A GUIDE TO RISK ASSESSMENT AND RISK MANAGEMENT

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PREFACE

Modern biotechnology is creating new platforms on new products in markets on many fronts in many fields including agriculture, healthcare, pharmaceuticals and manufacturing processes. However, given the limited use of GMOs and the relatively constrained conditions of their release, information about their effects on human and animal health, and the environment is still very sparse. There is a need for a thorough risk assessment at an early stage of development as well as for a monitoring system to evaluate risks in field tests and releases. Risk assessment, therefore, provides basis to make sound, science based decisions regarding safe transfer, handling and use of GMOs. This is a useful tool to ensure that the uncertainty and risks of a modern biotechnology are contained within manageable limits.

This Guide has been developed to serve as a simple and quick reference on how a risk assessment should be performed, how much detail should be presented by project proponents including measures to address the risks (risk management). The Guide also highlights on the importance of risk communication/interaction as an integral part of risk assessment and risk management to ensure adequate level of public awareness and acceptance.

The Guide is meant for use by trial managers, researchers, agents of the authorized party, and government officials engaged in planning, conducting or overseeing the transfer, handling and use of GMOs in Tanzania. It should be noted that the Guide will be reviewed periodically to accommodate emerging issues. Readers are encouraged to seek additional guidance from the National Biosafety Focal Point (NBFP) and other regulatory bodies. It is anticipated that the Guide will be useful to many users.

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Permanent Secretary
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ABBREVIATIONS AND ACRONYMS

BL	Biosafety Level
CPB	Cartagena Protocol on Biosafety
DNA	Deoxyribonucleic Acid
EC	European Community
GEP	Genetically Engineered Plant
GMO	Genetically Modified Organism
HEPA	High Efficiency Particulate Air
HV	Host-Vector
IBC	Institutional Biosafety Committee
MARI	Mikocheni Agricultural Research Institute
NBAC	National Biotechnology Advisory Committee
NBC	National Biosafety Committee
NBF	National Biosafety Framework
NBFP	National Biosafety Focal Point
OECD	Organisation for Economic Cooperation and Development
RA	Risk Analysis
RM	Risk Management
rDNA	recombinant Deoxy ribonucleic acid
UNEP	United Nations Environment Program
VPO	Vice President's Office

DEFINITION OF TERMS

Accidental Release	Any unauthorized release of regulated GE plants and plant products in the environment; human food and/or livestock feed chains.
Applicant	A party submitting an application for a contained research, confined field trial or commercial release. Typically, the Applicant shall be a permanent resident of the United Republic of Tanzania or in the case of a non-resident shall designate an agent who is a permanent resident of the United Republic of Tanzania. In the case of a corporation, permanent resident means a company incorporated in Tanzania, and in the case of a natural person, permanent resident means a citizen of the United Republic of Tanzania, either by birth or acquisition. The applicant need not be the owner of the GMO, in which case a signed statement is required from the owner authorizing representation by the applicant. All correspondence with respect to the application for confined field trial, including the notification of authorization, will be addressed to the applicant.
Authorized Party	The addressee of the letter of Authorization. The Authorized Party accepts full responsibility for compliance with the Terms and conditions of authorization, including all associated legal and financial obligation.
Biosafety	Avoidance of risk to the protection of the environment and to human and animal health, as a result of the use for research and commerce of GMOs, by instituting legal, administrative and policy instruments
Biotechnology	Any technological application that uses biological systems, living organisms, or derivatives thereof, to make or modify products or processes for specific use.
Compliance Infraction	Violation of the Terms and conditions of Authorization
Confinement	Restriction of an organism and its genetic traits to a specific and defined area of the environment, herein called the ‘confined field trial site’ or the ‘trial site’
Construct	A segment of DNA to be transferred into a cell or tissue and type using a specific genetic modification

Compliance	Fulfilling the requirements of the Terms and conditions of Authorization, especially with regard to confinement measures
Contained use	Any operation, undertaken within a facility, installation or other physical structure, which involves GMOs that are controlled by specific measures that effectively limit their contact with, and their impact on, the external environment
Containment	Act of restricting or preventing the spread, leak or escape of an experimental object
Event	A transformation event refers to each individual transgenic line produced from the modification of a single plant species using a specific genetic construct. For example, two lines of the same plant species transformed with the same or different constructs constitute two events
Genetically Engineered (GE) Plants and Plant Products	Are plants and plant products developed through genetic medication of organisms by recombinant DNA techniques
Genetically Modified Organism	Any organism which has been altered or produced through genetic engineering, or any product which contains such an organism or any other organism or product altered or produced through genetic engineering. For the purpose of this guideline the terms genetically engineered plants, genetically modified plants and transgenic plants should be used interchangeably
Permit	A written document issued by the appropriate authority for the introduction of a GMOs under conditions that it will not present a risk to Human, Health and Environment
Prohibited Plants	Plants that are sexually compatible with the GM plants being grown under confinement, and are thus prohibited from the established spatial isolation distance of a confined field trial
Regulatory body	an institution that has a legal mandate to enforce biosafety legal instruments such as legislation, regulations and guidelines
Receiver	A person who has been appointed by the Authorized party to receive the regulated GE plants and plant products for storing in the storage facility

