codex alimentarius commission

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS

WORLD HEALTH ORGANIZATION

JOINT OFFICE: Viale delle Terme di Caracalla 00100 ROME Tel: 39 06 57051 www.codexalimentarius.net Email: codex@fao.org Facsimile: 39 06 5705 4593

ALINORM 03/34A

JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX ALIMENTARIUS COMMISSION

Twenty-sixth Session

Rome, Italy 30 June - 7 July 2003

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

Yokohama, Japan 11-14 March 2003

Note: This document incorporates Codex Circular Letter CL 2003/12-FBT

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CL 2003/12- FBT
April 2003

To: Codex Contact Points
Interested International Organizations

From: Secretary, Codex Alimentarius Commission, Joint FAO/WHO Food Standards Programme, Viale delle Terme di Caracalla, 00100 Rome, Italy

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

MATTERS FOR ADOPTION BY THE 26TH SESSION OF THE CODEX ALIMENTARIUS COMMISSION

Draft Guideline for Microorganisms at Step 8 of the Procedure

- Draft Guideline for the Conduct of Food Safety Assessment of Foods Produced Using Recombinant-DNA Microorganisms (para 63, Appendix II)

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, Joint FAO/WHO Food Standards Programme, Viale delle Terme di Caracalla, 00100 Rome, Italy (fax +39 06 57054593; e-mail codex@fao.org), **not later than 20 May 2003.**

SUMMARY AND CONCLUSIONS

The Fourth 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 agreed to advance the Draft Guideline for the Conduct of Food Safety Assessment of Foods Produced using Recombinant-DNA Microorganisms to Step 8 (para 63, Appendix II).

OTHER MATTERS OF INTEREST TO COMMISSION

-The Task Force had an open discussion on traceability.(para 64-80)

-The Task Force had an exchange of opinions on potential future work on the food safety assessment of foods derived from biotechnology.(para 81-86)

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

Yokohama, Japan 11-14 March 2003

INTRODUCTION

1. The Codex Ad Hoc Intergovernmental Task Force on Foods Derived from Biotechnology (CX/FBT) held its Fourth Session in Yokohama, Japan from 11 to 14 March 2003, by courtesy of the Government of Japan. The Session was presided over by Professor Hiroshi Yoshikura, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare. The Session was attended by 168 delegates and observers representing 34 members countries and 3 international intergovernmental and 19 non-governmental organizations. A complete list of participants is included as Appendix I to this report.

OPENING OF THE SESSION

2. The Session was opened by Mr Yotaro Sawada, Vice-Minster of Health, Labour and Welfare, who welcomed the participants to Yokohama, Japan. He stressed that the food safety and consumer health had become a matter of serious consideration and that the safety of foods derived from biotechnology attracted considerable public concern. He expressed the wish that a worldwide consensus in this area could be reached as soon as possible.

3. In welcoming the delegates, the Representative of FAO, Mr. Ezzeddine Boutrif stated that biotechnology provides powerful tools for the sustainable development of agriculture, fisheries and forestry. When appropriately integrated with other technologies for the production of food, agricultural products and services, biotechnology can be of significant assistance in meeting the needs of an expanding and increasingly urbanised world population. However, for certain applications of biotechnology, in particular the production of genetically modified organisms, expected benefits must be analysed against its potential risks, both to human and animal health and to the environment. He emphasized the need for a strong scientific backing to all decisions concerning GM products. Mr. Boutrif, announced FAO's plan to conduct later in 2003, jointly with WHO, an expert consultation on safety assessment of foods derived from genetically modified animals, particularly fish. Mr. Boutrif thanked members of the Task Force for their hard work, and the Japanese Government for its excellent support. He expressed the wish that the spirit of consensus building that guided the work of the Task Force in previous sessions, would continue during the present session and invited the delegates to give thought to what needs to be done further to complement the international regulatory framework governing the production and distribution of foods derived from biotechnology.

4. The representative of WHO, Dr Jørgen Schlundt, Director, Food Safety Department gave a welcome address on behalf of the Director-General of the WHO. He mentioned that WHO has launched 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 consideration, and this report would be finalized

in the near future. He introduced that WHO has established a booklet entitled "20 Questions on Genetically Modified Foods" which gives information about GM foods using easy to understand language. Both representatives urged the Task Force to make maximum efforts to advance the finalization of the current draft text on its Agenda to respond to the pressing demand for the text.

ADOPTION OF THE AGENDA (AGENDA ITEM 1)[1]

5. The Task Force adopted the Provisional Agenda as the Agenda of the Session.

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

6. The Task Force noted that the 50th Session of the Codex Executive Committee had adopted "Proposed Draft Guideline for the Conduct of Food Safety Assessment of Foods Produced Using Recombinant-DNA Microorganisms" at Step 5.

