

codex alimentarius commission



FOOD AND AGRICULTURE
ORGANIZATION
OF THE UNITED NATIONS

WORLD
HEALTH
ORGANIZATION



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ALINORM 03/34

JOINT FAO/WHO FOOD STANDARD PROGRAMME

CODEX ALIMENTARIUS COMMISSION

TWENTY-FIFTH SESSION

ROME, ITALY 30 JUNE - 5 JULY 2003

REPORT OF THE THIRD SESSION OF THE CODEX *AD HOC* INTERGOVERNMENTAL TASK FORCE ON FOODS DERIVED FROM BIOTECHNOLOGY

YOKOHAMA, JAPAN 4-8 MARCH 2002

Note: This document incorporates Codex Circular Letter CL 2002/9-FBT

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CL 2002/9 - FBT
April 2002

To: Codex Contact Points
Interested International Organizations

From: Secretary, Codex Alimentarius Commission, FAO Viale delle Terme di Caracalla,
00100 Rome, Italy

Subject: Distribution of the Report of the Third Session of the Codex Ad Hoc Intergovernmental Task Force on Foods Derived from Biotechnology (ALINORM 03/34)

A. MATTERS FOR ADOPTION BY THE 25TH SESSION OF THE CODEX ALIMENTARIUS COMMISSION

Draft Principles and Guideline for Plant at Step 8 of the Procedure

1. Draft Principles for the Risk Analysis of Foods Derived from Modern Biotechnology (para. 34, Appendix II)
2. Main text of Draft Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants (para 61, Appendix III).

Proposed Draft Annex on the Assessment of Possible Allergenicity at step 5/8 of the Procedure

3. Proposed Draft Annex on the Assessment of Possible Allergenicity to the Draft Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants (para 74, Appendix IV)

Governments and interested international organizations are invited to comment on the above document and should do so in conformity with the Procedures for the Elaboration of Codex Standards and Related Texts at Step 8) (*Codex Alimentarius Procedural Manual*, Twelfth Edition, page 21). Comments should be forwarded to the Secretary, Codex Alimentarius Commission, FAO, Viale delle Terme di Caracalla, 00100 Rome, Italy (fax +39 06 57054593; e-mail codex@fao.org), **not later than 31 December 2002.**

B. MATTERS FOR ADOPTION BY THE 50TH SESSION OF THE CODEX EXECUTIVE COMMITTEE

Proposed Draft Guideline for Microorganisms at Step 5 of the Procedure

1. Proposed Draft Guideline for the Conduct of Food Safety Assessment of Foods Produced using Recombinant-DNA Microorganisms (para 88, Appendix V)

Governments and interested international organizations are invited to comment on the above document and should do so in conformity with the Procedures for the Elaboration of Codex Standards and Related Texts at Step 5) (*Codex Alimentarius Procedural Manual*, Twelfth Edition, page 20). Comments should be forwarded to the Secretary, Codex Alimentarius Commission, FAO, Viale delle Terme di Caracalla, 00100 Rome, Italy (fax +39 06 57054593; e-mail codex@fao.org), **not later than 20 May 2002.**

SUMMARY AND CONCLUSIONS

The Third Session of the Codex Ad Hoc Intergovernmental Task Force on Foods Derived from Biotechnology reached the following conclusions:

MATTERS FOR CONSIDERATION BY THE CODEX ALIMENTARIUS COMMISSION

The Task Force:

- a) Agreed to advance the Draft Principles for the Risk Analysis of Foods Derived from Modern Biotechnology to Step 8 of the procedure for the consideration of the 25th Session of the Codex Alimentarius Commission (para. 34, Appendix II);
- b) Agreed to advance the Draft Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants to Step 8 of the procedure for the consideration of the 25th Session of the Codex Alimentarius Commission (para. 61, Appendix III);
- c) Agreed to advance the Draft Annex on the Assessment of Possible Allergenicity to Step 5 and recommended that the Commission also adopt the text at Step 8 with omission of Steps 6 and 7 (para 74, Appendix IV).

MATTERS FOR CONSIDERATION BY THE CODEX EXECUTIVE COMMITTEE

The Task Force:

- a) Agreed to advance the Proposed Draft Guideline for the Conduct of Food Safety Assessment of Foods Produced using Recombinant-DNA Microorganisms to Step 5 (para 88, Appendix V).

OTHER MATTERS OF INTEREST TO THE COMMISSION

The Task Force:

- a) Agreed to a compromise text on product tracing in order to reach a final conclusion on the text of the Draft Principles (para 27);
- b) Agreed to have a fuller discussion on traceability at its next session in accordance with a consensus that such a discussion should not compromise the consensus that had already been achieved in the Draft General Principles and should not lead to specific recommendations or guidelines (para 90);
- c) Agreed to forward the list of validated methods for the detection or identification of foods or food ingredients derived from biotechnology to the Codex Committee on Methods of Analysis and Sampling for its consideration (para 94-95);
- d) Noted that FAO and WHO will hold a Joint Expert Consultation on genetically modified animals, the out come of which would be reported to the Task Force (para 96).

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ALINORM 03/34

**REPORT OF THE THIRD SESSION OF THE CODEX AD HOC
INTERGOVERNMENTAL TASK FORCE ON FOODS DERIVED FROM
BIOTECHNOLOGY**

YOKOHAMA, JAPAN 4-8 MARCH 2002

INTRODUCTION

1. The Codex Ad Hoc Intergovernmental Task Force on Foods Derived from Biotechnology (CX/FBT) held its Third Session in Yokohama, Japan from 4 to 8 March 2002, by courtesy of the Government of Japan. The Session was presided over by Professor Hiroshi Yoshikura, Inspection and Safety Division, Department of Food Safety, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare. A complete list of participants is included as Appendix I to this report.

OPENING OF THE SESSION

2. The Session was opened by Mr Jungoro Kondo, Vice-Minister for Health, Labour and Welfare, who welcomed the participants to Yokohama, Kanagawa, Japan. Mr Kondo stressed that the food safety and consumer health had become a matter of serious consideration and that the safety of foods derived from modern biotechnology attracted considerable public concern both in importing and exporting countries. He expressed the wish that a worldwide consensus in this area could be reached as soon as possible.
3. Mr Ezzeddine Boutrif, Senior Officer, Food Quality and Standards Service, FAO welcomed participants behalf of the Director-General of FAO. He highlighted the importance of food safety in FAO's current programme of work, and made particular reference to the recent Joint FAO/WHO Global Forum of Food Safety Regulators (Marrakech, January 2002), the Joint FAO/WHO Pan-European Conference on Food Safety and Quality (Budapest, February 2002) and the forthcoming World Food Summit – five years later (Rome, June 2002). Mr. Boutrif informed the Task Force of the preliminary results of a global inventory of agricultural biotechnology applications and products which show a definite increase in production of GM crops in developing countries, and stressed the importance of the work of the Task Force in providing proper guidance to ensure that GM crops make optimal contribution to world food security, food safety and nutritional quality, and sustainability. Mr Boutrif further informed the Task Force of efforts being made by FAO in collaboration with other agencies to launch a global project for “Capacity Building in the Development of Policy and Regulatory frameworks for Biotechnology for Food and Agriculture” and to establish a “Biosecurity Portal” to provide regulators with Internet-based information decision support tool in the field of food safety, biosafety, animal and plant health. He expressed FAO's readiness to continue to work with WHO to support the Task Force with the necessary scientific advice on specific issues, as required, and within available resources.
4. The representative of WHO, Dr Jørgen Schlundt, gave welcome address on behalf of the Director-General of the WHO. Dr Schlundt mentioned that WHO, with input from FAO and other organizations, is initiating a project namely “Biotech Mega Study” which attempts a review of the area related to a broader evaluation of foods derived from modern biotechnology as well as cost benefit and socio-economic considerations. Both representatives urged the Task Force to make efforts to advance the finalization of the texts on its Agenda to respond to the pressing demand for these texts.

ADOPTION OF THE AGENDA (AGENDA ITEM 1)¹

5. The Task Force adopted the Provisional Agenda as the Agenda of the Session. No other business was proposed.

MATTERS REFERRED TO THE TASK FORCE BY OTHER CODEX COMMITTEES (AGENDA ITEM 2)²

6. The Task Force noted that the 24th Session of the Codex Commission had approved the two main documents prepared by the Task Force at its 1st and 2nd Sessions, namely; “Proposed Draft Principles for The Risk Analysis of Foods Derived from Modern Biotechnology” and “Proposed Draft Guideline for The Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants”. These texts had been advanced to Step 6. The Commission had also approved new work on the elaboration of guidelines for the safety assessment of recombinant-DNA microorganisms.
7. The Task Force was informed that the Definitions proposed by the Codex Committee on Food Labelling in the Draft Amendment to the General Standard for the Labelling of Prepackaged Foods had been returned to Step 6 by the Commission.
8. The Task Force noted the discussions of the Executive Committee on traceability as a general issue confronting Codex. The Secretariat paper³ prepared for the Commission had pointed out that traceability was not new to Codex but that it had not been treated in a systematic manner. The paper also pointed out that any measures requiring traceability must be justified as having a food safety objective (i.e., as an SPS measure), or having a legitimate objective as a TBT measure. The Executive Committee had generally supported the analysis and approach outlined in the Secretariat paper. The Executive Committee had recommended that the Committee on General Principles consider the two aspects of traceability referred to above, however, it had been of the opinion that first consideration should be given to the use of traceability as a risk management option in the Working Principles for Risk Analysis. The Executive Committee had also noted in particular the role of the Committee on Food Import and Export Inspection and Certification Systems in relation to the development of procedures for the application of traceability in food import and export inspection and certification systems. Although some Members of the Executive Committee had believed that a sequential approach to the development of other texts should be followed, the Executive Committee had agreed that it should be for the Committees concerned (including the Committees on General Principles, Food Import and Export Inspection and Certification Systems, Food Hygiene and Food Labelling) to undertake work as they deemed appropriate, within their respective mandates.⁴

MATTERS OF INTEREST FROM OTHER INTERNATIONAL ORGANIZATIONS WITH RESPECT TO THE EVALUATION OF THE SAFETY AND NUTRITION ASPECTS OF FOODS DERIVED FROM BIOTECHNOLOGY (AGENDA ITEM 3)⁵

9. The Task Force noted that in line with its terms of reference, that when elaborating standards, guidelines or other principles, as appropriate, for foods derived from biotechnology it should take full account of existing work carried out by national authorities, FAO, WHO, other international

¹ CX/FBT 02/1

² CX/FBT 02/2

³ ALINORM 01/21, Part IV-Add.1

⁴ ALINORM 03/3 para 31

⁵ CX/FBT 02/3

organizations and other relevant international fora. The document before the Task Force provided information on the following:

- FAO/WHO Joint Activities
 - Convention on Biological Diversity (CBD)
 - United Nations Industrial Development Organization (UNIDO)
 - Organizations for Economic Co-Operation and Development (OECD)
 - G8 Heads of State and Government Meeting
10. The Representatives of FAO and WHO noted that these organizations had convened three Joint Expert Consultations and that a Global Forum of Food Safety Regulators had met in Marrakech, Morocco from 28 to 30 January 2002. This had been done in response to the call for “periodic international meetings of food safety regulators to advance the process of science-based public consultations” on biotechnology and other aspects of food safety in the G8 Summit Communiqué of Okinawa in 2000. It had been recommended that a similar forum would be held in two years’ time, subject to the availability of resources.

CONSIDERATION OF DRAFT PRINCIPLES FOR THE RISK ANALYSIS OF FOODS DERIVED FROM MODERN BIOTECHNOLOGY AT STEP 7 (AGENDA ITEM 4)⁶

BACKGROUND

11. The Task Force was informed that at its Second Session a consensus had been reached to forward the Draft Principles for the Risk Analysis of Foods Derived from Modern Biotechnology to Step 6.

TITLE

12. The Task Force discussed the proposals to change the title and agreed to leave it as it was. In regard to a proposal to replace the word “Modern Biotechnology” with “Genetically Modified Foods and Products derived therefrom”, the Task Force, recalled that the expression “Modern Biotechnology” had been chosen in order to ensure consistency between Codex texts and the Cartagena Protocol based on the internationally-agreed definition in the Protocol. The Task Force therefore decided not to reopen this issue. In general, the Task Force decided to use the expression “Modern Biotechnology” throughout the entire document in order to maintain consistency of terminology, although several delegations expressed their preference for the use of “genetically modified”.