Reproductive Isolation	Measures taken to prevent, principally, pollen-mediated gene flow from plant in the trial site to nearby sexually compatible species. Also known as ‘genetic confinement’
Resuscitation	Procedure of restoring to life after apparent death
Risk	The probability of harm associated with occurrence of any event
Risk Assessment	Risk assessment is a process of gathering diverse data to identify possible risk in research and development involving GMOs or processes. Risk assessment is, inter alia, used by Competent Authorities to make informed decisions regarding GMOs
Risk Management	A process of ensuring safe introduction of GMOs as defined and described in the guidelines
Sexually Compatible	Capable of cross-pollinating and forming viable hybrids without human intervention
Trial Manager	The individual at a particular trial site, designated by the Authorized Party as responsible for management and compliance of an authorized confined field trial. Trial managers are authorized to complete and sign documentation, forms and notes for the trial file
Shipper	An agent, company or a person that transports the regulated GE plants and plant products between research facilities, storage facilities, quarantine station, and field trial sites in Tanzania
Vector or Vector agent	Organisms or objects used to transfer Genetic material from the donor organism to the recipient organism

1.0 INTRODUCTION

Any human intervention into the environment carries an element of risk. The natural response to this uncertainty is to proceed cautiously and identify and analyze the risks. The Principles of risk analysis may be applied to all types of risks such as those involving environmental protection, chemical or nuclear hazards, food additives and drug residues. Similarly, they may be employed to ensure fair and safe trade of agriculture and food commodities and products.

1.1 Scope

This manual provides guideline to risk assessment and management of release to the environment of GMOs. The risk assessment and management for contained and confined field trials are mentioned in passing; a detailed description of these two is provided in other manual and not within the scope of this guide.

Measures for RA and RM for contained research and confined field trials are described in details in **Practical Manual for Safe Conduct of Confined Field Trials** and **Practical Manual for Contained Laboratory and Glasshouse Research.** Details for risk analysis of GM food and food products are guided by the general decisions of the Codex Alimentarius Commission as well as Codex working principles for risk analysis. The principles and guidelines for risk assessment of GM foods are presented in Annex 1, 2 and 3.

This manual includes:

- Relevant information on risk analysis;
- Purposes of Risk assessment and Management;
- Basis of Risk assessment and Management;
- General principles of Risk assessment and Management;
- Methodology of Risk assessment and Management;
- Handling of costs of Risk assessment and Management; and
- Risk communication

1.2 The Risk Analysis Concept

The probability of harm associated with the occurrence of any event in its concept is what is perceived as “risk”. The analysis of this probability of harm is identified by Codex Alimentarius Commission as a process consisting of three components: risk assessment, risk management and risk communication. Risk assessment evaluates and compares the scientific evidences regarding the risks associated with alternatives activities in contrast to the proposed activity. For example, it is just not limited to use of GM crop for insect resistance versus the same variety untransformed. It includes the untransformed variety along with the pesticide that would be used to protect it from getting damaged. Risk management then, develops strategies to prevent and control risks within acceptable limits and relies on risk assessment. In addition to the scientific assessment, it also takes into account other factors such as social values and

economies. Risk communication is the option exercised to bring to the forefront the two factors on an event related specific risk so that the regulators, developer of the technology and public are made aware of the same and at each level, appropriate decisions are taken. Therefore, the three wheeled structure of risk analysis is an integral unit of the gamut of GMO development, testing, release and usage.

2.0 RISK ASSESSMENT

2.1 Concept

The concept of risk assessment revolves around answering three basic questions like

- What might go wrong?
- How likely is to happen? and
- What are the consequences?

These questions can be answered by the assessment process of risk which has a potential to cause an adverse effect or hazard, through (a) hazard identification, (b) hazard characterization, (c) exposure assessment, and (d) risk characterization.

Thus

Risk = Hazard X Probability of its occurrence X Consequence of its use or release or commercialisation

A hazard is any event that can lead to something that is conceivably wrong. A hazard in itself does not constitute a risk. The probability associated with a hazard also depends in part on the management strategy adopted to control it. Risk can be underestimated if some hazards are not identified or characterized, if the probability of the hazard occurring is greater than expected or if its consequences are more severe than expected. Risk assessment is a scientific process that makes use of the best up-to-date knowledge and experience. The assessment of risk is sequential and takes into account systematically the degree of danger multiplied by probability at all steps. ***There is obviously no risk involved if there is no danger inherent in an experiment. It should also be understood that there is also no risk if the theoretical consequences of an experiment are very dangerous but whose probability of occurrence is zero.*** The methodologies for risk assessment for biotechnology products have been outlined in several perspectives by agencies like the UNEP International Technical Guidelines for Safety in Biotechnology, the Cartagena Protocol on Biosafety, OECD guidelines, EC Directive 2001/18/EEC at the international level. The Tanzania guidelines on risk assessment and management have kept all the above guidelines in view. The steps in risk assessment of GMOs include: identification of characteristics which may cause adverse effects, evaluation of their potential consequence, assessment of the likelihood of occurrence and estimation the risk posed by each identified characteristic of the GMOs. The definition includes quantitative risk assessment, which emphasizes reliance on numerical expressions of risk, and also qualitative expressions of risk, as well as an indication of the attendant uncertainties. The general steps are

a) Identification of potential adverse effects on human health and or environment;
b) An estimation of likelihood of these effects being realized;

c) An evaluation of the identified risks';
d) Considerations of appropriate risk management strategy ; and
e) Assessment of the overall potential environmental impact, including a consideration of the potential impacts that may be beneficial to human health or the environment.