7. The Task Force was informed that the "Definitions" in the Proposed Draft Recommendations for the Labelling of Foods obtained through Certain Techniques of Genetic Modification/Genetic Engineering, which were discussed by the Codex Committee on Food Labelling had been returned to Step 6 for further comments and discussion, and the rest of this text had been returned to Step 3 for further discussion.

8. The Task Force was also informed that the Codex Committee on Methods of Analysis and Sampling had discussed the "list of validated methods for the detection or identification of foods or food ingredients derived from biotechnology", which was forwarded from the Task Force, and had agreed that the criteria approach should be applied in the selection of methods of analysis for foods containing genetically modified material.

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)[3]

9. The Task Force noted that the information provided in document CX/FBT 03/3 introduced the current work carried out by relevant international organizations in the field of safety assessment of genetically modified organisms, especially those related to the Cartagena Protocol and OECD.

10. The Observer from the 49th Parallel Biotechnology Consortium expressed its opinion that the first sentence in paragraph 8 does not necessarily reflect the accurate status of the Cartagena Protocol due to the lack of a clear reference to the precautionary approach adopted in the Protocol.

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1 CX/FBT 03/1
2 CX/FBT 03/2
3 CX/FBT 03/3

CONSIDERATION OF DRAFT GUIDELINE FOR THE CONDUCT OF FOOD SAFETY ASSESSMENT OF FOODS PRODUCED USING RECOMBINANT-DNA MICROORGANISMS (AGENDA ITEM 4)[4]

11. The Task Force recalled that the 50th Session of the Codex Executive Committee had adopted the "Proposed Draft Guideline for the Conduct of Food Safety Assessment of Foods Produced Using Recombinant-DNA Microorganisms" at Step 5.

12. The Task Force recalled that in the last session a number of unresolved issues remained which the Task Force decided to put in brackets due to lack of time for discussion. However, the Task Force noted there was general support for the text, expressed by many delegations.

SECTION 1 - SCOPE

13. The Task Force had extensive discussions on several proposals to expand the Scope. First, the Task Force considered the proposal to include "microalgae" in footnote 1 of paragraph 1. However, the Task Force did not agree with this inclusion as the opinions diverged among delegations and observers as to the history of safe use of"microalgae" as food. It was also noted that they were not included in the definition used for the purpose of the FAO/WHO Expert Consultation.

14. In Paragraph 2, the Task Force also discussed proposals to include in the scope "indirect exposure" of recombinant-DNA microorganisms or their products either through the use in agricultural production or release into the environment as well as food additives and processing aids produced from recombinant-DNA microorganisms or their products. After an exchange of opinions, the Task Force concluded it would not change the scope as the entire text of the draft guideline had already been developed to conduct safety assessment of foods produced using recombinant DNA microorganisms where recipient strains had a history of safe use and therefore inclusion of those items would require different elements of safety assessment. It was also pointed out that the scope should not be changed from that adopted by the FAO/WHO Expert Consultation on Safety Assessment of Foods Derived from Genetically Modified Microorganisms as the present guideline was based on the scientific considerations by this consultation. However, the Task Force recognized the importance of these issues and the necessity to address them as future work in appropriate international bodies including the Codex Alimentarius Commission and its subsidiary bodies.

15. The Task Force deleted the third sentence in paragraph 3 "Microorganisms are amenable to modification using recombinant-DNA technology and new strains can be rapidly developed due to their rapid growth rates." as it was not necessary.

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[4] ALINORM 03/34 Appendix V; CL 2002/40-FBT; CX/FBT 03/4 (Comments of Brazil, Canada, Cuba, France, Netherlands, New Zealand, South Africa, Spain, Sweden, CI); CX/FBT 03/4 Add.1 (Comments of Denmark, Japan, United Kingdom, United States of America); CX/FBT 03/4 Add.2 (Comment of Iran (Islamic Republic of)); CRD 1 and 2 (Amendment of French text); CRD 3 and 4 (Amendment of Spanish text); CRD 5 (Comment of Argentina); CRD 6 (Comment of Italy); CRD 7 (Comment of Japan); CRD 8 (Comment of Spain); CRD 10 (Comment of Philippine); CRD 11 (Comment of Australia); CRD 12 (Comment of Republic of Korea); CRD 13 (Comment of Mexico); CRD 14 (Working Group on paragraph 7); CRD 16 (Working Group on paragraph 24); CRD 17 (Working Group on paragraph 33)

16. The Task Force revised sub-paragraph D of paragraph 4 on the issues specific to microorganisms to improve its clarity.