SECTION II - SCOPE AND DEFINITIONS

13. In Paragraph 7, the Task Force accepted a proposal to delete the word “other” before “ethical” in order to avoid misunderstanding that might be caused by the original formulation. Furthermore the

⁶ ALINORM 01/34A Appendix II; CL 2001/28-FBT; CX/FBT 02/4 (Comments of Argentina, Australia, Canada, Cuba, Japan, Mexico, Portugal, Singapore, Sweden, United States of America, IACFO); CRD 1 (Comments of Germany, Thailand); CRD 9 (Comments of Mexico); CRD 10 (Comments of Chile); CRD 13 (Comments of Cuba); CRD 14 (Comments of International Cooperative Alliance); CRD 15 (Comments of 49th Parallel Biotechnology Consortium), CRD 16 (Comments of Consumers International); CRD 17 (Proposal of the EU on Traceability); CRD 18 (Proposal on paragraphs 19 and 20 by Australia and Belgium); CRD 21 (Informal proposal elaborated by Canada, EC, UK Thailand and several other delegations); CRD 22 (Comments of the Philippines); CRD 26 (Informal proposal elaborated by a lunchtime meeting on March 5).

Task Force agreed to simplify the footnote to this paragraph dealing with animal feed and animals fed such feed and to introduce the standard terminology.

14. The Task Force did not agree to adopt a proposed change to the Definition of *Conventional Counterpart* that would limit the conventional counterpart to “non-genetically modified organisms”. It recalled the extensive debate on this issue at its last session⁷ which resulted in the present footnote to the paragraph and the indication that for the foreseeable future, foods derived from modern biotechnology will not be used as conventional counterparts.

SECTION III-PRINCIPLES

Risk Assessment

15. The Task Force discussed the proposal to rewrite the Paragraph 10 in such a manner to clearly separate the use of term “hazard” and “safety concern” in a different context and also to express the notion that risk assessment was an integral part of the safety assessment. The Task Force exchanged the opinions on this issue and as many delegates expressed that the safety assessment should be a part of risk assessment, finally decided not to change the present paragraph 10.
16. The Task Force agreed to insert “as appropriate” before the reference to quantity of data in Paragraph 12 in order to reflect the fact that the quantity of data in itself was not the determining factor in its scientific value.
17. In Paragraph 13, the Task Force added a new reference to the “Proposed Draft Guideline for the Conduct of Food Safety Assessment for Foods Produced Using Recombinant-DNA Microorganisms” in the relevant footnote.
18. The Task Force agreed to modify Paragraph 15 by stressing the need to take into account all available scientific data. However, it did not adopt the proposed inclusion of the wording of “scientifically validated” after “scientifically sound” recalling that validation was covered by the principle of peer review contained in paragraph 12.

Risk Management

19. The Task Force agreed to modify Paragraph 17 by replacing the wording “meeting the same objective” with “achieving the same level of protection” in order to maintain a clear linkage with the SPS Agreement.
20. In paragraph 19, the Task Force decided to separate the reference to risk management measures (e.g., labelling) and references the tools for the implementation and enforcement of risk management measures (e.g., development of analytical methods). It therefore decided to create a new paragraph (after Paragraph 20) to cover these tools and made specific mention of the development of analytical methods and the provision of reference materials.
21. In response to an enquiry from the Delegation of India, the Task Force noted that food ingredients derived from modern biotechnology would be covered by the Principles since food ingredients were treated in the same way as foods in accordance with the Codex definition of “food”.

⁷ ALINORM 01/34A, paras. 24-25.

Traceability

22. The Task Force recalled that the issue of “traceability” had been discussed at the 49th Executive Committee (see paragraph 8 above) and that consequently the issue was also under discussion in the Committee on General Principles and the Committee on Food Import and Export Inspection and Certification Systems and would probably be taken up in other Codex Committees as well.
23. The Delegation of Spain, speaking on behalf of the member states of EU, tabled a revised proposal⁸ as an alternative to the text of paragraph 21 that had been included in square brackets by the 2nd Session of the Task Force. The proposal outlined the situations in which traceability could be considered as a risk management option. The Delegation noted that discussions on traceability need not be restricted to its consideration within the context of Committee on General Principles. Several delegations expressed their support for this view.
24. The Delegation of the United States stated that the issue of traceability was not unique to foods derived from modern biotechnology, and that it would be discussed as a general issue of Codex by the Committee on General Principles and other Committees. On this basis, it should be possible to delete paragraph 21. These views were supported by several other delegations.
25. The Delegation of Brazil, Thailand and Indonesia expressed the view that the traceability should not be considered as a part of a mandatory system because it was mainly intended to provide information to trading partners. For this reason, paragraph 21 could be deleted. However, if traceability could be demonstrated as being useful in risk management, the practicability of its application and cost in developing countries needed to be considered.
26. Some NGOs observers representing consumer and environmental organizations stressed that traceability was a key risk management measure and could be specially effective for use in post-market monitoring of unintended effects and control of labelling. Other NGOs representing industry associations were of the opinion that traceback was a normal practice in industry but not specific to food derived from biotechnology. One NGO referred to the identification requirements of Article 18 of the Cartagena Protocol as having relevance to the use of traceability.
27. The Task Force was of the opinion that the resolution of this issue was important in order to reach a final conclusion on the text of the Draft Principles. It noted that the addition of a new paragraph after paragraph 20 (see para. 20, above) made it possible to place the question of traceability into context as one of the tools for implementation and enforcement of risk management measures, without prejudice to its use for other purposes. On this basis a compromise text⁹ was agreed to as follows.

“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 for the purpose of facilitating withdrawal from the market when a risk to human health has been identified or to support post-market monitoring in circumstances as indicated in paragraph 20.”
28. The Delegation of the Republic of Korea reserved its position in relation to the adoption of the new paragraph as its application is limited to SPS measures.
29. The representative of 49th Parallel noted that applications of product tracing would also need to be consistent with the provisions of the Cartagena Protocol after its entry into force. Secretariat noted that Article 18 of the Cartagena Protocol did not make direct reference to product tracing and a

⁸ CRD 17.

⁹ CRD 26.

number of delegations stated that discussion of the Commission should not be bound to agreements that were not yet in force. Other delegations were of the opinion that Commission should take into account all other applicable international agreements. The Task Force noted that further consideration of several broader issues surrounding product tracing would continue within Codex.

RISK COMMUNICATION

30. The Task Force agreed to delete a reference to “consultation with existing bodies” in the paragraph dealing with the consultation process as this was considered to introduce redundancy in the text.

CONSISTENCY

31. The Task Force exchanged opinions on a proposal of how to clearly express the necessity of maintaining consistency in the level of consumer protection against risks associated with foods, regardless whether the food is derived from biotechnology or a conventional counterpart. The Task Force reached a consensus to replace the second sentence with new formulation to state that unjustifiable differences in the level of risks between foods derived from modern biotechnology and similar foods should be avoided. In the same sentence, the Task Force also accepted a proposal to include “conventional” after “similar”.

CAPACITY BUILDING

32. The Task Force had an extended discussions on the proposals of several delegations to make specific references to the entities responsible for improving the capacity of regulatory authorities particularly in developing countries. The Task Force, noting that the present text already covered broad entities, did not agree to make explicit references in the sentence. However, based on the recognition of the importance of the capacity building for developing countries and also of the respective roles of bilateral and multilateral funding agencies as well as the technical international organizations to achieve that purpose, it agreed to add a new sentence to specify the importance of the assistance for developing countries in application of the principles with a footnote referring to the corresponding provisions of the SPS and TBT Agreements (Article 9 of SPS and Article 11 of TBT).

REVIEW PROCESS

33. The Task Force agreed to make small editorial changes to the final paragraph of the Principles.

STATUS OF THE DRAFT PRINCIPLES FOR THE RISK ANALYSIS OF FOODS DERIVED FROM MODERN BIOTECHNOLOGY

34. The Task Force agreed to advance the Draft Principles for the Risk Analysis of Foods Derived from Modern Biotechnology to Step 8 of the Codex Procedure for consideration by the 25th Session of the Commission. The text of the Draft Principles is contained in Appendix II to this report.

DRAFT GUIDELINE FOR THE CONDUCT OF FOOD SAFETY ASSESSMENT OF FOODS DERIVED FROM RECOMBINANT-DNA PLANTS (AGENDA ITEM 5)¹⁰

BACKGROUND

35. The Task Force was informed that at its Second Session a consensus had been reached to forward the Draft Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants to Step 5 and to circulate the Annex dealing with allergenicity at Step 3 for further comment and revision by a Working Group chaired by Canada. The 24th Session of the Commission had advanced the main text of the Guidelines to Step 6 of the Procedure.
36. The Task Force discussed the Draft Guideline paragraph by paragraph at Step 7 in the light of comments received at Step 6. It also discussed at Step 7 a re-drafting and re-arrangement of the section dealing with the assessment of possible toxicity as agreed at its 2nd Session¹¹. The Annex dealing with allergenicity was discussed at Step 4. Because of major rearrangements made to the text, the paragraph numbers given in the following discussion are those in the revised version of the Draft Guidelines attached to this report as Appendix III. The following report discusses the main changes in the text made by the Task Force; minor or editorial changes have been incorporated into the text of Appendix III directly.

TITLE

37. The Task Force discussed the proposals to change the title and agreed to retain the Title as it was. In regard to a proposal to replace the expression “Recombinant-DNA Plants” with “Plants Modified by DNA techniques”, the Task Force noted that such a change in the title could lead to extensive redrafting throughout the text with little net benefit.

SECTION 1 - SCOPE

38. The Task Force discussed at length the question of whether or not the expression “derived from” recombinant DNA-plant also included the plants themselves or was restricted to derived products. Although it was noted that whole, unprocessed plants were very infrequently consumed the Task Force agreed to provide for such cases. The Task Force also agreed to include a reference to altered traits as well as new traits and to make a reference to the use of “modern biotechnology” for consistency with the Principles. The Task Force also retained the reference to the fact that the Guidelines applied only to foods that been derived from plants with a history of safe use as sources of food; foods derived from other plant sources would need to be assessed by other procedures than those described in the Guidelines. (Paragraph 1)
39. The Task Force agreed to insert a new paragraph, taken from the proposed draft Annex on Allergenicity, to link risk management measures outlined in the Principles for Risk Analysis with the safety assessment procedures outlined in this Guideline. (Paragraph 6)

SECTION 2 - DEFINITIONS

40. The Task Force agreed to retain the definitions for consistency with those of the Draft Principles for the Risk Analysis of Foods Derived from Modern Biotechnology.

¹⁰ ALINORM 01/34A Appendix III

¹¹ ALINORM 01/34A, para. 77.

SECTION 3 – INTRODUCTION TO FOOD SAFETY ASSESSMENT

41. The Task Force had an extended discussion on the necessity of animal studies (feeding trials) on whole foods. The Delegation of Germany proposed that such studies may be necessary to confirm the safety of a foodstuff and this proposal received support from several delegations. Other delegations were of the opinion that feeding trials would present challenges in application and interpretation with regard to providing the assurance of safety that was needed for consumer protection. The Task Force agreed to specify that such studies could be envisaged when the characterization of the food indicated that data would be insufficient for a thorough safety assessment. (Paragraph 11)
42. In the paragraph dealing with the goal of the safety assessment, the Delegation of the United States proposed to amend the paragraph so as to remove the requirement that the endpoint of the assessment would be a conclusion regarding whether or not the new food would be “as ... nutritious as” the conventional counterpart. The objective of the amendment was to allow for new foods that would be more nutritious. The Task Force agreed to delete the reference to “nutritious” in this phrase but added a phrase to require that the dietary impact of any changes in nutritional content or value should be taken into account. (Paragraph 21)

SECTION 4 – GENERAL CONSIDERATIONS

Description of the New Variety

43. The Task Force agreed to replace term “new variety” with “recombinant-DNA plant” in the heading and throughout this section in view of the specific use of the term “variety” in plant breeding and genetics. (Paragraph 22) The need to identify unequivocally the recombinant-DNA plant was discussed by the Task Force, but it was noted that this was probably more on issue of risk management than risk assessment.

Description of the Donor organism(s)

44. The term “members of the corresponding genus” was replaced by “related species” in Paragraph 26.

Characterization of the Genetic Modification(s)

45. The Task Force had an extended discussion concerning the amount of information required on the sequence of the region surrounding the insertion site and whether or not sequence data were essential to the characterization of the genetic modification. Several delegations, in particular those of Belgium, France, Norway and Japan stressed the importance of the comprehensive sequence data. Other delegations were of the opinion that other data, such as analysis of the transcript products could in some cases be more revealing as to the nature of the modification. The representative of Greenpeace International called for sequencing of the entire genome of the modified plant. The Task Force agreed that first consideration should be given to the sequence data but that in cases where the transcript data were more useful, information on the sequence data need not be provided. It amended the paragraph accordingly. (Paragraph 31.C)

Safety Assessment of Expressed Substances (Non-Nucleic Acid Substances)

46. The structure of this sub-section was amended to reflect the structure of the safety assessment described in Paragraph 18 of the Draft Guideline.