From a practical standpoint, it is important to distinctly separate the risk assessment and management of confined field trials from unconfined releases. At the level of an unconfined (general) release, the focus must be on rigorous risk assessment as the intent is widespread introduction of the modified organism into agriculture, usually with few or no provisions for risk mitigation. For unconfined releases, there is little or no possibility of controlling the exposure component of risk; therefore, to minimize risk both to the environment and to people and animals, regulators must be satisfied that potential hazards are not significant. Conversely, for a confined field trial, where the potential hazards may be largely unknown or at least not likely to be fully appreciated without data collected during the trial, the focus must be on minimizing exposure through risk management – the terms and conditions that are necessary to permit safe trial conduct. This crucial distinction between unconfined environmental releases and confined field trials has not always been sufficiently well appreciated by regulators, national biosafety committees, or capacity builders and trainers.

2.2 Definition of Risk Assessment

Risk assessment is a process of gathering diverse data to identify possible risk in research and development involving GMOs or processes. Risk assessment is, inter alia, used by Competent Authorities to make informed decisions regarding GMOs.

Risk assessment is a science-driven "process of obtaining quantitative or qualitative measures of risk levels, including estimates of possible health effects and other consequences as well as the degree of uncertainties in those estimates" free of the emotive factors that influence risk perception.

2.3 Objective of Risk Assessment

The objective of the risk assessment is to identify and evaluate the potential adverse effects of GMOs on the conservation and sustainable use of biological diversity in the likely potential receiving environment taking also in account risk in human and animal health.

2.4 General Principles

a) Risk assessment should be carried out in a scientifically sound and transparent manner, and can take into account expert advice of, and guidelines developed by relevant international organizations.

b) Risk assessment should be conducted using a range of expertise which should be reflected in the competence and experience of those carrying out the assessment in a scientifically sound manner. The UNEP International technical guidelines gives example of scientific expertise (Table1) and information that may be considered in undertaking risk assessments relating to GMOs

Table 1: Examples of the type of scientific expertise and information required for undertaking risk assessments relating to GMOs

Expertise*1	Expertise*1
• DNA Technologies • Molecular Genetics • Population Genetics • Plant Breeding • Marine Biology • Ecology • Taxonomy • Microbiology • Virology/Pathology • Zoology/Enotomology	• Plant Biology And Botany • Evolution • Epidemiology • Agronomy • Forestry • Process Technology • Biochemistry • Toxicology • Sociology, • Economics
Source: UNEP International Technical guideline for safety in Biotechnology.pp 1-22	

*1 *This list is provided as a guide to the major fields of expertise which may be required and is not intended to be comprehensive. Not all of these are likely to be relevant in each case and, as knowledge and technology advance, other fields of expertise will be important in risk assessment*

c) Lack of scientific knowledge or scientific consensus should not necessarily be interpreted as indicating a particular level of risk, an absence of risk, or an acceptable risk.

d) Risks associated with GMOs or products thereof, namely, processed materials that are of GMOs origin, containing detectable novel combinations of replicable genetic material obtained through the use of modern biotechnology, should be considered in the context of the risks posed by the non-modified recipients or parental organisms in the likely potential receiving environment.

e) Risk assessment should be carried out on a case-by-case basis. The required information may vary in nature and level of detail from case to case, depending on the GMOs concerned, its intended use and the likely potential receiving environment.

2.5 Risk Assessment for Decision Making Procedure

a) The decision taken by the authorizing agency must be based on a risk assessment.

b) The Agency shall require the applicant to provide detailed risk assessment report.

2.6 Cost of Risk assessment

The cost of risk assessment shall be borne by the notifier/applicant.

2.7 Methodology

The risk assessment must be carried out in scientifically sound manner and taking into **account recognized risk assessment** techniques. Examples of such techniques would include UNEP International Technical Guidelines on Biosafety and OECD's work on risk assessment.

The process of risk assessment may give rise to a need for further information about specific subjects, which may be identified and requested during the assessment process.

To fulfill its objective, risk assessment should follow the following steps:

a) An identification of any novel genotypic and phenotypic characteristics associated with the genetically modified organism that may have adverse effects on biological diversity, environment, human and animal health, taking also into account socio-economic, cultural and ethical concerns;

b) An evaluation of the likelihood of these adverse effects being realized, taking into account the level and kind of exposure of the likely potential receiving environment to the genetically modified organism;

c) An evaluation of the consequences should these adverse effects be realized;

d) An estimation of the overall risk posed by the genetically modified organism based on the evaluation of the likelihood and consequences of the identified adverse effects being realized;

e) A recommendation as to whether or not the risks are acceptable or manageable, including, where necessary, identification of strategies to manage the risks; and

f) Where there is uncertainty regarding the level or risk, it may be addressed by requesting further information on the specific issues of concern or by implementing appropriate risk management strategies and/or monitoring the GMOs in the receiving environment.