17. For paragraph 5 and several following paragraphs, the Observer from the 49th Parallel Biotechnology Consortium expressed its concern over the approach adopted throughout the text, which according to the Observer, would conduct safety assessment mainly from the information on the introduced genes.

18. The Task Force agreed to include paragraph 20 from the Draft Principles for the Risk Analysis of Foods Derived from Modern Biotechnology on the "Post Market Monitoring" after paragraph 6 as a new paragraph to ensure consistency between the two guidelines.

19. In paragraph 7 (paragraph 8 in the new text), the Task Force agreed to delete the term [or] and the square brackets in the second sentence, that should read "the safety assessment will focus on the safety of the recombinant-DNA microorganism used in food production, and, where appropriate, on metabolites…".

20. The Task Force had an extensive discussion on the last part of the paragraph, that had been retained in square brackets at the last session. Some delegations and observers pointed out that the sentence reflected an inappropriate application of the concept of substantial equivalence as an end point and that it was not sufficient to ensure the safety of foods produced from recombinant-DNA microorganisms. They pointed out that even if the microorganism, the newly expressed protein and the secondary metabolite were safe, the food should not necessarily be considered as safe, especially due to the complex interaction of the microorganism with the food. Some delegations also pointed out that the sentence was not clear and repeated some provisions that were already included in other sections.

21. Other delegations proposed to retain the sentence as it addressed the main elements of the safety assessment that were further developed further in the document, and was consistent with its main recommendations in this respect. The Task Force discussed proposals for clarification put forward by the Delegations of Canada and Japan. The Representative of WHO pointed out that all aspects relevant to safety should be taken into account and proposed to rearrange the sentence accordingly in order to facilitate a compromise.

22. Following further discussion and a meeting of an informal drafting group, the Task Force considered a compromise text[5]. The Task Force agreed that the differences identified in the recombinant-DNA microorganism or the food produced using the microorganism should be taken into account, whether they were the result of intended or unintended effects. The Task Force also agreed that due consideration should be given to the interaction of the microorganism with the food matrix or the microflora and to the safety of any newly expressed protein(s) and secondary metabolic products. The Task Force agreed to delete the last sentence of the proposed text that referred to the result of the comparison with the conventional counterpart as it was addressed in another section (paragraph 24 (paragraph 26 in the new text)).

23. The revised text was inserted after the third sentence of the paragraph rather than at the end in order to improve the logical sequence of the text.

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[5] CRD 14 (Working Group on paragraph 7)

SECTION 2 - DEFINITIONS

24. In paragraph 8 “Definition” (paragraph 9 in the new text), the Task Force agreed to reword the definition of “Conventional Counterpart” for clarification purposes and to delete Footnote 4 as it was not necessary to list specific techniques.

SECTION 3 - INTRODUCTION TO FOOD SAFETY ASSESSMENT

25. The Task Force decided to modify paragraph 10 (paragraph 11 in the new text) by replacing the wording "the effect and safety" with "any effect on the safety" in order to clearly identify the effects concerned.

26. In paragraph 12 (paragraph 13 in the new text), the Task Force agreed to insert a sentence regarding the need for animal studies when available data are insufficient on the characteristics of foods produced by using genetically modified microorganisms, in order to maintain consistency with the Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants. Although the same sentences are found in paragraphs 13 and 57 (paragraphs 14 and 59 in the new text), the Task Force agreed that it was necessary to include this text in paragraph 12 (paragraph 13 in the new text) as the issue addressed was different.

27. In paragraph 13 (paragraph 14 in the new text), the Delegation of the United States proposed to amend the text to reflect that animal studies were not necessary in all cases when the donor organism was not a food source organism. Some delegations and observers, however, expressed the view that the current text should be retained to ensure adequate consumer protection. After an exchange of views, the Task Force agreed that appropriate animal studies should be used as indicated in the current text with the addition of the following clarification at the end of the sentence "taking into account available information regarding the donor and characterization of the modified genetic material and the gene product".

28. Regarding paragraph 14 (paragraph 15 in the new text), the first sentence was amended for clarification purposes and to ensure consistency with paragraph 3 concerning the approach to safety assessment, as proposed by the Representative of FAO. The Task Force also agreed that a new paragraph should start with the third sentence, as proposed by the Delegation of Japan, in order to make the text more easily readable.

29. The Task Force agreed with the proposal of the Delegation of the United States to clarify the fourth sentence concerning substantial equivalence as a starting point for safety assessment.

30. The Task Force discussed whether the seventh sentence should be deleted. It was noted that only the identification of the differences was mentioned elsewhere in the text, but not their evaluation and that this notion should be retained. After an exchange of views, it was agreed to indicate in the fifth sentence that the concept of substantial equivalence was used to identify similarities and differences “for evaluation”, in order to make it clear that these were two distinct processes. The seventh sentence was therefore deleted in order to simplify the text.