Assessment of possible toxicity

47. The Task Force was informed that at its Second Session a consensus had been reached to establish an open-ended Working Group on Allergenicity which had been hosted by the Government of Canada. This Working Group had also been invited to prepare a reorganization of the section on toxicology¹².
48. The Task Force agreed to amend the last sentence to “New substances might also include new metabolites resulting from the activity of enzymes generated by the expression of the introduced DNA”, for scientific accuracy. (Paragraph 34)
49. In Paragraph 35, the Task Force agreed to include reference to the chemical nature of the newly expressed substances to make the paragraph more precise.
50. In Paragraph 36, the Task Force agreed to delete the first sentence recommended by the Working Group as being redundant and unclear. The Task Force agreed that food processing could also degrade or eliminate anti-nutrients as well as deactivate them, and amended the paragraph accordingly.
51. In Paragraph 37, the Task Force discussed the appropriateness of excluding substances closely related to those that had been safely consumed in food from the requirement of conventional toxicological testing. Some Delegations and representatives of NGOs expressed their concern that term “closely related” was quite vague and it should be deleted, while other delegations and NGOs stated that this term was essential in view of the other requirements of the paragraph. The Task Force agreed to maintain the term. The Task Force agreed, however, that studies other than conventional toxicological studies may be more appropriate in some cases and amended the paragraph accordingly.
52. The Task Force agreed that oral toxicity studies may need to be carried out in cases where the protein present in the food was not similar to proteins that have been safely consumed in food, provided that the biological function of the protein (where known) was taken into account. (Paragraph 38)
53. The Task Force debated at length the requirements that would apply to introduced non-protein substances that had not been safely consumed in food. It agreed that these should be assessed on a case-by-case basis in all cases taking into account the other conditions set out in the paragraph. (Paragraph 39)

Assessment of possible allergenicity (proteins)

54. The Task Force noted that this paragraph was intended set out the basic approach to be used in the assessment of potential allergenicity and also to provide a linkage to the Annex. The Task Force agreed that an integrated, stepwise, case-by-case approach should be used, however there was a divergence of opinions as to whether this should be presented as a decision-tree or not. The Delegation of the Netherlands, supported by several other delegations and observers made reference to the decision tree developed by the Joint FAO/WHO 2001 Expert Consultation. These delegations were of the opinion that the use of a decision-tree provided improved transparency in understanding the decisions being made. Other delegations were of the opinion that the use of a decision tree did not provide enough insight into the judgements needed at each step and also noted that the Working Group had recommended a more holistic approach that took into account evidence derived from several types of information and data, based on the concept of a

¹² ALINORM 01/34A para 70

“preponderance of data”. In either case, the Task Force agreed that no single criterion was sufficient to determine either the allergenicity or non-allergenicity of a protein.

55. The Task Force decided to make a reference to the work of the Joint FAO/WHO Expert Consultation in a footnote to this paragraph, but decided against the elaboration of a decision tree. (Paragraph 41)
56. The delegation of Spain requested that paragraphs dealing with gluten-sensitive enteropathy be referred to the Codex Committee on Nutrition and Foods for Special Dietary Uses for their information and this was agreed to by the Task Force (Paragraph 42,43).

Nutritional Modification

57. The Task Force amended the paragraph dealing with the modification of the food to provide guidance for identification of appropriate comparators where composition of a food product had been significantly altered or when dealing with individual food components. (Paragraph 51)

SECTION 5- OTHER CONSIDERATIONS

58. The Task Force agreed to include a new paragraph proposed by the delegation of Belgium and Canada and dealing with the potential for altered metabolism or accumulation of exogenous substances. (Paragraph 54)

Use of Antibiotic resistance marker genes

59. The Task Force, after an extended discussion, recognized that the use of wording “in general ” could leave a room for an unintended interpretation that there may be cases where antibiotic genes that encode resistance to clinically used antibiotics could be present in foods and therefore decided to delete it. It also agreed that this would apply to all foods and not only to “widely disseminated” foods as had been the case in the previous text. (Paragraph 58)

Review of Safety assessment

60. The Task Force agreed to modify the reference to nutrition in this paragraph to maintain consistency with the text of Paragraph 20. (Paragraph 59)

STATUS OF THE DRAFT GUIDELINE FOR THE CONDUCT OF FOOD SAFETY ASSESSMENT OF FOODS DERIVED FROM RECOMBINANT-DNA PLANTS

61. The Task Force agreed to forward the main text of the Draft Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants to the Commission for adoption at Step 8. The complete text of the Guideline is attached to this report as Appendix III.

PROPOSED DRAFT ANNEX ON THE ASSESSMENT OF POSSIBLE ALLERGENICITY: CONSIDERATION AT STEP 4 (AGENDA ITEM 5 B)¹³

62. The Task Force was informed that at its Second Session it had been agreed to establish an open-ended Working Group on Allergenicity hosted by the Government of Canada to revise the proposed draft Annex on allergenicity¹⁴. The Delegation of Canada (Chair of the Working Group) introduced the revised Annex prepared by the Working Group. He noted that the Joint FAO/WHO Expert Consultation in January 2001 provided a valuable source of expert input for the Working Group to draw upon for the development of the draft annex and encouraged the Working Group to also take into consideration relevant information available since the publication of the consultation as well as such aspects as practicality and validation. The Working Group had discussed the outcome of FAO/WHO Expert Consultation but come to the conclusion that it was not possible scientifically to arrive at clear “Yes/No” decisions at each and every step in the decision process. It had therefore recommended a more holistic approach that took into account a broad range of information that was to be examined in a step-wise and structured manner. This approach differed from the decision tree approach used in the previous draft.

SECTION 1 - INTRODUCTION

63. The Task Force agreed to modify Paragraph 2 to take into account the above discussion. In particular it deleted a reference to the “preponderance of evidence”.

64. The Task Force agreed to include a new paragraph, taken from paragraph 17 of the Working Group’s draft, that gave an explicit indication of the endpoint of the assessment for possible allergenicity. (Paragraph 3)

SECTION 2 - ASSESSMENT STRATEGY

65. In Paragraph 4, the Task Force agreed to insert a sentence “and heat stability and/or acid and enzymatic treatment” at the end of this paragraph in order to make this paragraph clearer. The Task Force also agreed to include a text provided by the Delegation of Italy on the attention that should be given to the choice of the expression host.

Section 3.1 – Source of the Protein

66. In Paragraph 7, the Task Force agreed to insert a reference to “physiochemical and immunological properties” at the end of this paragraph to make this paragraph clearer.

Section 3.2 – Amino Acid Sequence Homology

67. In Paragraph 9, the Task Force agreed to modify the paragraph to make an explicit reference the need to report the outcome of the comparison of the sequence homology. In paragraphs 10 (also 14), the Task Force accepted the wording provided by Argentina in relation to the epitopes capable of binding with IgE antibodies.

¹³ ALINORM 01/34A Appendix III, CL2001/38-FBT, CX/FBT 02/6 (Comments of Argentina, Australia, Canada, Japan, Sweden, United States of America, Consumer International), CRD 3 (Comments of Brazil, Italy, Thailand), CRD 13 (Comments of Cuba), CRD 16 (Comments of Consumer International), CRD 22 (Comments of Philippines), CRD 27 (Informal proposal elaborated by Belgium and Canada), CRD 28 (Informal proposal elaborated by Consumer International), CRD 29 (Informal proposal elaborated by Australia and Canada)

¹⁴ ALINORM 01/34A paras 69 and 70

SECTION 4 – SPECIFIC SERUM SCREENING

68. The Task Force noted that whereas it was desirable to perform immunological assays on proteins from a source known to be allergenic, it recognized that the ability to carry out such assays depended on the availability of appropriate sera, and amended Paragraph 14 accordingly. The Task Force agreed to include consideration of targeted serum screening for protein from sources not known to be allergenic (Paragraph 14).
69. The Task Force noted the unusual reference to *ex vivo* testing and agreed to make a reference in a footnote to the extended description of these procedures contained in the Joint FAO/WHO 2001 Expert Consultation report. (Paragraph 15).
70. The Task Force deleted a paragraph proposed by the Working Group that dealt with the commercialization of products containing identified allergens, considering that this was a matter of risk management and not risk or safety assessment and was therefore better dealt with in the context of the Principles of Risk Analysis.

SECTION 5 – OTHER CONSIDERATIONS

71. The Task Force agreed to rename this section and add to it the following Section previously entitled “Areas requiring Further Development”.
72. As noted above (para.64) the Task Force agreed to move the opening sentence of the Working Group’s recommendation to the introduction to the Annex, where it served the useful purpose of providing an overall framework for the assessment process. The remainder of Paragraph 17 was modified to indicate that as new knowledge and techniques continued to be developed they should be considered together with the other techniques described in the Annex.
73. The Task Force agreed that the Working Group’s recommendation concerning post-market monitoring and its usefulness in informing the safety assessment process had broader implications than the assessment of potential allergens, and agreed to incorporate this paragraph, with consequent amendments, into the main Guideline (see para. 39 above).

STATUS OF THE PROPOSED DRAFT ANNEX ON THE ASSESSMENT OF POSSIBLE ALLERGENICITY

74. The Task Force agreed to forward to Proposed Draft Annex on the Assessment of Possible Allergenicity to the Commission for adoption at Step 5 of the procedure and recommended that the Commission also adopt the Annex at Step 8, by the omission of Steps 6 and 7. The text of the revised Annex is contained in Appendix IV to this report.

PROPOSED DRAFT GUIDELINE FOR THE CONDUCT OF FOOD SAFETY ASSESSMENT OF RECOMBINANT-DNA MICROORGANISMS IN FOODS (AGENDA ITEM 6)¹⁵**BACKGROUND**

75. The Task Force recalled that at its second Session, it had agreed to initiate a new work on the elaboration of the guideline for the conduct of food safety assessment of modified microorganisms

¹⁵ CX/FBT 02/7, CX/FBT 02/7 Add.1 (Comments of IACFO), CRD 5 (Comments of Brazil, Canada, Germany, Italy, Thailand, Consumer International), CRD 6 (Comments of United States of America), CRD 7 (Comments of Argentina), CRD 13 (Comments of Cuba), CRD 14 (Comments of International Cooperative Alliance), CRD 23 (Comments of Consumer International).

and had established an open-ended Working Group chaired by the United States of America in order to prepare a proposed draft guideline. Following the approval of this new work by the Codex Alimentarius Commission at its 24th Session, the Working Group met in Oakland, California in November 2001.

76. In introducing the document, the delegation of the United States noted that the Working Group had based on the guideline on the Proposed Draft Guideline for the Conduct of Food Safety Assessment of the Foods derived from Recombinant-DNA Plants. The Task Force expressed its gratitude to the Government of the United States for hosting the meeting and to the Working Group for its accomplishment.
77. The Task Force noted that there were safety assessment procedures that should be applied to both the recombinant-DNA plant and recombinant-DNA microorganisms. The Task Force therefore agreed to use the text of the guideline document for recombinant-DNA plant wherever possible with a view to maintaining consistency between two documents. On the other hand, the Task Force also noted that there were issues specific to microorganisms such viability and colonization of the microorganisms in the digestive tract, transfer of plasmids and other genetic material, etc. that would have to be dealt with in the present text.
78. Due to time constraints, the Task Force made a number of editorial changes and corrections for clarity and also approved proposals from delegations to provide guidance for the continued elaboration of the document. It decided to include as many proposals for amendment as seemed appropriate, but placed them in square brackets for the time being so that member countries and observer organizations could reflect on them and provide comment in advance of the next session of the Task Force. The following discussion represents the main decisions reached by the Task Force.

TITLE

79. The Task Force approved the proposal by the Working Group to change the title of the document as “Proposed Draft Guideline for the Conduct of Food Safety Assessment of Foods Produced Using Recombinant-DNA Microorganisms” because the object of the assessment should be the food rather than the modified organism *per se*.

SECTION 1 – SCOPE

80. In regard to the Scope of the document, the Task Force had extensive discussions on the exclusions listed in paragraph 2 and whether or not the “indirect exposure” of recombinant-DNA microorganisms either through the use in agricultural production or release to the environment should be included in the scope. The delegation of Consumers International pointed out that the report of the joint FAO/WHO Expert Consultation held in September 2001 that discussed the safety assessment of the foods produced with the aide of genetically modified microorganisms dealt with this issue. It noted that the proposed draft Guideline was limited in its scope, and the use of recombinant microorganisms outside the scope of the Guideline would require a different kind of safety assessment than the one described in the Guideline. For example, the Task Force noted that the enzymes used as food additives and produced using genetically modified microorganisms were out of the scope of this guideline but were covered by the activities of the Joint FAO/WHO Committee on Food Additives (JECFA) and Codex Committee on Food Additives and Contaminants (CCFAC). The Task Force stressed that the chapeau of the paragraph 2 clearly stated that issues not addressed in the present Guidelines would have to be addressed by other appropriate bodies.