2.8 Technical issueS to consider

Depending on the case, risk assessment takes into account the relevant technical and scientific details regarding the characteristics of the following subjects:

a) Recipient organism or parent organism

   The biological characteristics of the recipient organism or parental organisms, including information on taxonomic status, common name, origin, centers of origin and centers of genetic diversity, if known, and a description of the habitat where the organisms may persist or proliferate.

b) Donor organism or organisms

   Taxonomic status and common name, source, and the relevant biological characteristics of the donor organisms.

c) Vector
   Characteristics of the vector, including its identity, if any, and its source or origin, and its host range.

d) Insert or inserts and/or characteristics of modification

   Genetic characteristics of the inserted nucleic acid and the function it specifies, and/or characteristics of the modification introduced.

e) Genetically modified organism

   Identity of the genetically modified organism, and the differences between the biological characteristics of the modification introduced.

f) Detection and identification of the genetically modified organism

   Suggested detection and identification methods and their specificity, sensitivity and reliability.

g) Information relating to the intended use

   Information relating to the intended use of the genetically modified organism, including new or changed use compared to the recipient organism or parental organisms; and

h) Receiving environment

Information on the location, geographical, climatic and ecological characteristics, including relevant information on biological diversity and centers of origin of the likely potential receiving environment.

2.9 Risk Assessment Parameters

The user should carry out an assessment prior to the use or release of GMOs or products thereof as regards the risks to human and animal health, biological diversity, the environment and the socio-economic welfare of societies,. This assessment should take the following parameters into consideration including any other parameter deemed to be relevant:

a) Characteristics of donor and recipient organisms or parental organisms:

i) Scientific name and taxonomy;
ii) Strain, cultivar or other name;
iii) Species it is related to and degree of relatedness;
iv) The degree of relatedness between the donor and recipient organisms, or between the parental organisms;
v) All sites from where the donor and recipient organisms or parental organisms were collected, if known;
vi) Information on the type of reproduction (sexual/asexual) and the length of reproductive cycle or generation time, as appropriate, as well as the formation of resting and survival stages;
vii) History of prior genetic manipulation, whether the donor or recipient organisms are already genetically modified;
viii) Phenotypic and genetic markers of interest;
ix) Description of identification and detection techniques for the organisms, and the sensitivities of these techniques;
x) Geographic distribution and natural habitats of the organisms including information on natural predators, prey, parasites, competitors, symbionts and hosts;
xi) Climatic characteristics of original habitats;
xii) Ability of the organisms to survive and colonize the environment to which release is intended or otherwise;
xiii) Genetic stability of the organisms, and factors affecting the stability;
xiv) The presence of endogenous mobile genetic elements of viruses likely to affect the genetic stability;
xv) The potential of the organisms to transfer or exchange genes with other organisms, either vertically or horizontally;
xvi) Pathogenicity to humans or animals, if any;
xvii) If pathogenic, their virulence, infectivity, toxicity and modes of transmission;
xviii) Known allogenicity and/or toxicity of biochemical and metabolic products; and

xix) Availability of appropriate therapies for pathogenicity, allergenicity and toxicity.

b) Characteristics of the vector(s)

i) Nature and source of the vector(s);
ii) Genetic map of the vector(s), position of the gene(s) inserted for the transfer, other coding and non-coding sequences affecting the expression of introduced gene(s), and marker gene(s);
iii) Ability of the vector(s) to mobilize and transfer genes by integration and methods for determining the presence of the vector(s);
iv) History prior to genetic manipulation, whether the donor or recipient organisms are already genetically modified;
v) Potential for pathogenicity and virulence;
vi) Natural and host range of vectors;
vii) Natural habitat and geographic distribution of natural and potential hosts;
viii) Potential impacts on human and animal health and the environment;
ix) Measures for counteracting adverse impacts;
x) Potential to survive and multiply in the environment, or to form genetic recombinants; and
xi) Genetic stability of vectors, such as hypermutability.

c) Characteristics of Genetically Modified Organism:

i) The description of the modifications made using gene technology;
ii) The function of the genetic modifications and/or the new insert, including any marker gene(s);
iii) Purpose of the modification and intended use in relation to need or benefit;
iv) Method of modification and in case of transgenic organisms, the methods for constructing inserts and to introduce them into the recipient organism;
v) Whether introduced gene(s) integrated or extra chromosomal;
vi) Number of insert(s), positions in the host genome, and its/their structure(s), for example, the copy number whether in tandem or other types of repeats;
vii) Product(s) of the transferred gene(s), levels of expression and methods for measuring expression;
viii) Stability of the introduced gene(s) in terms of expression(s), structure(s) and site(s) of integration;
ix) Biochemical and metabolic differences of genetically modified organism compared with the unmodified organism;
x) Probability of vertical or horizontal gene transfer to other species;
xi) Probability of inserts or transferred gene(s) to generate pathogenic recombinants with endogenous viruses, plasmids and bacteria;
xii) Allergenicities, toxicities, pathogenicities and unintended effects;
xiii) Autecology of the genetically modified organism compared with that of the unmodified organism;

xiv) Susceptibility of the genetically modified organism to diseases and pests compared with the unmodified organism; and
xv) Detailed information on past uses including results on all experiments leading to previous releases;

d) Characteristics of resuscitated organism(s) and gene(s) and fossil DNA sequences

Resuscitated organism

i) Scientific name and taxonomy;
ii) Identity of nearest species and their characteristics which are of relevance to the intended use;
iii) Site at which it was found;
iv) Method used for resuscitation;
v) Purpose of introducing the organism and benefits, if any;
vi) Impacts on human and animal health and the environment;
vii) Measures for counteracting adverse impacts;
viii) Length of time the organism has been in use;
ix) Genetic stability;
x) Likelihood of gene transfer to other organisms;
xi) Fossil and living nearest relative species;
xii) Biological and biochemical differences form related living species; and
xiii) Information on previous uses since resuscitation.

