edible portions of the plant; and
(e) where possible, the amount of the target gene product(s) if the function of the expressed sequence(s)/gene(s) is to alter the accumulation of a specific endogenous mRNA or protein[26].

14. Paragraph 33 of the Codex Plant Guideline applies.

[25] The text of this paragraph was adapted from paragraph 26 of the Codex Plant Guideline.

[26] The text of this paragraph was adapted from paragraph 32 of the Codex Plant Guideline.

Safety Assessment

Expressed Substances (non-nucleic acid substances)

Assessment of Possible Toxicity

15. The safety assessment should take into account the chemical nature and function of the newly expressed substance and identify the concentration of the substance in the edible parts of the recombinant-DNA plant, including variations and mean values[27].

16. Information should be provided to ensure that genes coding for known toxins present in the donor organisms are not transferred to recombinant-DNA plants that do not normally express those toxic characteristics. This assurance is particularly important in cases where a recombinant-DNA plant is processed differently from a donor plant, since conventional food processing techniques associated with the donor organisms may deactivate, degrade or eliminate toxicants[28].

17. Paragraph 37 of the Codex Plant Guideline applies.

18. In the case of proteins, the assessment of potential toxicity should focus on amino acid sequence similarity between the protein and known protein toxins as well as stability to heat or processing and to degradation in appropriate representative gastric and intestinal model systems. appropriate oral toxicity studies[29] may need to be carried out in cases where the protein present in the food is not similar to proteins that have previously been consumed safely in food, and taking into account its biological function in the plant where known.[30]

19. Paragraphs 39 and 40 of the Codex Plant Guideline apply.

Assessment of Possible Allergenicity (proteins)

20. Paragraphs 41, 42 and 43 of the Codex Plant Guideline apply.

Analyses of Key Toxicants and Allergens

21. Analyses of key toxicants[31] and allergens are important in certain cases of foods from recombinant-DNA plants (e.g., those that are commonly consumed whole and undiluted, such as potatoes, tomatoes, and papaya). Analyses of concentrations of key toxicants and allergens of the recombinant-DNA plant typical of the food should be compared with an equivalent analysis of a conventional counterpart grown and harvested under the same conditions. 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 should ideally be 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. The purpose of this comparison is to establish that substances that can affect the safety of the food have not been altered in a manner that would have an adverse impact on human health[32].

22. The location of trial sites should be representative of the range of environmental conditions under which the plant varieties would be expected to be grown. The number of trial sites should be sufficient to allow accurate assessment of key toxicants and allergens over this range. Similarly, trials should be conducted over a sufficient number of generations to allow adequate exposure to the variety of conditions met in nature. To minimize environmental effects, and to reduce any effect from naturally occurring genotypic variation within a crop variety, each trial site should be replicated. An adequate number of plants should be sampled and the methods of analysis should be sufficiently sensitive and specific to detect variations in key toxicants and allergens[33].

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[27] The text of this paragraph was adapted from paragraph 35 of the Codex Plant Guideline.

[28] The text of this paragraph was adapted from paragraph 36 of the Codex Plant Guideline.

[29] Guidelines for oral toxicity studies have been developed in international fora, for example, the OECD Guidelines for the Testing of Chemicals.

[30] The text of this paragraph was adapted from paragraph 38 of the Codex Plant Guideline.

[31] Key toxicants are those toxicologically significant compounds known to be inherently present in the plant, such as those compounds whose toxic potency and level may be significant to health (e.g. solanine in potatoes if the level is increased).

[32] The text of this paragraph was adapted from paragraph 44 of the Codex Plant Guideline.

[33] The text of this paragraph was adapted from paragraph 45 of the Codex Plant Guideline.

Evaluation of Metabolites

23. Some recombinant-DNA plants may have been modified in a manner that could result in new or altered levels of various metabolites in the food. In certain cases of foods from recombinant-DNA plants (e.g., those that are commonly consumed whole and undiluted), consideration should be given to the potential for the accumulation of metabolites in the food that would adversely affect human health. Food safety assessment in situations of low level presence of recombinant-DNA material in foods from such plants requires investigation of residue and metabolite levels in the food. Where altered residue or metabolite levels are identified in foods, consideration should be given to the potential impacts on human health using conventional procedures for establishing the safety of such metabolites (e.g. procedures for assessing the human safety of chemicals in foods)[34].

Food Processing

24. The potential effects of food processing, including home preparation, on foods derived from recombinant-DNA plants should also be considered. For example, alterations could occur in the heat stability of an endogenous toxicant. Information should therefore be provided describing the processing conditions used in the production of a food ingredient from the plant. For example, in the case of vegetable oil, information should be provided on the extraction process and any subsequent refining steps[35].

Potential Accumulation of Substances Significant to Human Health

25. Some recombinant-DNA plants may exhibit traits (e.g. herbicide tolerance) which may indirectly result in the potential for accumulation of pesticide residues, altered metabolites of such residues, toxic metabolites, contaminants, or other substances which may be relevant to human health. In certain cases of foods from recombinant-DNA plants (e.g. those that are commonly consumed whole and undiluted), the risk assessment should take this potential for accumulation into account. Conventional procedures for establishing the safety of such compounds (e.g. procedures for assessing the human safety of chemicals) should be applied[36].

Use of Antibiotic Resistance Marker Genes

26. Paragraphs 55, 56, 57 and 58 of the Codex Plant Guideline apply.

Section 3 – Guidance on Data and Information Sharing

27. In order for Codex Members to use this Annex, it is essential that they have access to requisite data and information.

28. Codex Members should make available to a publicly accessible central database to be maintained by FAO information on recombinant-DNA plants authorized in accordance with the Codex Plant Guideline. This information should be presented in accordance with the following format:

(a) name of product applicant;
(b) summary of application;
(c) country of authorization;
(d) date of authorization;
(e) scope of authorization;
(f) unique identifier;
(g) links to the information on the same product in other databases maintained by relevant international organizations, as appropriate;
(h) summary of the safety assessment, which should be consistent with the framework of food safety assessment of the Codex Plant Guideline;

[34] The text of this paragraph was adapted from paragraph 46 of the Codex Plant Guideline.

[35] The text of this paragraph was adapted from paragraph 47 of the Codex Plant Guideline.

[36] The text of this paragraph was adapted from paragraph 54 of the Codex Plant Guideline.

(i) where detection method protocols and appropriate reference material (non-viable, or in certain circumstances, viable) suitable for low-level situation may be obtained[37]; and
(j) contact details of the competent authority(s) responsible for the safety assessment and the product applicant.

29. This process should facilitate rapid access by importing Codex Members to additional information relevant to the assessment of food safety assessment in situations of low-level presence of recombinant-DNA plant material in foods in accordance with this Annex.

30. The authorizing Codex Members should make available complementary information to other Codex Members on its safety assessment in accordance with the Codex Plant Guideline, in conformity with its regulatory/legal framework.

31. The product applicant should provide further information and clarification as necessary to allow the assessment according to this Annex to proceed, as well as a validated protocol for an event-specific or trait-specific detection method suitable for low level situations and appropriate reference materials (non-viable, or in certain circumstances, viable). This is without prejudice to legitimate concerns to safeguard the confidentiality of commercial and industrial information.

32. As appropriate, new scientific information relevant to the conclusions of the food safety assessment conducted in accordance with the Codex Plant Guideline by the authorizing Codex member should be made available.

[37] This information may be provided by the product applicant or in some cases by Codex members.

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