81. A number of delegations and observer organizations questioned the intent of paragraph 7, especially the reference to the endpoint of the assessment as being that a food would be “unlikely” to be harmful to human health. Many delegations and observer organizations that spoke were of the opinion that this was an insufficient expression of the level of consumer protection required. Some observer organizations were of the opinion that the risk assessment as described in paragraph 7 was not sufficient guarantee to consumer protection.
82. The Task Force agreed to amend the definition of Conventional Counterpart by deleting reference to a preference for the “parent or recipient strain” as the basis for comparison, as this was thought to be too vague for a definition. It noted that the substantive requirement later in the document indicated that the ideal comparator was the near isogenic parent strain and agreed that this provided the guidance needed in this regard. It also agreed to define the conventional counterpart of the foods produced using by recombinant-DNA microorganisms should not be derived from modern biotechnology by shifting the footnote to the entire title of *Conventional Counterpart* in paragraph 8.
83. The representative of Greenpeace expressed serious concern at the treatment of the concept of substantial equivalence as contained in paragraph 14. In its opinion, the paragraph should clearly express the idea that the determination of substantial equivalence was not a safety assessment in itself, but rather was a starting point used to structure the safety assessment. The representative of Consumers International also requested to modify this paragraph so that comparison to its conventional counterpart in safety assessment should be conducted not only between microorganisms themselves but also between the foods produced from modified and unmodified microorganisms. Delegations pointed out that these concerns were addressed in paragraph 14.
84. Several delegations supported the proposal of Italy to provide that “all recombinant-DNA microorganisms should be deposited in an international culture collection with appropriate identification using modern molecular methods”. It was noted that this had been discussed by the Working Group, but had not been included as it was not a requirement for safety assessment. The Task Force agreed to include the text in square brackets for further consideration. (Paragraph 24)
85. The Task Force also took note of the proposal of Argentina relating to the stability of the microorganism in successive generations, and included the text in square brackets in a footnote to paragraph 35 C.
86. The Task Force agreed to include alternative texts concerning the viability of the microorganism in the human gut and its ability for colonization, for consideration at the next session.
87. The Task Force noted several comments in relation to the content of paragraph 36, in particular to the precision (or lack of precision) of the changes brought about by genetic modification. Although part of the text was modified to make it consistent with the wording of the Guideline on recombinant-DNA plants, the Task Force agreed to place the entire paragraph in square brackets for further consideration.

STATUS OF THE PROPOSED DRAFT GUIDELINE FOR THE CONDUCT OF FOOD SAFETY ASSESSMENT OF FOODS PRODUCED USING RECOMBINANT-DNA MICROORGANISMS

88. The Task Force noted that although there had been many proposals for change to individual paragraphs in the text, the general approach and outline of the text was accepted. It also noted that most of the text proposed by the Working Group had proved to be acceptable to the Task Force. On this basis it decided to advance the Proposed Draft Guidelines to Step 5 for consideration of the next session of the Executive Committee. The revised text is contained in Appendix V to this report.

DISCUSSION PAPERS ON TRACEABILITY (AGENDA ITEM 7)¹⁶

89. The Task Force noted that it had embarked on a general discussion on Traceability at its First Session in order to provide the background for inclusion of appropriate wording in the Draft General Principles for the Risk Analysis of Foods Derived from Biotechnology. Papers prepared by the Delegations of France and the United States had been circulated for comment to assist in this regard.
90. In view of the compromise reached on this issue in the context of the Draft General Principles (see paras 22 to 27 above), the Task Force decided not to undertake an extended discussion on traceability at this time. It agreed however that the information obtained in response to the discussion papers should be transmitted to other relevant Codex committees to assist them in their consideration of the issue. It also agreed to have a fuller discussion at its next session, but also agreed that such a discussion should not compromise the consensus that had already been achieved in the Draft General Principles and should not lead to specific recommendations or guidelines.

CONSIDERATION OF ANALYTICAL METHODS (AGENDA ITEM 8)¹⁷

91. The task Force recalled that in the last session it agreed to document the present status of validation of the methods that had been reported by the member countries. The task force also recommended that a register or depository containing relevant information on methods for the detection or identification of foods or food ingredients derived from biotechnology (as well as the availability of reference materials) be established. It further decided to send the list of collected information to the Committee on Methods of Analysis and Sampling (CCMAS) for its consideration.
92. Based on this decision, the circular letter was delivered to member countries: to complement the existing list with documented information on further validated detection methods as well as extraction methods; to provide information on the criteria of validation as well as performance criteria and specificity of methods; to comment on the status of publication of validated methods; to provide opinions on the purpose, appropriate place(s) of a register containing relevant information on methods; to provide opinions on how the access to reference materials could be guaranteed.
93. The Chairperson of the Working Group on Analytical Methods informed the Task Force that the second session of the Working Group on Analytical Methods had been convened on 1 March 2001 and had considered the list of methods elaborated from the information reported by member countries in response to the circular letter and country comment on the registry. It finally agreed on the list of validated methods of analysis that contain the Annex 1 of CX/FBT 02/9 and methods reported later by Japan and United States.
94. The Working Group decided to recommend the Task Force;
- to forward to the CCMAS for its consideration this agreed list submitted to the Task Force as Appendix 1, 2, 3 of CRD12

¹⁶ CX/FBT 01/6 (Discussion Papers on Traceability), CRD 3 (Comments of United States of America of the Second Session), CX/FBT 02/8 (Comments of Argentina, Brazil, Canada, Côte d'Ivoire, Japan, Mexico, New Zealand, Singapore, South Africa, Sweden, Switzerland, UK, United States of America, Uruguay, EC, 49th Parallel Biotechnology Consortium, Association des Amidonneries de céréales de l'UE), CRD 8 (Comments of Brazil, Italy, Thailand), CRD 13 (Comments of Cuba), CRD 14 (Comments of International Cooperative Alliance), CRD 17 (Informal proposal elaborated by EU), CRD 25 (Comments of EC).

¹⁷ CX/FBT 02/9, CRD 12 (Report of Working Group elaborated by Germany).

- to propose to CCMAS to consider further methods of analysis with respect to foods derived biotechnology on the basis of the proposal from member countries
 - to propose through Codex Alimentarius Commission (CAC) that FAO, WHO and the FAO/IAEA Joint Division for Nuclear Techniques in Food and Agriculture encourage the development and maintenance of information of methods under development or not yet validated in co-operation with national/regional institutions.
95. The Task Force expressed its gratitude to the delegation of Germany for its work and approved the recommendation by the working Group. In relation to the registry, the Codex Secretariat informed the Task Force that the FAO Biosecurity Portal was under development in cooperation with WHO and other agencies. This will provide an electric information exchange mechanism that will provide a single access point for official national and international information on food quality and safety, plant and animal life and health. It was envisaged that registries of official information, such as methods of analysis would be available through the Portal.

OTHER BUSINESS, FUTURE WORK AND DATE AND PLACE OF NEXT SESSION (AGENDA ITEM 9)

OTHER BUSINESS

96. The Representatives of FAO and WHO announced that they were planning to convene a Joint FAO/WHO Expert Consultation on genetically modified animals, the outcome of which would be reported to the Task Force.

FUTURE WORK

97. The Task Force noted the following matters would be considered at the Fourth Session:
- Matters Referred to the Task Force by other Codex Committee
 - Matters of Interest from the Other International Organizations with respect to the Evaluation of the Safety and Nutrition Aspects of Foods Derived from Biotechnology
 - Proposed Draft Guideline for the Conduct of Food Safety Assessment of Foods Produced Using Recombinant-DNA Microorganisms
 - Open discussion on traceability

DATE AND PLACE OF NEXT SESSION

98. The Task Force noted that the Fourth Session was scheduled to be held in Yokohama from 10 to 14 March 2003, subject to confirmation by the Codex and Host Government Secretariats.

SUMMARY STATUS OF WORK

Subject Matter	Step	Action by	Document Reference in ALINORM 03/34
Draft Principles for the Risk Analysis of Foods Derived from Modern Biotechnology	8	Governments, 25 th CAC	para. 34 Appendix II
Draft Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants	8	Governments, 25 th CAC	para. 61 Appendix III
Proposed Draft Annex on the Assessment of Possible Allergenicity	5/8	Governments, 25 th CAC	paras.74 Appendix IV
Proposed Draft Guideline for the Conduct of Food Safety Assessment of Foods Produced Using Recombinant-DNA Microorganisms	5	Government, 50 th CCEXEC	para. 88, Appendix V
FAO/WHO Joint Expert Consultation on genetically modified animals	-	FAO and WHO	para 96

APPENDIX I

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Les chefs de délégation figurent en tête et les suppléants et conseillers sont énumérés en ordre alphabétique.

Figuran en primar lugar los Jefes de las delegaciones, los Suplentes y Asesores aparecen par orden alfabético.

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Appendix II

**DRAFT PRINCIPLES FOR THE RISK ANALYSIS OF FOODS DERIVED FROM
MODERN BIOTECHNOLOGY**

(At Step 8 of the Elaboration Procedure)***SECTION 1 - INTRODUCTION***

1. For many foods, the level of food safety generally accepted by the society reflects the history of their safe consumption by humans. It is recognised that in many cases the knowledge required to manage the risks associated with foods has been acquired in the course of their long history of use. Foods are generally considered safe, provided that care is taken during development, primary production, processing, storage, handling and preparation.
2. The hazards associated with foods are subjected to the risk analysis process of the Codex Alimentarius Commission to assess potential risks and, if necessary, to develop approaches to manage these risks. The conduct of risk analysis is guided by general decisions of the Codex Alimentarius Commission (CAC)¹ as well as the Codex Working Principles for Risk Analysis².
3. While risk analysis has been used over a long period of time to address chemical hazards (*e.g.* residues of pesticides, contaminants, food additives and processing aids), and it is being increasingly used to address microbiological hazards and nutritional factors, the principles were not elaborated specifically for whole foods.
4. The risk analysis approach can, in general terms, be applied to foods including foods derived from modern biotechnology. However, it is recognised that this approach must be modified when applied to a whole food rather than to a discrete hazard that may be present in food.
5. The principles presented in this document should be read in conjunction with the Codex Working Principles for Risk Analysis to which these principles are supplemental.
6. Where appropriate, the results of a risk assessment undertaken by other regulatory authorities may be used to assist in the risk analysis and avoid duplication of work.

SECTION 2 – SCOPE AND DEFINITIONS

7. The purpose of these Principles is to provide a framework for undertaking risk analysis on the safety and nutritional aspects of foods derived from modern biotechnology. This document does not address environmental, ethical, moral and socio-economic aspects of the research, development, production and marketing of these foods³.
8. The definitions below apply to these Principles:
“**Modern Biotechnology**” means the application of:
 - (i) *In vitro* nucleic acid techniques, including recombinant deoxyribonucleic acid (DNA) and direct injection of nucleic acid into cells or organelles, or

¹ These decisions include the *Statements of principle concerning the role of science in the Codex decision-making process and the extent to which other factors are taken into account* and the *Statements of principle relating to the role of food safety risk assessment* (Codex Alimentarius Commission Procedural Manual; Twelfth edition).

² Currently under consideration at Step 3 in CCGP (ALINORM 01/33 APPENDIX III, Report of the Fifteenth Session of the Codex Committee on General Principles).

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

(ii) Fusion of cells beyond the taxonomic family, that overcome natural physiological reproductive or recombinant barriers and that are not techniques used in traditional breeding and selection⁴.

“**Conventional Counterpart**” means a related organism/variety, its components and/or products for which there is experience of establishing safety based on common use as food⁵.

SECTION 3 – PRINCIPLES

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

RISK ASSESSMENT

10. Risk assessment includes a safety assessment, which is designed to identify whether a hazard, nutritional or other safety concern is present, and if present, to gather information on its nature and severity. The safety assessment should include a comparison between the food derived from modern biotechnology and its conventional counterpart focusing on determination of similarities and differences. If a new or altered hazard, nutritional or other safety concern is identified by the safety assessment, the risk associated with it should be characterized to determine its relevance to human health.
11. A safety assessment is characterized by an assessment of a whole food or a component thereof relative to the appropriate conventional counterpart:
- a) taking into account both intended and unintended effects;
 - b) identifying new or altered hazards;
 - c) identifying changes, relevant to human health, in key nutrients.
12. A pre-market safety assessment should be undertaken following a structured and integrated approach and be performed on a case-by-case basis. The data and information, based on sound science, obtained using appropriate methods and analysed using appropriate statistical techniques, should be of a quality and, as appropriate, of quantity that would withstand scientific peer review.
13. Risk assessment should apply to all relevant aspects of foods derived from modern biotechnology. The risk assessment approach for these foods is based on a consideration of science-based multidisciplinary data and information taking into account the factors mentioned in the accompanying Guidelines⁶.
14. Scientific data for risk assessment are generally obtained from a variety of sources, such as the developer of the product, scientific literature, general technical information, independent scientists, regulatory agencies, international bodies and other interested parties. Data should be assessed using appropriate science-based risk assessment methods.
15. Risk assessment should take into account all available scientific data and information derived from different testing procedures, provided that the procedures are scientifically sound and the parameters being measured are comparable.