DNA sequences from fossils or from resuscitated organism

i) Scientific name and taxonomy of the species whether resuscitated or a fossil;
ii) Site of origin of the fossil;
iii) Site of the gene in the resuscitated genome, if known;
iv) Base sequence of the extracted gene;
v) Method used in extracting the gene
vi) Function of gene, if known;
vii) Purpose of use and benefits, if any;
viii) Environment in which it lived before fossilization;
ix) Fossil species related to the species from which the gene was taken; and
x) Living species related to the species from which the gene was taken

e) Safety considerations for human and animal health

Information on the genetically modified organism and when it is genetically engineered, information on the donor and recipient organisms as well as the vector before it was disarmed or disabled in cases where it has been disarmed or disabled regarding;

i) Capacity for colonization;

ii) If the genetically modified organism is pathogenic to humans or animals the following information is required:
    a) diseases caused and mechanism of pathogenicity, including invasiveness and virulence, and property of virulence;
    b) communicability;
    c) infective dose;
    d) host range and possibilities of alteration;
    e) ability to survive outside of the human or animal host;
    f) the existence of vectors or other means of transmission;
    g) biological stability;
    h) allergenicity; and
    i) availability of appropriate therapies.

f) Environmental considerations

Information on the genetically modified organism, and when it is genetically engineered, information on the donor and recipient organizations as well as the vector before it was disarmed or disabled in cases where it has been disarmed or disabled, regarding:

i) Factors affecting the survival, reproduction and spread of the genetically modified organism in the environment;
ii) Available techniques for detection, identification and monitoring of the GMOs;
iii) Available techniques for detecting transmission of genes from the genetically modified organism to other organisms;
iv) Known and predicted habitats of the genetically modified organism;
v) Description of the ecosystems which could be affected by accidental release of the genetically modified organism;
vi) Possible interactions between the genetically modified organism and other organisms in the ecosystem which might be affected by accidental release;
vii) Known or predicted effects on plants and animals such as pathogenicity, infectivity, toxicity, virulence, being a vector or pathogens, allergenicity, and colonization;
viii) Possible involvement in biogeochemical processes;
ix) Availability of methods for decontamination of the area in case of accidental releases; and
x) Effects on agricultural practices with possible undesirable impacts on the environment.

g) Socio-economic considerations

In parallel to and simultaneous with the scientific risk assessment, an evaluation of the socio-economic risks should be undertaken by relevant Ministries in consideration of the following, but not limited to:

i) Anticipated changes in the existing social and economic patterns resulting from the introduction of the genetically modified organism or product thereof;
ii) Possible threats to biological diversity, traditional crops or other products and, in particular, farmers' varieties and sustainable agriculture;
iii) Impacts likely to be posed by the possibility of substituting traditional crops, products and indigenous technologies through modern biotechnology outside of their agro-climatic zones;
iv) Anticipated social and economic costs due to loss of genetic diversity, employment, market opportunities and, in general, means of livelihood of the communities likely to be affected by the introduction of the GMOs or products thereof;
v) Possible countries and/or communities to be affected in terms of disruptions to their social and economic welfare; and
vi) Possible effects, which are contrary to the social, cultural, ethical and religious values of communities arising from the use or release of the genetically modified organism.

h) Guidelines for socio-economic risk assessment

Detailed guidelines for socioeconomic risk assessment will be provided by the Ministry responsible for biosafety

3.0 RISK MANAGEMENT

3.1 Definition

Risk management is the use or application of procedures and means to reduce the negative consequences of a risk to an acceptable level. The risks can be limited by proper handling and use of various preventive measures. The process itself is distinct from risk assessment involving weighing of policy alternatives in consultation with all interested parties, considering risk assessment and other factors relevant for the health protection of consumers and for the promotion of fair trade practices, and, if needed, selecting appropriate prevention and control options. But it should be noted that both risk assessment and management need to be integrated appropriately while planning the GMO development or use.

3.2 Objectives

The objective of risk management is to establish and maintain appropriate mechanisms, measures and strategies to regulate, manage and control risks identified in the risk assessment regarding the use, handling, introduction and field release of GMOs.