31. As a consequence of the rewording of the paragraph, the sixth and eighth sentences were also deleted in order to avoid duplication. The Task Force agreed to add a new sentence

to clarify the use of substantial equivalence that corresponded to a similar recommendation in paragraph 13 of the Draft Guidelines for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants, as proposed by the Delegation of Belgium.

32. The Task Force agreed that the comparison to the conventional counterpart should apply not only to the recombinant-DNA microorganism but also to the food produced using the microorganism. The text was therefore amended accordingly in this paragraph and throughout the document where relevant.

Unintended Effects

33. In paragraph 15 (paragraph 17 in the new text), the Task Force agreed to delete the second sentence. The Task Force discussed differences between "unintended effect" and "unexpected effect", and agreed that these two terms have different meanings and retained these two words as currently used. After some discussion, the Task Force agreed to retain the last sentence deleting square brackets, in order to ensure consistency with the Draft Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants.

Framework of Food Safety Assessments

34. In paragraph 20 (paragraph 22 in the new text), the Task Force reviewed the titles of sections a) to f) describing the factors that should be considered under section F) Safety Assessment in conjunction with the text of the respective sections, and agreed that points a) and f) should read as follows:

    a) expressed substances: assessment of potential toxicity and other traits related to pathogenicity (see also paragraph 52)

    f) assessment of viability and residence of microorganisms in the human gastro-intestinal tract

35. In paragraph 22 (paragraph 24 in the new text), the Delegation of Brazil proposed to delete the last sentence as all analytical data had to be documented. However the Task Force agreed to retain the current sentence referring only to the sensitivity of the analytical method in consistency with the Draft Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants.

36. In paragraph 23 (paragraph 25 in the new text), the Task Force agreed that, in the case of viable microorganisms, the interaction with the gastrointestinal flora and the impact on the immune system should be considered where appropriate, and amended the sentence accordingly. In the last sentence it was agreed that the measures taken by risk managers were needed "to protect the health of consumers" and some editorial amendments were also made to the paragraph.

SECTION 4 – GENERAL CONSIDERATION

Description of the Recombinant-DNA Microorganism

37. The Task Force discussed extensively the last sentence of paragraph 24 (paragraph 26 in the new text) concerning the culture collections of recombinant DNA-microorganisms. Some delegations and observers proposed that all such microorganisms be deposited in an international culture collection, in order to ensure access to the original reference material. Some delegations and observers also proposed that the cultures should be made available to requesting parties. Other delegations expressed the view that it might adversely affect intellectual property rights, but that the cultures should be made available to regulatory authorities on request. The Representative of WHO indicated that in the scientific community these microorganisms were deposited in international collections and noted the importance of their availability for the purpose of public health protection.

38. Following an informal Working Group, the Task Force agreed on a compromise text[6] recommending that Recombinant DNA-Microorganisms should be conserved as stock cultures with appropriate identification using molecular methods, preferably in established culture collections, that they should be made available to regulatory authorities upon request, and noting that this may facilitate the review of the original safety assessment.

Description of the Recipient Microorganisms and its Use in Food Production

39. In paragraph 25 (paragraph 27 in the new text), the Task Force agreed to amend the introductory paragraph and section C) to reflect the need to consider antibiotics and antibiotic resistance factors. A reference to "safe consumption in food" was also added to the "history of safe use in food production" (section D), as proposed by the Delegation of Japan.

40. The Delegation of Australia proposed to add a new section (E) addressing culture parameters as these could affect the production of secondary metabolites and was therefore relevant for safety assessment. After an exchange of views, the Task Force agreed to add a simplified text referring to "relevant production parameters used to culture the recipient microorganism".

41. In paragraph 26 (paragraph 28 in the new text), the Task Force agreed to clarify that information on genetic stability should be considered including "as appropriate" the presence of mobile DNA elements.

Description of the Donor Organism (s)

42. In paragraph 28 (paragraph 30 in the new text), the Task Force agreed to delete the last section E) on opportunistic pathogenicity, as it was already covered in section C) and made some editorial amendments to ensure consistency with the rest of the document.

Description of the Genetic modification (s) including the Vector and Construct

43. In paragraph 29 (paragraph 31 in the new text), it was agreed that reference should be made to the identification of "all" genetic material for clarification purposes. In paragraph 30 B) (paragraph 32 B) in the new text), the Delegation of Iran proposed that the

[6] CRD 16 (Working Group on paragraph 24)

description of the strain construction process include the complete sequence of the transgene(s), plasmid or carrier DNA used during genetic modification of the microorganism. However, the Task Force agreed that this question should be addressed in the section on the characterization of the genetic modification in paragraph 33 (paragraph 35 in the new text).