RISK MANAGEMENT

16. Risk management measures for foods derived from modern biotechnology should be proportional to the risk, based on the outcome of the risk assessment and, where relevant, taking into account other

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

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

⁶ Reference is made to the Draft Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants and the Proposed Draft Guideline for the Conduct of Food Safety Assessment of Foods Produced using Recombinant-DNA Microorganisms.

legitimate factors in accordance with the general decisions of the Codex Alimentarius Commission (CAC)⁷ as well as the Codex Working Principles for Risk Analysis.

17. It should be recognised that different risk management measures may be capable of achieving the same level of protection with regard to the management of risks associated with safety and nutritional impacts on human health, and therefore would be equivalent.
18. Risk managers should take into account the uncertainties identified in the risk assessment and implement appropriate measures to manage these uncertainties.
19. Risk management measures may include, as appropriate, food labelling⁸, conditions for marketing approvals and post-market monitoring.
20. Post-market monitoring may be an appropriate risk management measure in specific circumstances. Its need and utility should be considered, on a case-by-case basis, during risk assessment and its practicability should be considered during risk management. Post-market monitoring may be undertaken for the purpose of:
 - A) verifying conclusions about the absence or the possible occurrence, impact and significance of potential consumer health effects; and
 - B) monitoring changes in nutrient intake levels, associated with the introduction of foods likely to significantly alter nutritional status, to determine their human health impact.
21. Specific tools may be needed to facilitate the implementation and enforcement of risk management measures. These may include appropriate analytical methods; reference materials; and, the tracing of products⁹ for the purpose of facilitating withdrawal from the market when a risk to human health has been identified or to support post-market monitoring in circumstances as indicated in paragraph 20.

RISK COMMUNICATION

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

CONSISTENCY

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

⁷ See footnote 1.

⁸ Reference is made to the CCFL in relation to the Proposed Draft Recommendations for the Labelling of Foods and Food Ingredients obtained through certain techniques of genetic modification/genetic engineering (proposed Draft Amendment to the General Standard for the Labelling of Prepacked Foods) at Step 3 of the procedures.

⁹ It is recognised that there are other applications of product tracing. These applications should be consistent with the provisions of the SPS and TBT Agreements. The application of product tracing to the areas covered by both Agreements is under consideration within Codex on the basis of decisions of 49th Session of Executive Committee.

data requirements, assessment frameworks, acceptable level of risk, communication and consultation mechanisms and timely decision processes.

CAPACITY BUILDING AND INFORMATION EXCHANGE

27. Efforts should be made to improve the capability of regulatory authorities, particularly those of developing countries, to assess, manage and communicate risks, including enforcement, associated with foods derived from modern biotechnology or to interpret assessments undertaken by other authorities or recognised expert bodies, including access to analytical technology. In addition capacity building for developing countries either through bilateral arrangements or with assistance of international organizations should be directed toward effective application of these principles¹⁰.
28. Regulatory authorities, international organisations and expert bodies and industry should facilitate through appropriate contact points including but not limited to Codex Contact Points and other appropriate means, the exchange of information including the information on analytical methods.

REVIEW PROCESSES

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

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

Appendix III

**DRAFT GUIDELINE FOR THE CONDUCT OF FOOD SAFETY ASSESSMENT OF
FOODS DERIVED FROM RECOMBINANT-DNA PLANTS**

(At Step 8 of the Elaboration Procedure)***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 Draft 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 food¹.

SECTION 3 - INTRODUCTION TO FOOD SAFETY ASSESSMENT

9. Traditionally, new varieties of food plants have not been systematically subjected to extensive chemical, toxicological, or nutritional evaluation prior to marketing, with the exception of foods for specific groups, such as infants, where the food may constitute a substantial portion of the diet. Thus, new varieties of corn, soya, potatoes and other common food plants are evaluated by breeders for agronomic and phenotypic characteristics, but generally, foods derived from such new plant varieties are not subjected to the rigorous and extensive food safety testing procedures, including studies in animals, that are typical of chemicals such as food additives or pesticide residues that may be present in food.
10. The use of animal models for assessing toxicological endpoints is a major element in the risk assessment of many compounds such as pesticides. In most cases, however, the substance to be tested is well characterised, of known purity, of no particular nutritional value, and, human exposure to it is generally low. It is therefore relatively straightforward to feed such compounds to animals at a range of doses some several orders of magnitude greater than the expected human exposure levels, in order to identify any potential adverse health effects of importance to humans. In this way, it is possible, in most cases, to estimate levels of exposure at which adverse effects are not observed and to set safe intake levels by the application of appropriate safety factors.
11. Animal studies cannot readily be applied to testing the risks associated with whole foods, which are complex mixtures of compounds, often characterised by a wide variation in composition and nutritional value. Due to their bulk and effect on satiety, they can usually only be fed to animals at low multiples of the amounts that might be present in the human diet. In addition, a key factor to consider in conducting animal studies on foods is the nutritional value and balance of the diets used, in order to avoid the induction of adverse effects which are not related directly to the material itself. Detecting any potential adverse effects and relating these conclusively to an individual characteristic of the food can therefore be extremely difficult. If the characterization of the food indicates that the available data are insufficient for a thorough safety assessment, properly designed animal studies could be requested on the whole foods. Another consideration in deciding the need for animal studies is whether it is appropriate to subject experimental animals to such a study if it is unlikely to give rise to meaningful information.
12. Due to the difficulties of applying traditional toxicological testing and risk assessment procedures to whole foods, a more focused approach is required for the safety assessment of foods derived from food plants, including recombinant-DNA plants. This has been addressed by the development of a multidisciplinary approach for assessing safety which takes into account both intended and unintended changes that may occur in the plant or in the foods derived from it, using the concept of *substantial equivalence*.
13. The concept of substantial equivalence is a key step in the safety assessment process. However, it is not a safety assessment in itself; rather it represents the starting point which is used to structure the safety assessment of a new food relative to its conventional counterpart. This concept is used to identify similarities and differences between the new food and its conventional counterpart². 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.

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

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

UNINTENDED EFFECTS

14. In achieving the objective of conferring a specific target trait (intended effect) to a plant by the insertion of defined DNA sequences, additional traits could, in some cases, be acquired or existing traits could be lost or modified (unintended effects). The potential occurrence of unintended effects is not restricted to the use of *in vitro* nucleic acid techniques. Rather, it is an inherent and general phenomenon that can also occur in conventional breeding. Unintended effects may be deleterious, beneficial, or neutral with respect to the health of the plant or the safety of foods derived from the plant. Unintended effects in recombinant-DNA plants may also arise through the insertion of DNA sequences and/or they may arise through subsequent conventional breeding of the recombinant-DNA plant. Safety assessment should include data and information to reduce the possibility that a food derived from a recombinant-DNA plant would have an unexpected, adverse effect on human health.
15. Unintended effects can result from the random insertion of DNA sequences into the plant genome which may cause disruption or silencing of existing genes, activation of silent genes, or modifications in the expression of existing genes. Unintended effects may also result in the formation of new or changed patterns of metabolites. For example, the expression of enzymes at high levels may give rise to secondary biochemical effects or changes in the regulation of metabolic pathways and/or altered levels of metabolites.
16. Unintended effects due to genetic modification may be subdivided into two groups: those that are "predictable" and those that are "unexpected". Many unintended effects are largely predictable based on knowledge of the inserted trait and its metabolic connections or of the site of insertion. Due to the expanding information on plant genome and the increased specificity in terms of genetic materials introduced through recombinant-DNA techniques compared with other forms of plant breeding, it may become easier to predict unintended effects of a particular modification. Molecular biological and biochemical techniques can also be used to analyse potential changes at the level of gene transcription and message translation that could lead to unintended effects.
17. The safety assessment of foods derived from recombinant-DNA plants involves methods to identify and detect such unintended effects and procedures to evaluate their biological relevance and potential impact on food safety. A variety of data and information are necessary to assess unintended effects because no individual test can detect all possible unintended effects or identify, with certainty, those relevant to human health. These data and information, when considered in total, provide assurance that the food is unlikely to have an adverse effect on human health. The assessment for unintended effects takes into account the agronomic/phenotypic characteristics of the plant that are typically observed by breeders in selecting new varieties for commercialization. These observations by breeders provide a first screen for plants that exhibit unintended traits. New varieties that pass this screen are subjected to safety assessment as described in Sections 4 and 5.

FRAMEWORK OF FOOD SAFETY ASSESSMENT

18. The safety assessment of a food derived from a recombinant-DNA plant follows a stepwise process of addressing relevant factors that include:
 - A) Description of the recombinant-DNA plant;
 - B) Description of the host plant and its use as food;
 - C) Description of the donor organism(s);
 - D) Description of the genetic modification(s);
 - E) Characterization of the genetic modification(s);
 - F) Safety assessment:
 - a) expressed substances (non-nucleic acid substances);
 - b) compositional analyses of key components;
 - c) evaluation of metabolites ;
 - d) food processing;

- e) nutritional modification; and
 - G) Other considerations.
19. In certain cases, the characteristics of the product may necessitate development of additional data and information to address issues that are unique to the product under review.
 20. Experiments intended to develop data for safety assessments should be designed and conducted in accordance with sound scientific concepts and principles, as well as, where appropriate, Good Laboratory Practice. Primary data should be made available to regulatory authorities at request. Data should be obtained using sound scientific methods and analysed using appropriate statistical techniques. The sensitivity of all analytical methods should be documented.
 21. The goal of each safety assessment is to provide assurance, in the light of the best available scientific knowledge, that the food does not cause harm when prepared, used and/or eaten according to its intended use. The expected endpoint of such an assessment will be a conclusion regarding whether the new food is as safe as the conventional counterpart taking into account dietary impact of any changes in nutritional content or value. In essence, therefore, the outcome of the safety assessment process is to define the product under consideration in such a way as to enable risk managers to determine whether any measures are needed and if so to make well-informed and appropriate decisions.

SECTION 4 - GENERAL CONSIDERATIONS

DESCRIPTION OF THE RECOMBINANT-DNA PLANT

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

DESCRIPTION OF THE HOST PLANT AND ITS USE AS FOOD

23. A comprehensive description of the host plant should be provided. The necessary data and information should include, but need not be restricted to:
 - A) common or usual name; scientific name; and, taxonomic classification;
 - B) history of cultivation and development through breeding, in particular identifying traits that may adversely impact on human health ;
 - C) information on the host plant's genotype and phenotype relevant to its safety, including any known toxicity or allergenicity; and
 - D) history of safe use for consumption as food.
24. Relevant phenotypic information should be provided not only for the host plant, but also for related species and for plants that have made or may make a significant contribution to the genetic background of the host plant.
25. The history of use may include information on how the plant is typically cultivated, transported and stored, whether special processing is required to make the plant safe to eat, and the plant's normal role in the diet (e.g. which part of the plant is used as a food source, whether its consumption is important in particular subgroups of the population, what important macro- or micro-nutrients it contributes to the diet).

DESCRIPTION OF THE DONOR ORGANISM(S)

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

- A) its usual or common name;
- B) scientific name;
- C) taxonomic classification;
- D) information about the natural history as concerns food safety;
- E) information on naturally occurring toxins, anti-nutrients and allergens; for microorganisms, additional information on pathogenicity and the relationship to known pathogens; and
- F) information on the past and present use, if any, in the food supply and exposure route(s) other than intended food use (e.g. possible presence as contaminants).

DESCRIPTION OF THE GENETIC MODIFICATION(S)

27. Sufficient information should be provided on the genetic modification to allow for the identification of all genetic material potentially delivered to the host plant and to provide the necessary information for the analysis of the data supporting the characterization of the DNA inserted in the plant.
28. The description of the transformation process should include:
- A) information on the specific method used for the transformation (e.g. *Agrobacterium*-mediated transformation);
 - B) information, if applicable, on the DNA used to modify the plant (e.g. helper plasmids), including the source (e.g. plant, microbial, viral, synthetic), identity and expected function in the plant; and
 - C) intermediate host organisms including the organisms (e.g. bacteria) used to produce or process DNA for transformation of the host organism;
29. Information should be provided on the DNA to be introduced, including:
- A) the characterization of all the genetic components including marker genes, regulatory and other elements affecting the function of the DNA;
 - B) the size and identity;
 - C) the location and orientation of the sequence in the final vector/construct; and
 - D) the function.