3.3 General principles

a) Parties shall endeavour to ensure that any GMO, **whether imported or locally developed,** has undergone an appropriate period of observation that is commensurate with its life cycle or generation time before it is put into use.

b) In identification of risk management mechanisms, measures and strategies it is important to consider many different views of those affected by the introduction into the environment of the GMOs so as to ensure that **differing technical assessments, public values, knowledge and perceptions are considered.**

c) The parties shall establish and maintain appropriate mechanisms, measures and strategies to **regulate, manage and control** risks identified in the risk assessment provisions of this guideline associated with the use, research, handling and transboundary movement of GMOs.

d) Measures based on risk assessment shall be imposed to the extent necessary to prevent adverse effects on the living modified organism on the conservation and sustainable use of biological diversity, taking also into consideration risks to human and animal health, within Tanzania.

e) For release of GMOs that are plants, risk management measures that are commonly applied include the following:
    i) Isolation distance or buffer zones to minimize pollen transfer;
    ii) Border rows with non transgenic plants to catch pollen;
    iii) After release treatment: inactivation of remaining plants and seeds and specific soil treatment after harvest;

iv) After release control (eg removal of volunteers in the next years); and
v) partial or full restrictions preventing in specific area (e.g. prevent of gene flow).

f) In addition to the scientific approach, the risk management options should also take into consideration the policies of the regulatory authorities of Tanzania and the measures that are possible economically.

g) Measures for contained research and confined field trials are described in details in Practical Manual for Safe Conduct of Confined Field Trials and Practical Manual for Contained Laboratory and Glasshouse Research

3.4 Cost of Risk Management

The costs of risk management are borne by the **applicant/ authorized party** and therefore it is important to ensure necessary risk management requirements are worked out in such a way that both private as well as public funded research organizations can undertake the activities related to the process.

3.5 Risk Management Schemes

The user should employ the following risk management schemes and procedures from the development, through all stages of testing of the genetically modified organism or the product thereof, to its intended use or commercialisation.

a) Imported products of GMOs used for human or animal health

i) observation to ensure that changes in food habits, nutrition and other factors that could conceivably modify the expected impacts are insignificant;

ii) Such observation can be limited in scope when it is shown that adequate trials on the specific products have been made on humans or animals, as appropriate, in areas other than the state of import.

b) Imported microbial genetically modified organisms for human and animal health

Besides the limited observation specified in 3.5.1, experiments should be carried out to evaluate viability and risks of reacquiring virulence or lending virulence to other micro-organisms when in the body and in the environment, since some spilling is inevitable.

c) Imported GMOs for contained use

i) The products of GMOs will be treated as in 3.5.1 above;

ii) Experiments will be made in complete laboratory containment to determine: (i) longevity of the genetically modified organism in cases of unintended release in the premises and in the surrounding environment, and (ii) genetic transfer into

other micro-organisms and implications thereof on human and animal health and the environment; and

iii) Methods of counteracting adverse impacts resulting from unintended releases should be specified.

d) Products of genetically modified organism made locally

i) Trial on experimental animals will be made when the product of the GMOs in intended to be used on humans;

ii) In all other cases, trials will be made on species for which the product of the genetically modified organism has been designed.

e) GMOs made locally for use as human or animal vaccines

i) Initial molecular, tissue culture, serological and other related studies should be conducted in laboratory in complete containment;

ii) Trials with experimental animals should be done under strict containment;

iii) Experiments to evaluate the extent of transfer of the genes of the vector introduced or of other genes through the agency of the vector to the genetically modified organism or to other species which will be found in association with the genetically modified organism should be done in complete containment to ensure that virulence is not acquired by the genetically modified organism in question or by other micro-organisms;

iv) Trials on animals should be completely contained from their species and from related species and species known to be susceptible to the gene recipient micro-organism from which the GMOs has been made; and

v) Statistically valid trials should be made in conditions in which the vaccinated individuals live in their communities.

f) Imported genetically modified plant or microbes for release

i) The reports from releases in areas other than the state of import should be thoroughly evaluated by the National Biosafety Committee. Particular emphasis should be given to whether the applicable regulations in the previous release have been adequate to ensure safety;

ii) If the Regulations mentioned in (a) above have not been found adequate, the National Biosafety Committee will decide at which step in item 3.8.8 the observations should begin;

iii) If it is decided that the previous release mechanisms have been rigorous enough, observations should be made in experimental conditions completely contained from the outside environment, but otherwise kept at the same soil community, moisture, air temperature and plant and animal community conditions as the intended area of release;

iv) The observations will include the health of the genetically modified organism, the health of the organism within the area or limited release, and the biological diversity and the ecology the area; and

v) Nationally approved limited field releases will be carried out with appropriate emergency procedures in place to deal with possible cases of escape.

g) Imported genetically modified animal for release

i) The reports from releases in areas other than the state of import should be thoroughly evaluated by the National Biosafety committee. Particular emphasis should be given to whether the applicable regulations in the previous release have been adequate to ensure safety;

ii) If the regulations mentioned in (a) above have not been found adequate, the National Biosafety Committee will decide a which step in item 3.5.9 the observations should begin;

iii) If it is decided that the regulations used in the previous release have been rigorous enough, then observations will be made in complete containment in the expected ambient climatic nutritional and other environmental conditions to monitor physiological functions, adaptations and gene transfers; and

iv) When the results have met the stated requirements, then a trial release may be authorized with adequate emergency plans put in place to deal with cases of escape.