44. The Task Force agreed to delete Footnote 6 as it was not necessary to list specific techniques and this would be consistent with its earlier decision to delete Footnote 4 in the Definitions.

Characterization of the Genetic Modification (s)

45. In paragraph 32 (paragraph 34 in the new text), the Delegation of Iran pointed out that as it was not always feasible to insert only the sequences necessary for the intended functions and the Task Force agreed that the DNA inserted should "preferably" be limited to those sequences.

46. The Task Force had an extensive discussion on the information to be provided on the DNA modification, as presented in paragraph 33 (paragraph 35 in the new text) and agreed to retain the current text of point A) but to concentrate on the revision of point C).

47. The Delegation of Iran expressed the view that the complete sequence of inserted material should be described and that the copy number should be required as a general requirement, not "if applicable". The Delegation of Australia proposed to follow more closely the approach taken in the Draft Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants and to delete the requirement concerning the sequence information in electronic format in order to allow more flexibility. The Delegation of the United States pointed out that the sequence did not always provide the information necessary for safety assessment and that other data had to be taken into account. Several delegations proposed that data should be provided on the material "inserted, modified or deleted", in order to address all types of genetic modifications. Following an informal working group[7] and further discussion, the Task Force agreed on a compromise text that referred to the sequence data of inserted, modified or deleted material, plasmides or carrier DNA, and the surrounding sequences; and recognized that this would enable the identification of any substances expressed in the process.

48. In point D), the Task Force agreed to delete the reference to "the expression of fusion protein" and to retain only "fusion protein" as proposed by some delegations to ensure consistency with the Draft Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants. The Task Force agreed that point E) should cover any sequences known to encode "or to influence the expression" of potentially harmful functions.

49. Some editorial amendments were made to paragraphs 34, 35 (paragraphs 36 and 37 in the new text) and footnote 8 for clarification purpose. A reference to the changes that may occur during storage was introduced in point A) of paragraph 35 (paragraph 37 in the new text), as proposed by the Delegation of Argentina.

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[7] CRD 17 (Working Group on paragraph 33)

Safety Assessment

50. The Task Force agreed to delete the three first sentences of paragraph 36 (paragraph 38 in the new text) as they were not directly relevant to recommendations on safety assessment. A new sentence concerning the need for a case by case safety assessment was introduced, as proposed by the Delegation of Germany.

51. The Task Force discussed the type of studies that were required where the substance or a closely related substance had been consumed safely in food. Some delegations and several observers expressed their concerns with the term "closely related" as this reflected the concept of substantial equivalence and they reiterated their earlier position that it would not provide adequate consumer protection. Several delegations pointed out that the notion of identity would be too restrictive and that "closely related substances" were mentioned in the Draft Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants. The Task Force agreed to insert the wording used in paragraph 37 (paragraph 39 in the new text) of the Draft Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants as it adequately addressed this issue. An additional sentence was included at the end of the paragraph concerning the need for properly designed animal or in vitro studies when available data were insufficient for a thorough safety assessment.

Expressed substances: Assessment of Potential Toxicity and Other Traits Related to Pathogenicity

52. The Delegation of Germany proposed to delete the reference to toxin and other traits related to pathogenicity in the title and to retain only "expressed substances" as this was the most important aspect. Other delegations noted that, as the text of the section did refer to toxins and pathogenicity, there was no contradiction with the title. After some discussion, the Task Force agreed with the proposal of the Delegation of Australia to refer to "assessment of potential toxicity" in the title rather than to "toxins".

53. In paragraph 37 (paragraph 39 in the new text), some delegations and observers proposed to delete the sentence in square brackets on the synthesis or production of the substance from an alternative source and indicated that this could be justified in the case of plants, but not for microbes. Several delegations however pointed out that the use of an alternative source was necessary to obtain sufficient material. The Task Force therefore agreed to retain the current text without square brackets and to add that the use of an alternative source may be required "if necessary".

54. In paragraph 38 (paragraph 40 in the new text), the Task Force agreed that all quantitative measurements should be analyzed using appropriate statistical techniques, as proposed by the Delegation of Sweden. In the first sub-paragraph, it was agreed that the assessment of potential toxicity should "take into account the structure and function of the protein". The Task Force agreed that oral toxicity studies may be carried out when the protein was not "closely similar" to proteins that have been safely consumed in food, as a compromise between the current text and a proposal to refer to an "identical" protein.