CHARACTERIZATION OF THE GENETIC MODIFICATION(S)

30. In order to provide clear understanding of the impact on the composition and safety of foods derived from recombinant-DNA plants, a comprehensive molecular and biochemical characterization of the genetic modification should be carried out.
31. Information should be provided on the DNA insertions into the plant genome; this should include:
- A) the characterization and description of the inserted genetic materials;
 - B) the number of insertion sites;
 - C) the organisation of the inserted genetic material at each insertion site including copy number and sequence data of the inserted material and of the surrounding region, sufficient to identify any substances expressed as a consequence of the inserted material, or, where more appropriate, other information such as analysis of transcripts or expression products to identify any new substances that may be present in the food; and
 - D) identification of any open reading frames within the inserted DNA or created by the insertions with contiguous plant genomic DNA including those that could result in fusion proteins.
32. Information should be provided on any expressed substances in the recombinant-DNA plant; this should include:
- A) the gene product(s) (e.g. a protein or an untranslated RNA);

- B) the gene product(s)' function;
 - C) the phenotypic description of the new trait(s);
 - D) the level and site of expression in the plant of the expressed gene product(s), and the levels of its metabolites in the plant, particularly in the edible portions; and
 - E) where possible, the amount of the target gene product(s) if the function of the expressed sequence(s)/gene(s) is to alter the accumulation of a specific endogenous mRNA or protein.
33. In addition, information should be provided:
- A) to demonstrate whether the arrangement of the genetic material used for insertion has been conserved or whether significant rearrangements have occurred upon integration;
 - B) to demonstrate whether deliberate modifications made to the amino acid sequence of the expressed protein result in changes in its post-translational modification or affect sites critical for its structure or function;
 - C) to demonstrate whether the intended effect of the modification has been achieved and that all expressed traits are expressed and inherited in a manner that is stable through several generations consistent with laws of inheritance. It may be necessary to examine the inheritance of the DNA insert itself or the expression of the corresponding RNA if the phenotypic characteristics cannot be measured directly;
 - D) to demonstrate whether the newly expressed trait(s) are expressed as expected in the appropriate tissues in a manner and at levels that are consistent with the associated regulatory sequences driving the expression of the corresponding gene;
 - E) to indicate whether there is any evidence to suggest that one or several genes in the host plant has been affected by the transformation process; and
 - F) to confirm the identity and expression pattern of any new fusion proteins.

SAFETY ASSESSMENT

Expressed Substances (non-nucleic acid substances)

Assessment of possible toxicity

34. *In vitro* nucleic acid techniques enable the introduction of DNA that can result in the synthesis of new substances in plants. The new substances can be conventional components of plant foods such as proteins, fats, carbohydrates, vitamins which are novel in the context of that recombinant-DNA plant. New substances might also include new metabolites resulting from the activity of enzymes generated by the expression of the introduced DNA.
35. The safety assessment should take into account the chemical nature and function of the newly expressed substance and identify the concentration of the substance in the edible parts of the recombinant-DNA plant, including variations and mean values. Current dietary exposure and possible effects on population sub-groups should also be considered.
36. Information should be provided to ensure that genes coding for known toxins or anti-nutrients present in the donor organisms are not transferred to recombinant-DNA plants that do not normally express those toxic or anti-nutritious characteristics. This assurance is particularly important in cases where a recombinant-DNA plant is processed differently from a donor plant, since conventional food processing techniques associated with the donor organisms may deactivate, degrade or eliminate anti-nutrients or toxicants.
37. For the reasons described in Section 3, conventional toxicology studies may not be considered necessary where the substance or a closely related substance has, taking into account its function and exposure,

been consumed safely in food. In other cases, the use of appropriate conventional toxicology or other studies on the new substance may be necessary.

38. In the case of proteins, the assessment of potential toxicity should focus on amino acid sequence similarity between the protein and known protein toxins and anti-nutrients (e.g. protease inhibitors, lectins) as well as stability to heat or processing and to degradation in appropriate representative gastric and intestinal model systems. Appropriate oral toxicity studies³ 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.⁴
42. The newly expressed proteins in foods derived from recombinant-DNA plants should be evaluated for any possible role in the elicitation of gluten-sensitive enteropathy, if the introduced genetic material is obtained from wheat, rye, barley, oats, or related cereal grains.
43. The transfer of genes from commonly allergenic foods and from foods known to elicit gluten-sensitive enteropathy in sensitive individuals should be avoided unless it is documented that the transferred gene does not code for an allergen or for a protein involved in gluten-sensitive enteropathy.

Compositional Analyses of Key Components

44. Analyses of concentrations of key components⁵ 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

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

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

⁵ Key nutrients or key anti-nutrients are those components in a particular food that may have a substantial impact in the overall diet. They may be major constituents (fats, proteins, carbohydrates as nutrients or enzyme inhibitors as anti-nutrients) or minor compounds (minerals, vitamins). Key toxicants are those toxicologically significant compounds known to be inherently present in the plant, such as those compounds whose toxic potency and level may be significant to health (e.g. solanine in potatoes if the level is increased, selenium in wheat) and allergens.

may not be feasible at all times, in which case a line as close as possible should be chosen. The purpose of this comparison, in conjunction with an exposure assessment as necessary, is to establish that substances that are nutritionally important or that can affect the safety of the food have not been altered in a manner that would have an adverse impact on human health.

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

Evaluation of Metabolites

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

Food Processing

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

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

POTENTIAL ACCUMULATION OF SUBSTANCES SIGNIFICANT TO HUMAN HEALTH

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

USE OF ANTIBIOTIC RESISTANCE MARKER GENES

55. Alternative transformation technologies that do not result in antibiotic resistance marker genes in foods should be used in the future development of recombinant-DNA plants, where such technologies are available and demonstrated to be safe.
56. Gene transfer from plants and their food products to gut microorganisms or human cells is considered a rare possibility because of the many complex and unlikely events that would need to occur consecutively. Nevertheless, the possibility of such events cannot be completely discounted⁶.
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,

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

including neutral or alkaline stomach conditions and the need for enzyme cofactors (e.g. ATP) for enzymatic activity and estimated concentration of such factors in food.)

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

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

REVIEW OF SAFETY ASSESSMENTS

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

Appendix IV**Proposed Draft Annex on the Assessment of Possible Allergenicity of the Draft Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants**

(Advanced to Steps 5 and 8 of the Procedure)

Section 1 – Introduction

1. All newly expressed proteins¹ 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.

¹ 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 [Draft] 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 results². Validated search and evaluation procedures should be used in order to produce biologically meaningful results.
9. IgE cross-reactivity between the newly expressed protein and a known allergen should be considered a possibility when there is more than 35% identity in a segment of 80 or more amino acids (FAO/WHO 2001) or other scientifically justified criteria. All the information resulting from the sequence homology comparison between the newly expressed protein and known allergens should be reported to allow a case-by-case scientifically based evaluation.
10. Sequence homology searches have certain limitations. In particular, comparisons are limited to the sequences of known allergens in publicly available databases and the scientific literature. There are also limitations in the ability of such comparisons to detect non-contiguous epitopes capable of binding themselves specifically with IgE antibodies.
11. A negative sequence homology result indicates that a newly expressed protein is not a known allergen and is unlikely to be cross-reactive to known allergens. A result indicating absence of significant sequence homology should be considered along with the other data outlined under this strategy in assessing the allergenic potential of newly expressed proteins. Further studies should be conducted as appropriate (see also sections 4 and 5). A positive sequence homology result indicates that the newly expressed protein is likely to be allergenic. If the product is to be considered further, it should be assessed using serum from individuals sensitized to the identified allergenic source.

² 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.

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 potential³. 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 provided⁴.

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 individuals⁵. 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* protocols⁶. A positive result in such tests would indicate a potential allergen.

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.

³ The method outlined in the U.S. Pharmacopoeia (1995) was used in the establishment of the correlation (Astwood et al. 1996).

⁴ Report of Joint FAO/WHO Expert Consultation on Allergenicity of Foods Derived from Biotechnology (2001): Section "6.4 Pepsin Resistance"

⁵ 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.

⁶ *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)

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.

Appendix V

**PROPOSED DRAFT GUIDELINE FOR THE CONDUCT OF FOOD SAFETY
ASSESSMENT OF FOODS PRODUCED USING RECOMBINANT-DNA
MICROORGANISMS**

(At Step 5 of the Elaboration Procedure)

SECTION 1 – SCOPE

1. This Guideline supports the Principles for the Risk Analysis of Foods Derived from Modern Biotechnology and addresses safety aspects of foods produced through the actions of recombinant-DNA microorganisms.¹ The recombinant-DNA microorganisms that are used to produce these foods are typically derived using the techniques of modern biotechnology from strains that have a history of safe, purposeful use in food production. However, in instances where the recipient strains do not have a history of safe use their safety will have to be established.² Such food and food ingredients contain viable or non-viable recombinant-DNA microorganisms or may be produced by fermentation using recombinant-DNA microorganisms from which the recombinant-DNA microorganisms may have been removed.
2. Recognizing that the following issues may have to be addressed by other bodies or other instruments, this document does not address:
 - safety of microorganisms used in agriculture (for plant protection, biofertilizers, in animal feed or food derived from animals fed the feed etc.);
 - risks related to environmental releases of recombinant-DNA microorganisms used in food production;
 - safety of substances produced by microorganisms that are used as additives or processing aids, including enzymes for use in food production;³
 - specific purported health benefits or probiotic effects that may be attributed to the use of microorganisms in food; or
 - issues relating to the safety of food production workers handling recombinant-DNA microorganisms.
3. A variety of microorganisms used in food production have a long history of safe use that predates scientific assessment. Few microorganisms have been assessed scientifically in a manner that would fully characterize all potential risks associated with the food they are used to produce, including, in some instances, the consumption of viable microorganisms. Microorganisms are amenable to modification using recombinant-DNA technology and new strains can be rapidly developed due to their rapid growth rates. Furthermore, 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 specific chemical or microbial contaminants that have identifiable hazards and risks; they were not originally intended to apply to intentional uses of microorganisms in food processing or in the foods transformed by microbial fermentations. The safety assessments that have been conducted have focused primarily on the absence of properties associated with pathogenicity in these organisms and the absence of reports of adverse events attributed to ingestion of these organisms, rather than evaluating the results of prescribed studies. Further, many foods contain

¹ The microorganisms included in these applications are bacteria, yeasts, and filamentous fungi. (Such uses include, but are not limited to, production of yogurt, cheese, fermented sausages, natto, kimchi, bread, beer, and wine.)

² The criterion for establishing the safety of microorganisms used in the production of foods where there is no history of safe use is beyond the scope of the current document.

³ The Working Group noted that the Joint FAO/WHO Committee on Food Additives (JECFA) is revising guidelines for General Specifications and Considerations for Enzyme Preparations used in food processing. These guidelines have been used to evaluate enzyme preparations derived from genetically modified microorganisms.

substances that would be considered harmful if subjected to conventional approaches to safety testing. Thus, an alternative approach is required where the safety of a whole food is being considered.

4. Information considered in developing this approach includes:
 - A) uses of living microorganisms in food production;
 - B) consideration of the types of genetic modifications likely to have been made in these organisms;
 - C) the types of methodologies available for performing a safety assessment;
 - D) issues specific to microorganisms used in food production, including their genetic stability, gene transfer, colonization of the intestinal tract and persistence therein and, interactions with the recombinant-DNA microorganism, the gastrointestinal flora and the mammalian host, and impacts on the immune system.
5. This approach is based on the principle that the safety of foods produced using recombinant-DNA microorganisms is assessed relative to the conventional counterparts that have a history of safe use, not only for the food produced using a recombinant-DNA microorganism, but also for the microorganism itself. This approach takes both intended and unintended effects into account. Rather than trying to identify every hazard associated with a particular food or the microorganism, the intention is to identify new or altered hazards relative to the conventional counterpart.
6. 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 or component of food, such as a microorganism used in production, 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.
7. The Guideline describes approaches recommended for making safety assessments of foods produced using recombinant-DNA microorganisms, using comparison to a conventional counterpart. The safety assessment will focus on the safety of the recombinant-DNA microorganisms used in food production, [or] and, where appropriate, on metabolites produced by the action of recombinant-DNA microorganisms on food. The Guideline identifies the data and information that are generally applicable to making such assessments. While this Guideline is designed for foods produced using recombinant-DNA microorganisms or their components, the approach described could, in general, be applied to foods produced using microorganisms that have been altered by other techniques. [On the condition that the microorganism is considered to be safe when compared with the conventional counterpart taking into account its interactions with the food matrix or the microflora, that any newly expressed protein(s) encoded by the modified DNA is considered to be safe, and that any secondary metabolic products present as a consequence of the genetic modifications are deemed to be safe, it is unlikely that the food produced by the microorganism would be harmful to human health.]

SECTION 2 – DEFINITIONS

8. The definitions below apply to this Guideline:

“Recombinant-DNA Microorganism” - means bacteria, yeasts or filamentous fungi in which the genetic material has been changed through in vitro nucleic acid techniques⁴ including recombinant deoxyribonucleic acid (DNA) and direct injection of nucleic acid into cells or organelles.

“Conventional Counterpart”⁵ – means:

- a microorganism/strain used for food production or processing related to the recombinant-DNA strain with a known history of safe use in producing the food to be produced by the recombinant-DNA microorganism. The microorganism may be viable in the food or may be removed in processing or rendered non-viable during processing; or
- food produced using the traditional food production microorganisms for which there is experience of establishing safety based on common use in food production.