h) Genetically modified plant or microbes produced locally for eventual release

i) Laboratory experiments on transformation of resuscitation and other phenomena will be carried out in complete containment;

ii) Tissue culture experiments to develop the genetically modified organism, when required, will be carried out in complete containment;

iii) Observations aimed at understanding the nature of the genetically modified organism should be carried out in complete containment;

iv) Experiments with the soil, soil micro-organisms, plant and animals species, under the environmental conditions of the area of intended release, will be carried out in complete containment;

v) Complete observations of the interactions of the genetically modified organism with the environment (soil including micro-organisms and terrestrial communities) will be made in enclosed fields but not fully contained. At the end of the experiment, the products of the genetically modified micro-organisms may be used on an experimental basis, otherwise they should be destroyed;

vi) The product form the genetically modified organism should be subjected to the procedure in 3.5.4; and

vii) The monitoring of the spread and behavior of any released plant or micro-organism genetically modified organism should continue for at least 150 years in the case of trees, and for at least 30 years in the case of annuals and micro-organisms, the duration for perennials which live shorter than trees being in between. The user who was responsible for releasing the GMOs or its successor should provide annual reports to the competent authority.

i) Genetically modified animal produced locally for eventual release

i) Laboratory bimolecular experiments on transformation for resuscitation if it is possible) and other phenomena will be carried out in complete containment;

ii) Methods of incubating the transformed generative cell or the resuscitated animal will be carried out in complete containment;

iii) The rearing of and observations on the genetically modified organism will be carried out under complete containment;

iv) The genetically modified organism should be observed under complete containment in an experimental environment which simulates the intended area of release in climatic, microbial, animal and plant communities. The observations should include the condition of the transgenic animal and those of its micro-organisms especially in the context of gene transfer and those of the microbial, plant and animal communities in the experiment, again including gene transfer:

v) A limited release will be carried out in an area with appropriate enclosure and emergency measures put in place to prevent escape. Observations will include the condition of the genetically modified organism, its micro-organisms focusing on gene transfer, and the ecology of the microbial, plant and animal communities in the area, again including gene transfer;

vi) If the animal is intended to yield a product, the regulation of the production will follow the procedure in item 3.5.4; and

vii) The monitoring of the spread and behavior of any genetically modified animal will continue for at least **30 years**.

j) General Requirements

(a) All trials, experiments or observations specified in all the above cases (1-9) are put in their logical sequence and should be subjected to the hierarchical procedures of review by the institutional and the national level bodies, namely the Institutional Biosafety Committees or the Ministerial Competent Authority and the National Biosafety Committee;

(b) Experiments starting from transformation of living organisms or resuscitation of fossil organisms carried out under completely contained laboratory conditions and continuing in the development of GMOs or products thereof should be subject to review by the Institutional Biosafety Committee or by National Biosafety Committee as the case may be. All experiments outside of strict laboratory isolation and initial experiments involving imported GMOs or products thereof should be subject to review by the National Biosafety Committee. All final approval for the use of GMOs or products thereof should be made by the Minister;

4.0 RISK COMMUNICATION

4.1 Definition and concept

While the risk assessment and risk management procedures are intended to identify and minimize potential negative effects on human health and the environment, risk communication is an integral part of biosafety procedures to ensure public acceptance of GMOs. It is important to interact with public at large about the specific risks and actions taken to alleviate them before announcing GMO field tests and commercialisation. The interactive exchange of information and opinions throughout the risk analysis process concerning hazards and risks, risk-related factors and risk perceptions, among risk assessors, risk managers, consumers, industry, the academic community and other interested parties, including the explanation of risk assessment findings and the basis of risk management decisions. Risk communication is the science of understanding scientific and technological risk and how it is communicated within a sociopolitical structure. Risk communication is recognized as an effective tool of disseminating information to public and other stakeholders. It is important that only accurate information should be given as risk communication tends to influence psychological and cultural beliefs. Assessing the scientific risks of agri-food technologies must be coupled with appropriate, research-based risk management and communication activities, in order to provide consumers, the media, and others with a balanced, science-based assessment of both the potential benefits and risks of a particular technology, and to positively impact the development of public policy. The challenge is to incorporate public perceptions into policy development without abdicating the leadership role of science.

4.2 Purpose

Risk communication can assist in the understanding of public perceptions of modern biotechnology, how the media translates this information, and how government, industry, and other organizations can better relate risk information over a wide range of disciplines. The disconnect between the way the public and scientists measure risk may help explain why public concern does not always reflect scientifically-determined levels of risk, or in some cases leads to complete misperception about associated risks. The public discussion of modern biotechnology is evolving much like the public discussion of pesticides before in terms of risk versus benefit, rather than as a richer discussion about maximizing benefit while minimizing risk.

In the absence of credible messages on the nature of the risks of biotechnology and the efforts taken by regulators to reduce these risks, opponents of genetic engineering have filled the void with their own memorable messages. Media coverage of genetically engineered food (and modern biotechnology in general) has often been polarized: safety versus risk; science moving forward versus science out of control; competitiveness versus safety. Films and novels have a long history of feeding the public an image of science out of control.

4.3 Tools

Media analysis is a tool used to help understand the formation of public opinion, to look at what people are saying and what they are being told. Consumers receive much of their science information from media. This reliance on the media helps to define the public sense of reality and their perceptions of risks or benefits. Media not only reflect public perceptions of an issue but also shape public perceptions by telling society what to think about. As such, the way in which the media portrays issues surrounding modern biotechnology and food safety can have an effect on consumer perception.