Evaluation of Metabolites

55. In paragraph 41 (paragraph 43 in the new text), the Task Force agreed to delete the reference to "residue" as this could create confusion due to other uses of that term, and to consider only "altered metabolites".

Assessment of Immunological Effects

56. With regard to the annex on allergenicity, the Task Force decided to adopt the second option in paragraph 44 (paragraph 46 in the new text) to append the annex specific for microorganisms to this guideline. The Task Force agreed on the draft prepared by Japan as annex of CRD 7.

57. The Task Force agreed to revise paragraph 45 (paragraph 47 in the new text) in view of consistency with the Draft Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants as paragraph 43 of the guideline refers to "gluten-sensitive enteropathy" and to improve its clarity. For this purpose, the Task Force inserted the second sentence of paragraph 6 in the Annex on Allergenicity of the Draft Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants as the first sentence in paragraph 45 (paragraph 47 in the new text) with a slight modification to express clearly the avoidance of genes derived from known allergens. Furthermore, the Task Force incorporated paragraph 43 of the Draft Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants with a slight modification to deal with the case of "gluten-sensitive enteropathy".

58. In paragraph 46 (paragraph 48 in the new text), regarding the interaction of recombinant-DNA microorganisms that may remain viable in foods with immune system in gastrointestinal tract, the delegation of Italy proposed to add that "Efforts should be made to establish animal models or in vitro models to study above interactions.". The Task Force agreed that this was a useful recommendation for the purpose of research but that it should not be included in the current guideline as its purpose was to provide recommendations to safety assessment.

Assessment of Viability and Residence of Microorganisms in the Human Gastrointestinal Tract

59. In paragraph 47 (paragraph 49 in the new text), the Task Force agreed with the revision of footnote 12 (footnote 11 in the new text) by adding a sentence from the FAO/WHO Expert Consultation on possible Influence of microorganisms on microflora. The Task Force also amended the 3rd sentence of footnote 12 (footnote 11 in the new text) to change the subject from "Residence" to "Persistence", and moved the sentence to a new footnote to paragraph 4 D) in order to provide an explanation of the term "persistence" as proposed by the delegation of Denmark.

60. The Task Force considered paragraph 48 (paragraph 50 in the new text) where several options were proposed as to how the safety assessment would deal with the case in which recombinant-DNA microorganisms remain viable in the final food. The Task Force agreed that it "may be desirable" to demonstrate the viability of the microorganism alone and the viability of microorganism in the food matrix in the digestive tract and the impact on the intestinal microflora by "appropriate system". It was noted that this option

allowed flexibility and practicability under the present situation where methods for evaluation had not been fully established. It was also agreed that the nature of intended and unintended effects should be taken into account for determining the extent of such testing.

Antibiotic Resistance and Gene Transfer

61. The Task Force had an extensive discussion on the case where strains had transmissible anti-biotic resistance when it considered the first bracketed sentence in paragraph 49 (paragraph 51 in the new text). During the discussion, the Representative of WHO stressed the importance of a global approach in the prevention of antibiotic resistance and encouraged the Task Force to provide clear recommendations in this area. The Task Force considered whether such a strain should be avoided as a candidate for recipient for construction of recombinant-DNA microorganisms or whether such strain should be prohibited from food production. An alternative proposal was made to specify that such strains should not remain in the final foods. As a result of discussion, the Task Force agreed not to use the strains for food production in which anti-biotic resistance is encoded by transmissible antibiotic genes where such strain and gene element were present in the foods.

62. In paragraph 52 (paragraph 54 in the new text), the Task Force agreed to replace the bracketed sentence in the second bullet with the sentence "where the recombinant-DNA microorganism will remain viable in the gastrointestinal tract, genes should be avoided in the genetic construct that could provide a selective advantage to recipient organisms to which the genetic material is unintentionally transferred**.**" which was proposed by the Delegation of United States to improve clarity.

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

63. The Task Force agreed to forward the Draft Guideline for the Conduct of Food Safety Assessment of Foods Produced Using Recombinant-DNA Microorganisms to the Commission for adoption at Step 8. The text with Annex on Allergenicity is attached to this report as Appendix II.

OPEN DISCUSSION ON TRACEABILITY (AGENDA ITEM 5)[8]

64. The Task Force recalled its decision in the last session to hold an open discussion on traceability, and that this discussion should not compromise the consensus that had already been achieved in the document of Draft Principles for the Risk Analysis of Foods derived from Modern Biotechnology, and that it should not lead to specific recommendation or guidelines. The Secretariat informed the Task Force about current consideration of traceability or product tracing in Codex Committees and Regional Coordinating Committees.