SECTION 3 - INTRODUCTION TO FOOD SAFETY ASSESSMENT

9. Most foods produced as a result of the purposeful growth of microorganisms have their origins in antiquity, and have been deemed safe long before the emergence of scientific methods for assessing safety. Microorganisms possess properties, such as fast growth rates, that enable genetic modifications, whether employing conventional techniques or modern biotechnology, to be implemented in short time frames. Microorganisms used in food production derived using conventional genetic techniques have not customarily been systematically subjected to extensive chemical, toxicological, epidemiological, or medical evaluations prior to marketing. Instead microbiologists, mycologists, and food technologists have evaluated new strains of bacteria, yeasts and filamentous fungi for phenotypic characteristics that are useful in relation to food production.
10. Safety assessments of recombinant-DNA microorganisms should document the use of related microorganisms in foods, the absence of properties known to be characteristic of pathogens in the recombinant-DNA microorganisms or the recipient strains used for constructing the recombinant-DNA microorganisms, and known adverse events involving the recipient or related organisms. In addition, when a recombinant DNA microorganism directly affects or remains in the food, the effects and safety of the food should be examined.
11. The use of animal models for assessing toxicological effects 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 characterized, 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.
12. Animal studies cannot readily be applied to testing the risks associated with whole foods, which are complex mixtures of compounds, and often characterized 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 that are not related directly to the material itself. Detecting any potential adverse effects and relating these conclusively to an individual characteristic

⁴ These include but are not limited to: recombinant-DNA techniques that use vector systems and techniques involving the direct introduction into the organism of hereditary materials prepared outside the organism such as microinjection, macroinjection, chemoporation, electroporation, microencapsulation, and liposome fusion.

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

of the food can therefore be extremely difficult. 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.

13. Animal studies typically employed in toxicological evaluations also cannot be readily applied to testing potential risks associated with ingestion of microorganisms used for food production. Microorganisms are living entities, containing complex structures composed of many biochemicals, and therefore are not comparable to pure compounds. In some processed foods, they can survive processing and ingestion and can compete and, in some cases, be retained in the intestinal environment for significant periods of time. Appropriate animal studies should be used to evaluate the safety of recombinant-DNA microorganisms where the donor, or the gene or gene product do not have a history of safe use in food. Further, appropriately designed studies in animals may be used to assess the nutritional value of the food or the bioavailability of the newly expressed substance in the food.
14. Due to the difficulties of applying traditional toxicological testing and risk assessment procedures to whole foods produced using microorganisms, an alternative approach is required for the safety assessment of foods produced using microorganisms, including recombinant-DNA microorganisms. This has been addressed by the development of a multidisciplinary approach for assessing safety, that takes into account the intended effect, the nature of the modification, and detectable unintended changes that may occur in the microorganism or in its action on the food, using the concept of *substantial equivalence*⁵. While the focus of a safety assessment will be on the recombinant-DNA microorganism, additional information on its interaction with the food matrix should be taken into consideration when applying the concept of substantial equivalence, which is a key step in the safety assessment process. However, the concept of substantial equivalence is not a safety assessment in itself; rather it represents the starting point that is used to structure the safety assessment of [both] a recombinant-DNA microorganism relative to its conventional counterpart [as well as the food produced with the aid of the RDM relative to its conventional counterpart]. This concept is used to identify similarities and differences between a recombinant-DNA microorganism used in food processing and its conventional counterpart. Generally, the comparison should be between the recombinant-DNA microorganism and its recipient strain used in its development. [An evaluation of the differences between the recombinant-DNA microorganism and its conventional counterpart could be a starting point to address safety concerns.] However, there will be instances when the food or specific gene product(s) encoded by the modified DNA and produced by the recombinant DNA microorganism should be compared with the appropriate conventional counterpart. 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 recombinant-DNA microorganism can be considered relative to its conventional counterpart.

UNINTENDED EFFECTS

15. In achieving the objective of conferring a specific target trait (intended effect) to a microorganism by the addition, substitution, removal, or rearrangement of defined DNA sequences, including those used for the purpose of DNA transfer or maintenance in the recipient organism, additional traits could, in some cases, be acquired or existing traits could be lost or modified. Such unanticipated changes are referred to as unintended effects. The potential for 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 the development of strains using traditional genetic techniques and procedures, or from exposure of microorganisms to intentional or unintended selective pressures. Unintended effects may be deleterious, beneficial, or neutral with respect to competition

⁵ The concept of *substantial equivalence* as described in FAO /WHO Expert Consultation on Foods Derived from Biotechnology- Safety aspects of genetically modified plants, 29 May – 2 June, 2000, Geneva, Switzerland, and Section 4.3 of the Joint FAO/Who Expert Consultation of Foods Derived from Biotechnology,- Safety assessment of foods derived from genetically modified microorganisms, 24-28 September, 2001, Geneva, Switzerland.

with other microorganisms, ecological fitness of the microorganism, the microorganism's effects on humans after ingestion, or the safety of foods produced using the microorganism. Unintended effects in recombinant-DNA microorganisms may also arise through intentional modification of DNA sequences or they may arise through recombination or other natural events in the recombinant-DNA microorganism. [Safety assessment should include data and information to reduce the possibility that a food derived from a recombinant-DNA microorganism would have an unexpected, adverse effect on human health.]

16. Unintended effects can result from the insertion of DNA sequences new to a microorganism into the microbial genome; they may be compared with those observed following the activity of naturally occurring transposable genetic elements. Insertion of DNA may lead to changes in expression of genes in the genome of the recipient. The insertion of DNA from heterologous sources into a gene may also result in the synthesis of a chimeric protein, also referred to as a fusion protein. In addition genetic instability and its consequences need to be considered.
17. Unintended effects may also result in the formation of new or changed patterns of metabolites. For example, the expression of enzymes at high levels or the expression of an enzyme new to the organism may give rise to secondary biochemical effects, changes in the regulation of metabolic pathways, or altered levels of metabolites.
18. Unintended effects due to genetic modification may be subdivided into two groups: those that could be predicted and those that are "unexpected." Many unintended effects are largely predictable based on knowledge of the added trait, its metabolic consequences or of the site of insertion. Due to the expanding knowledge of microbial genomes and physiology, and the increased specificity in function of genetic materials introduced through recombinant-DNA techniques compared with other forms of genetic manipulation, it may become easier to predict unintended effects of a particular modification. Molecular biological and biochemical techniques can also be used to analyse changes that occur at the level of transcription and translation that could lead to unintended effects.
19. The safety assessment of foods produced using recombinant-DNA microorganisms 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 is 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, should provide assurance that the food is unlikely to have an adverse effect on human health. The assessment of unintended effects takes into account the biochemical, and physiological characteristics of the microorganism that are typically selected for improving strains for commercial food or beverage uses. These determinations provide a first screen for microorganisms that exhibit unintended traits. Recombinant-DNA microorganisms that pass this screen are subjected to safety assessment as described in Section 4.

FRAMEWORK OF FOOD SAFETY ASSESSMENT

20. The safety assessment of a food produced using a recombinant-DNA microorganism is based on determining the safety of using the microorganism, which follows a stepwise process of addressing relevant factors that include:
 - A) Description of the recombinant-DNA microorganism;
 - B) Description of the recipient microorganism and its use in food production;
 - C) Description of the donor organism(s);
 - D) Description of the genetic modification(s) including vector and construct;
 - E) Characterization of the genetic modification(s);
 - F) Safety assessment:
 - a. expressed substances including toxins or other traits related to pathogenicity (e.g., adhesins, invasins);

- b. compositional analyses of key components;
 - c. evaluation of metabolites;
 - d. effects of food processing;
 - e. assessment of immunological effects;
 - f. assessment of viability, viable population and residence of microorganisms in the human gut;
 - g. antibiotic resistance and gene transfer; and,
 - h. nutritional modification .
21. In certain cases, the characteristics of the microorganisms may necessitate generation 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 upon 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 will not cause harm when prepared or consumed according to its intended use, nor should the organism itself cause harm when viable organisms remain in the food. Safety assessments should address the health aspects for the whole population, including immunocompromised individuals, infants, and the elderly. 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. Where the microorganism is likely to be viable upon ingestion, the safety of the microorganism should be compared to a conventional counterpart taking into account residence of the recombinant-DNA microorganism in the GI tract. In essence, the outcome of the safety assessment process is to define the product under consideration in such a way as to enable risk managers to determine whether any measures are needed and if so to make well-informed and appropriate decisions.

SECTION 4- GENERAL CONSIDERATIONS

DESCRIPTION OF THE RECOMBINANT-DNA MICROORGANISM

24. A description of the bacterial, yeast, or fungal strain and the food being presented for safety assessment should be provided. This description should be sufficient to aid in understanding the intended differences in the nature of the organism or food produced using the organism being submitted for safety assessment[All recombinant-DNA microorganisms should be deposited into an international culture collection with appropriate identification using modern molecular methods.]

DESCRIPTION OF THE RECIPIENT MICROORGANISM AND ITS USE IN FOOD PRODUCTION

25. A comprehensive description of the recipient microorganism or microorganism subjected to the modification should be provided. Recipient microorganisms should have a history of safe use in food production or safe consumption in foods. Organisms that produce toxins, antibiotics or other substances that should not be present in food, or that bear genetic elements that could lead to genetic instability, or that are likely to contain genes conferring functions associated with pathogenicity (i.e., also known as pathogenicity islands or virulence factors) should not be considered for use as recipients. The necessary data and information should include, but need not be restricted to:
- A) Identity: scientific name, common name or other name(s) used to reference the microorganism, strain designation, information about the strain and its source, or accession numbers or other information from a recognized culture repository from which the organism or its antecedents may be obtained, if applicable, information supporting its taxonomical

- assignment;
- B) history of use and cultivation, known information about strain development (including isolation of mutations or antecedent strains used in strain construction); in particular, identifying traits that may adversely impact human health;
 - C) information on the recipient microorganism's genotype and phenotype relevant to its safety, including any known toxins, other factors related to pathogenicity, or immunological impact, and information about the genetic stability of the microorganism; and
 - D) history of safe use in food production.
26. Relevant phenotypic and genotypic information should be provided not only for the recipient microorganism, but also for related species and for any extrachromosomal genetic elements that contribute to the functions of the recipient strain, particularly if the related species are used in foods or involved in pathogenic effects in humans or other animals. Information on the genetic stability of the recipient microorganism should be considered when available including the presence of mobile DNA elements, i.e. insertion sequences, transposons, plasmids, and prophages.
27. The history of use may include information on how the recipient microorganism is typically grown, transported and stored, Quality Assurance measures typically employed, including those to verify strain identity and production specifications for microorganisms and foods, and whether these organisms remain viable in the processed food or are removed or rendered non-viable as a consequence of processing.

DESCRIPTION OF THE DONOR ORGANISM

28. Information should be provided on the donor organism(s) and any intermediate organisms, when applicable, and, when relevant, related organisms. It is particularly important to determine if the donor or intermediate organism(s) or other closely related species naturally exhibit characteristics of pathogenicity or toxin production, or have other traits that affect human health. The description of the donor or intermediate organism(s) should include:
- A) identity: scientific name, common name or other name(s) used to reference the microorganism, strain designation, information about the strain and its source, or accession numbers or other information from a recognized culture repository from which the organism or its antecedents may be obtained, if applicable, and information supporting its taxonomic assignment;
 - B) information about the organism or related organisms that concerns food safety;
 - C) information on the microorganisms' genotype and phenotype relevant to its safety including any known toxins, other factors related to pathogenicity, or immunological impact;
 - D) 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); and
 - E) information on opportunistic pathogenicity.

DESCRIPTION OF THE GENETIC MODIFICATION (S) INCLUDING VECTOR AND CONSTRUCT

29. Sufficient information should be provided on the genetic modification(s) to allow for the identification of genetic material potentially delivered to or modified in the recipient microorganism and to provide the necessary information for the analysis of the data supporting the characterization of the DNA added to, inserted into, modified in, or deleted from the microbial genome.
30. The description of the strain construction process should include:
- A) information on the specific method(s) used for genetic modification⁶;
 - B) information, on the DNA used to modify the microorganism, including the source (e.g., plant, microbial, viral, synthetic), identity and expected function in the recombinant-DNA

⁶ General mechanisms of genetic exchange have been specified in footnote 4. Mobile promoter elements or virus-mediated exchange events and processes may not yet be available but are equally as valid as the general categories listed.

- microorganism, and copy number for plasmids; and
C) intermediate recipient organisms including the organisms (*e.g.*, other bacteria or fungi) used to produce or process DNA prior to introduction into the final recipient organism.

31. Information should be provided on the DNA added, inserted, deleted, or modified, including:
- A) the characterization of all genetic components including marker genes, vector genes, regulatory and other elements affecting the function of the DNA;
 - B) the size and identity;
 - C) the location and orientation of the sequence in the final vector/construct; and
 - D) the function.

CHARACTERIZATION OF THE GENETIC MODIFICATION (S)

32. In order to provide clear understanding of the impact of the genetic modification on the composition and safety of foods produced using recombinant-DNA microorganisms, a comprehensive molecular and biochemical characterization of the genetic modification should be carried out. To facilitate the safety assessment, the DNA to be inserted should be limited to the sequences necessary to perform the intended functions.