Insufficient or inaccurate information leads to wrong perceptions of risk resulting in adverse public opinion. For example, risk controversies like the current debate over GM food can be divided into technical and non-technical components. The technical components are generally regarding the scientific hazards evaluated in a risk assessment and the management options arising from the assessment. The non-technical components include the cultural and ethical issues generally raised by non-experts, allegations about secretive regulatory decisions etc.

4.4 Communication strategies

It is a valuable exercise to have effective risk communication and some of the communication strategies are:

i) Accept and involve the pubic as a legitimate partner and treat adversaries with respect;
ii) Coordinate, collaborate and provide information through credible sources;
iii) Be honest, frank and open, don't keep secrets and acknowledge mistakes made;
iv) Listen to and acknowledge people's concerns;
v) Be pro-active and speak clearly with a balanced and realistic information strategy;
vi) Meet the needs of the media and identify and train communicators;
vii) Make and use risk comparisons (compare familiar risk with unfamiliar risk);
viii) Attempt to communicate messages using a two-way communication process (do not presume what the public needs to know);
ix) Be honest and clarify about the existence of scientific uncertainty and also about the risk associated with this uncertainty;
x) Focus on a specific issue (do not try to tackle all the issues at once);
xi) Educate experts about their own biases and about competing systems for evaluating risk;
xii) Try to address the public's real sources of concern (focus on 'outrage' factors); and
xiii) Be aware that communication will not always reduce conflict and create acceptance.

Public opinion about modern biotechnology is based on misperceptions of risk fuelled by insufficient or inaccurate information. More fully informed opinions can arise only

when people have a better and more realistic understanding of how biotechnology will affect their immediate lives and the environment in which they live.

ANNEXES

ANNEX 1: PRINCIPLES FOR THE RISK ANALYSIS OF FOODS DERIVED FROM MODERN BIOTECHNOLOGY[1]

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 recognized 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[2] as well as the Codex Working Principles for Risk Analysis[3].

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 recognized 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.

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

[2] 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).

[3] "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)

SECTION 2 – PRINCIPLES

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

SECTION 2.1 – RISK ASSESSMENT

2. 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.

3. 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.

4. 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.

5. 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[4].

6. 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.

7. 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.

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

SECTION 2.2 – RISK MANAGEMENT

8. 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[5] as well as the Codex Working Principles for Risk Analysis.

9. 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.

10. Risk managers should take into account the uncertainties identified in the risk assessment and implement appropriate measures to manage these uncertainties.

11. Risk management measures may include, as appropriate, food labelling[6] conditions for marketing approvals and post-market monitoring.

12. 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.

13. 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[7] 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.

SECTION 2.3 – RISK COMMUNICATION

14. 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.

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[5] See footnote 1

[6] Reference is made to the CCFL in relation to the Proposed Draft Guidelines for the Labelling of Foods and Food Ingredients obtained through certain techniques of genetic modification/genetic engineering at Step 3 of the Codex Elaboration Procedure.

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

15. 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.

16. 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.

SECTION 2.4 – CONSISTENCY

17. 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.

18. 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.

SECTION 2.5 – REVIEW PROCESSES

19. Risk analysis methodology and its application should be consistent with new scientific knowledge and other information relevant to risk analysis.

20. 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.

ANNEX 2: 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.

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[8].

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.

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

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[9]. 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.

SECTION 3.1 – 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.

15. 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.

16. 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.

17. 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

[9] 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).

be used to analyse potential changes at the level of gene transcription and message translation that could lead to unintended effects.

18. 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.

19. 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.

SECTION 3.2 – FRAMEWORK OF FOOD SAFETY ASSESSMENT

20. 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:
        i) expressed substances (non-nucleic acid substances);
        ii) compositional analyses of key components;
        iii) evaluation of metabolites ;
        iv) food processing;
        v) nutritional modification; and
    g) Other considerations.

21. 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.

22. 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.

23. 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

SECTION 4.1 – DESCRIPTION OF THE RECOMBINANT-DNA PLANT

24. 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.

SECTION 4.2 – DESCRIPTION OF THE HOST PLANT AND ITS USE AS FOOD

25. 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.

26. 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).

SECTION 4.3 – DESCRIPTION OF THE DONOR ORGANISM(S)

27. 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).

SECTION 4.4 – DESCRIPTION OF THE GENETIC MODIFICATION(S)

28. 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.

SECTION 4.5 – 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.

SECTION 4.6 – 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[10] 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 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 the Annex to this document[11].

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.

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

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

SECTION 4.7 – COMPOSITIONAL ANALYSES OF KEY COMPONENTS

44. Analyses of concentrations of key components[12] 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.

SECTION 4.7 – 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).

SECTION 4.8 – FOOD PROCESSING

[12] 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.

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.

SECTION 4.9 – 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.

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

SECTION 5.1 – 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.

SECTION 5.2 – 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.

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.

SECTION 5.3 – 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. 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 3: ASSESSMENT OF POSSIBLE ALLERGENICITY

SECTION 1 – INTRODUCTION

1. All newly expressed proteins[13] 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.

[13] 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.

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 3.2 – 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 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[14].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

[14] 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.

allergenic. If the product is to be considered further, it should be assessed using serum from individuals sensitized to the identified allergenic source.

SECTION 3.3 – 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[15]. 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[16].

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.[17] 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[18]. A positive result in such tests would indicate a potential allergen.

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

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

[17] 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.

[18] 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.