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[8] CX/FBT 03/2, CRD 9 (Comment of United States of America), CRD 13 (Comment of Mexico), CRD 15 (Comments of European Union)

65. The Delegation of France informed Task Force that the next session of the Committee on General Principles would consider a discussion paper prepared by Codex Secretariat that included consideration of a definition of traceability and took into account the results of the discussion in all Regional Coordinating Committees.

66. Several delegations recalled that the discussion on traceability had been initiated in the Task Force and supported further discussion of this issue in all relevant Codex committees.

67. The Delegation of Greece, speaking on behalf of the member countries of the European Union, welcomed the inclusion of this item in the agenda of this Task Force, and expressed its view that traceability was an important tool not only as a risk management measure related to food safety, but also as a measure enabling the control and verification of various labelling claims. It also expressed its appreciation of the inclusion of traceability in the "Draft Principles for the Risk Analysis of Food Derived from Modern Biotechnology", which was finalized last year. These views were supported by the Delegation of Norway.

68. The Delegation of the United States welcomed the discussion of traceability in the Task Force and supported the use of product tracing for the purpose of public health, but did not agree with its application of this concept to the labelling of food derived from biotechnology. The delegation also noted that the Food and Drug Administration would propose a new regulation which contains the concept of product tracing – one step back and one step forward - and it would require the establishment and maintenance of appropriate records for all foods regulated by FDA.

69. The Observer from the European Community mentioned, that the European Community was currently developing legislation on the authorization, labelling and traceability of genetically modified food and feed. This legislation, which has been notified to the SPS and TBT Committees in draft form, would require traceability of genetically modified food for the purpose of public health and consumer information. He further stated that current European Community legislation already requires the traceability of all food but provides that specific traceability requirements may be laid down in respect of certain categories of food. He also expressed the view that the discussion of traceability should be continued within Codex.

70. The Observer from the 49th Parallel Biotechnology Consortium expressed its view that consumer groups have been urging governments to accept the concept of traceability, for example, in establishing liability if any adverse health effects were to occur, and it is an important aspect especially for genetically modified food.

71. The Observer from the International Association of Consumer Food Organizations expressed its appreciation to the Task Force for the opportunity to discuss traceability in this Task Force, and noted that consumers were strongly interested in discussion of traceability and its practical application to protect consumers.

72. The Delegation of Canada recognized the importance of paragraph 21 in the Draft Principles for the Risk Analysis of Foods derived from Modern Biotechnology and supported its application, and also expressed its view that the key application of traceability was its contribution to risk management through the ability to identify and withdraw products of public health concern.

73. The Observer from Greenpeace International expressed the opinion that the comments of the Delegation of Canada were very important for handling genetically engineered food. It also stated that traceability could play an important role to provide consumer information on processing and marketing of food, especially genetically engineered food, and to ensure transparency.

74. The Delegation of Brazil expressed its view, on behalf of developing countries, that although the importance of traceability had been recognized, the most difficult point until the introduction of this concept was the cost of traceability and that it might be used as a barrier to trade. It also noted that the Task Force had initiated discussions on traceability within Codex and that such discussions should continue.

75. The Delegation of Mexico expressed its view that traceability should be considered for all foods, and also noted that traceability was an important element for risk management in human health and international trade. It highlighted the relations between traceability and the Cartagena Protocol.

76. The Delegation of Japan expressed its concern that there was no common, clear understanding of the definition of traceability in Japan. It also noted that elements of traceability were highlighted in Japan and had been introduced after experiences of BSE cases. It expressed its view that within Codex, discussion on traceability should not be limited to genetically modified food. It also expressed the view that traceability/product tracing plays an important role not only as a safety measure but also as a TBT measure such as consumer information. It explained that the government of Japan would revise its food laws and introduce a more comprehensive system of traceability/product tracing, especially for beef products.

77. The Delegation of Argentina supported the comment of the Delegation of Brazil, and expressed its view that traceability, when necessary for public health, should be applied to all foods. It also stated that the use of genetically modified technology in developing countries might be restricted due to requirements of importing countries as regards traceability.

78. The Delegation of Australia also commented that traceability was applicable to all food safety issues and therefore welcomed the broader discussion of this issue in Codex. It also expressed its view that the term “product tracing”, rather than traceability, was gaining acceptance in the Codex system. It noted that while product tracing was an important tool for recalling unsafe food, priority should be given to ensuring that food is safe before entering the market place.

79. The Delegation of China noted that although traceability is important for all foods, it was unfortunately costly. It expressed its view that further discussion of traceability and its application for developing countries would be necessary.