33. Information should be provided on the DNA modifications in the recombinant DNA microorganism; this should include:

- A) the characterization and description of the added, inserted, deleted, or otherwise modified genetic materials, including plasmids or other carrier DNA used to transfer desired genetic sequences. This should include an analysis of the potential for mobilization of any plasmids or other genetic elements used, the locations of the added, inserted, deleted, or otherwise modified genetic materials (site on a chromosomal or extrachromosomal location); if located on a multicopy plasmid, the copy number of the plasmid;
- B) the number of insertion sites;
- C) the organization of the modified genetic material at each insertion site, including copy number, if applicable. Sequence data of the inserted material and of the surrounding region should be provided in electronic format to facilitate analysis using sequence databases;
- D) identification of any open reading frames within inserted DNA, or created by the modifications to contiguous DNA in the chromosome or in a plasmid, including those that could result in fusion proteins, and expression of fusion proteins; and
- E) particular reference to any sequences known to encode potentially harmful functions.

34. Information should be provided on any expressed substances in the recombinant-DNA microorganism; this should include, when applicable:

- A) the gene product(s) (*e.g.*, a protein or an untranslated RNA) or other information such as analysis of transcripts or expression products to identify any new substances that may be present in the food;
- B) the gene product's function;
- C) the phenotypic description of the new trait(s);
- D) the level and site of expression (intracellular, periplasmic - for Gram-negative bacteria, organellar - in eukaryotic microorganisms, secreted) in the microorganism of the expressed gene product(s), and, when applicable, the levels of its metabolites in the organism;
- E) the amount of the inserted gene product(s) if the function of the expressed sequence(s)/gene(s) is to alter the level of a specific endogenous mRNA or protein; and
- F) the absence of a gene product, or alterations in metabolites related to gene products, if applicable to the intended function(s) of the genetic modification(s).

35. In addition, information should be provided:

- A) to demonstrate whether the arrangement of the modified genetic material has been conserved⁷ or whether significant rearrangements have occurred after introduction to the cell and propagation of the recombinant strain to the extent needed for its use(s) in food production;
- 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 for the extent of propagation needed for its use(s) in food production and is consistent with laws of inheritance. It may be necessary to examine the inheritance of the inserted or modified DNA or the expression of the corresponding RNA if the phenotypic characteristics cannot be measured directly;⁸
- D) to demonstrate whether the newly expressed trait(s) is expressed as expected and targeted to the appropriate cellular location or is secreted in a manner and at levels that is 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 recipient microorganism has been affected by the modifications or the genetic exchange process; and
- F) to confirm the identity and expression pattern of any new fusion proteins.

SAFETY ASSESSMENT

[36. *In vitro* nucleic acid techniques enable the introduction of new DNA to cells or enable precise changes to DNA in cells, which can result in the synthesis of new substances in or by microorganisms, alterations to the substances produced by microorganisms, or the regulation of these substances. Methods for implementing precise genetic changes are readily available for application to microorganisms and DNA is easily integrated into microbial genomes. These can be normal cellular components such as proteins, fats, carbohydrates, or other compounds such as vitamins or metabolites that are not normally present or produced by the recipient organism. Conventional toxicology studies may not be considered necessary where the substance or a closely related substance has been consumed safely in food or used in food processing, taking into account its function and exposure. Effects of the recombinant-DNA microorganisms on the food matrix should be considered.]

Expressed Substances Including Toxins or Other Traits Related to Pathogenicity

37. When a substance is new to foods or food processing, the use of conventional toxicology studies or other applicable studies on the new substance will be necessary. This may require the isolation of the new substance from the recombinant-DNA microorganism, the food product if the substance is secreted, [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 microorganism.] Information on the anticipated exposure of consumers to the substance, the potential intake and dietary impact of the substance should be provided.
38. The safety assessment of the expressed substance should take into account its function and concentration in the food. The number of viable microorganisms remaining in the food should be also determined, compared to a conventional counterpart. All quantitative measurements should include variations and mean values. Current dietary exposure and possible effects on population sub-groups should also be considered.

⁷ Microbial genomes are more fluid than those of higher eukaryotes; that is, the organisms grow faster, adapt of changing environments, and are more prone to change. Chromosomal rearrangements are common. The general genetic plasticity of microorganisms may affect recombinant DNA in microorganisms and must be considered in evaluating the stability of recombinant DNA microorganisms.

⁸ Modified strains should be maintained by successive subculture or new culture to be used in an uninterrupted way during the successive productions in order to verify the genetic stability.]

- 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, siderophores) as well as stability to heat or processing and to degradation in appropriate representative gastric and intestinal model systems. Appropriate oral toxicity studies⁹ may be carried out in cases where the protein is present in the food, but is not similar to proteins that have been safely consumed in food, and has not previously been consumed safely in food, and taking into account its biological function in microorganisms where known.
 - Potential toxicity of non-protein substances that have not been safely consumed in food should be assessed in a case-by-case basis depending on the identity, concentration, and biological function of the substance and dietary exposure. The type of studies to be performed may include evaluations of metabolism, toxicokinetics, chronic toxicity/carcinogenicity, impact on reproductive function, and teratogenicity.
39. The newly expressed or altered properties should be shown to be unrelated to any characteristics of donor organisms that could be harmful to human health. 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 microorganisms that do not normally express those toxic or anti-nutritious characteristics.
- Additional *in vivo* or *in vitro* studies may be needed on a case-by-case basis to assess the toxicity of expressed substances, taking into account the potential accumulation of any substances, toxic metabolites or antibiotics that might result from the genetic modification.

Compositional Analyses of Key Components

40. Analyses of concentrations of key components¹⁰ of foods produced by recombinant-DNA microorganisms should be compared with an equivalent analysis of a conventional counterpart produced under the same conditions. The statistical significance of any observed differences should be assessed in the context of the range of natural variations for that parameter to determine its biological significance. Ideally, the comparator(s) used in this assessment should be food produced using the near isogenic parent strain. The purpose of this comparison, in conjunction with an exposure assessment as necessary, is to establish that substances that can affect the safety of the food have not been altered in a manner that would have an adverse impact on human health.

Evaluation of Metabolites

41. Some recombinant-DNA microorganisms may be modified in a manner that could result in new or altered levels of various metabolites in foods produced using these organisms. 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).
42. New or altered levels of metabolites produced by a recombinant-DNA microorganism may change the population of microorganisms in mixed culture, potentially increasing the risk for growth of harmful organisms or accumulation of harmful substances. Possible effects of genetic modification of a microorganism on other microorganisms should be assessed when a mixed culture of microorganisms is used for food processing, such as for production of natural cheese, miso, soy sauce, etc.

⁹ Guidelines for oral toxicity studies have been developed in international fora, for example the OECD Guidelines for the Testing of Chemicals.

¹⁰ 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 nutritional constituents (fats, proteins, carbohydrates), enzyme inhibitors as anti-nutrients, or minor compounds (minerals, vitamins). Key toxicants are those toxicologically significant compounds known to be produced by the microorganism, such as those compounds whose toxic potency and level may be significant to health. Microorganisms traditionally used in food processing are not usually known to produce such compounds under production conditions.

Effects of Food Processing

43. The potential effects of food processing, including home preparation, on foods produced using recombinant-DNA microorganisms 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. For example, in the case of yoghurt, information should be provided on the growth of the organism and culture conditions.

Assessment of immunological effects

44. When the protein(s) resulting from an inserted gene is present in the food, it should be assessed for its potential to cause allergy. The likelihood that individuals may already be sensitive to the protein and whether a protein new to the food supply will induce allergic reactions should be considered. A detailed presentation of issues to be considered is presented in [an annex for the proposed draft guideline for the conduct of food safety assessment of foods derived from recombinant-DNA plants¹¹][in the Annex to this guideline].

45. The transfer of genes from species that are commonly allergenic when ingested as food should be avoided, unless the proteins associated with allergy from those species have been identified and do not include the protein encoded by the transferred gene.

46. Recombinant-DNA microorganisms that remain viable in foods may interact with the immune system in the intestinal tract. Closer examination of these interactions will depend on the types of differences between the recombinant-DNA microorganism and its conventional counterpart.

Assessment of Viability and Residence of Microorganisms in the Human Gut

47. In some foods produced using recombinant-DNA microorganisms, ingestion of these microorganisms and their residence¹² may have an impact on the human intestinal tract. The need for further testing of such microorganisms should be based on the presence of their conventional counterpart in foods, and the nature of the intended and unintended effects of genetic modifications. If processing of the final food product eliminates viable microorganisms (by heat treatment in baking bread, for example), or if accumulations of endproducts toxic to the microorganism (such as alcohol or acids) eliminate viability, then viability and residence of microorganisms in the alimentary system need no examination.

48. For applications in which recombinant-DNA microorganisms used in production remain viable in the final food product, (for example, organisms in some dairy products), [it may be desirable to demonstrate the viability of the microorganism in the digestive tract in animal model systems or to establish the residence times for the microorganisms in the alimentary tract and how dose affects other microorganisms in the alimentary system] / [it is desirable to demonstrate the viability and colonization of the microorganism in the digestive tract as well as how dose affect other microorganisms in the alimentary system] / [the viability (or residence time) of the microorganism alone and within the respective food matrix in the digestive tract and the impact on the intestinal microflora should be examined in appropriate systems.] [The nature of the intended effects and the degree of differences from the conventional counterpart will determine the extent of such testing.]

¹¹ Codex Draft Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants (under development at Step 7) including the Proposed Draft Annex on the Assessment of Possible Allergenicity of the Draft Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants (under development at Step 4).

¹² Permanent life-long colonization by ingested microorganisms is rare. Some orally administered microorganisms have been recovered in faeces or in the colonic mucosa weeks after feeding ceased. Residence connotes survival of microorganisms in the GI tract longer than two intestinal transit times (International Life Science Institute, *The safety assessment of viable genetically modified microorganisms used as food*, 1999, Brussels; WHO/FAO Joint Expert Consultation on Foods Derived from Biotechnology- *Safety assessment of foods derived from genetically modified microorganisms*, 24-28 September, 2001, Geneva, Switzerland).

Antibiotic Resistance and Gene Transfer

49. In general, traditional strains of microorganisms developed for food processing uses have not been assessed for antibiotic resistance. Many microorganisms used in food production possess intrinsic resistance to specific antibiotics. Such properties need not exclude such strains from consideration as recipients in constructing recombinant-DNA microorganisms. However, strains with transmissible antibiotic resistance should be avoided [when such a resistance is present in genetic elements] as candidate recipients for constructing recombinant-DNA strains. The absence of plasmids, transposons, and integrons containing such resistance genes should be [verified].
50. Alternative technologies, demonstrated to be safe, that do not rely on antibiotic resistance marker genes in viable microorganisms present in foods should be used for selection purposes in recombinant-DNA microorganisms. In general, use of antibiotic resistance markers for constructing intermediate strains should pose no significant hazards that would exclude the use of the ultimate strains in food production, provided that the antibiotic resistance marker genes have been removed from the final construct.
51. Transfer of plasmids and genes between the resident intestinal microflora and ingested recombinant-DNA microorganisms may occur. The possibility and consequences of gene transfer from recombinant-DNA microorganisms and food products produced by recombinant-DNA microorganisms to gut microorganisms or human cells should also be considered. Transferred DNA would be unlikely to be maintained in the absence of selective pressure. Nevertheless, the possibility of such events cannot be completely discounted.
52. In order to minimize the possibility of gene transfer, the following steps should be considered:
- chromosomal integration of the inserted genetic material may be preferable to localization on a plasmid;
 - genes that could provide a selective advantage [under the condition in which the recombinant microorganisms is used in the food production and stays viable in the human GI tract after its consumption,] should be avoided in constructing the introduced genetic material; and,
 - sequences that mediate integration into other genomes should be avoided in constructing the introduced genetic material.

Nutritional Modification

53. The assessment of possible compositional changes to key nutrients, which should be conducted for all foods produced using recombinant-DNA microorganisms, has already been addressed under 'Compositional analyses of key components.' If such modifications have been implemented, the food should be subjected to additional testing 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.
54. 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 produced using the recombinant-DNA microorganism. 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.

55. The use of modern biotechnology to change nutrient levels in foods produced using microorganisms could result in broad changes to the nutrient profile. The intended modification in the microorganism could alter the overall nutrient profile of the product, which, in turn, could affect the nutritional status of individuals consuming the food. The impact of changes that could affect the overall nutrient profile should be determined.
56. When the modification results in a food product 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 whose nutritional composition is closer to that of the food produced using the recombinant-DNA microorganism) as appropriate comparators to assess the nutritional impact of the food.
57. Some foods may require additional testing. For example, animal-feeding studies may be warranted for foods produced using recombinant-DNA microorganisms 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 an assessment beyond the scope of these guidelines such as 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.

REVIEW OF SAFETY ASSESSMENTS

58. The goal of the safety assessment is a conclusion as to whether the food produced using a recombinant-DNA microorganism 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.