80. The Chair thanked the delegations and observers for their constructive comments and summarized the main elements of the discussion: consideration of traceability had started in this Task Force and there was consensus to continue further discussion in the framework of Codex; traceability or product tracing was an important element to ensure food safety throughout the food chain; it could address the request of consumers for

transparency and improved information; and its implications for developing countries should be further considered, especially to ensure fair trade.

OTHER BUSINESS (AGENDA ITEM 6)

81. The representative of WHO expressed the appreciation of the parent bodies of the work of the Task Force and stated that this was a good example of efficient Codex work, even in a very complicated area. It was impressive that the Task Force had managed to establish three important, high quality documents in a short four year period. He stressed the importance of continuing work on genetically modified food within the Codex, especially in the field of genetically modified animals, genetically modified microorganisms used in agriculture or without a history of safe use as well as methodology for safety assessment testing. He also informed the meeting that FAO and WHO was considering to hold an Expert Consultation on the Safety Assessment of Food Derived from Genetically Modified Animals including Fish soon. The representative of WHO and the Observer from the European Community stressed the importance to discuss broader issues related to genetically modified food, e.g. ethics and socio-economic considerations etc. as they pertain to genetically modified food. He proposed the Task Force to take action to refer to the next Codex Commission the question of the continuation of work on genetically modified food within Codex.

82. The Task Force noted other proposals were forwarded by delegations and observers, such as;
    - cloned animals
    - low level presence of unauthorized genetically engineered food
    - other legitimate factors related to modern biotechnology
    - specific needs for developing countries
    - genetically modified crops developed for pharmaceutical purposes and industrial chemicals
    - Novel Foods other than GMOs

83. Several delegations and observers appreciated WHO's contributions on future work on foods derived from modern biotechnology, and supported further work of FAO and WHO in this area. They also appreciated the work of the Task Force and proposed to continue the work on foods derived from modern biotechnology within Codex. The Delegation of the United States and the Observer from the European Community hoped that the government of Japan would continue to host a task force on foods derived from biotechnology in the future. The Delegation of Brazil expressed its view that it would be important to allow the possibility to discuss foods derived from modern biotechnology within Codex, also in the future due to its importance to developing countries.

84. The Delegations of the United States and Australia expressed their opinions that the proposal from the representative of WHO should be discussed at the Codex Alimentarius Commission, and that future work on genetically modified food should focus on food safety issues. Additionally, the Delegation of Australia noted that any future work should be in the context of the Medium Term Plan.

85. The Delegation of Canada expressed its view that the proposals of the Representative of WHO reflected important considerations regarding work on genetically modified food. The Delegation noted, however, that several of the items proposed represented work

which fell outside the Codex mandate and encouraged FAO and WHO, or other international organizations to consider these topics as appropriate.

86. The Delegation of South Africa expressed the view that it is very important for developing countries to have an international reference point on the assessment of genetically modified food through Codex and other FAO/WHO efforts.

SUMMARY STATUS OF WORK

Subject	Step	Action by	Document Reference (ALINORM 03/34A)
Draft Guideline for the Conduct of Food Safety Assessment of Foods Produced Using Recombinant-DNA Microorganisms	8	Governments 26th CAC	para. 63

APPENDIX I

LIST OF PARTICIPANTS
LISTE DES PARTICIPANTS
LISTA DE PARTICIPANTES

CHAIRPERSON/PRESIDENT/PRESIDENTE

Prof. Hiroshi Yoshikura
Pharmaceutical and Food Safety Bureau
Ministry of Health, Labor and Welfare
1-2-2 Kasumigaseki, Chiyoda-ku
Tokyo 100-8916, Japan
Phone: +81 3 3595 2146
Fax: +81 3 3595 2251
Email: codexj@mhlw.go.jp

MEMBER COUNTRIES

ARGENTINA
ARGENTINE
ARGENTINA

Mr. Marcelo Carlos Cesa
Secretary for Embassy
Embassy of the Republic of Argentina
2-14-14, Moto-Azabu, Minato-ku, Tokyo,
106-0046, JAPAN
Phone: +81 3 3473 7171
Fax: +81 3 3471 7173
E-Mail: ejapo@mb.rosenet.ne.jp

AUSTRALIA
AUSTRALIE
AUSTRALIA

Dr. Marion Joy Healy
Chief Scientist
Food Standards Australia New Zealand
PO Box 7186, Canberra BC ACT, 2610,
AUSTRALIA
Phone: +61 2 6271 2215
Fax: +61 2 6271 2204
E-Mail: marion.healy@foodstandards.gov.au

Mrs. Lois Ransom
Counsellor (Agriculture)
Market Access and Biosecurity
Department of Agriculture, Fisheries and Forestry-Australia
Australian Embassy, 2-1-14 Mita, Minato-ku, Tokyo,
108-8361, JAPAN
Phone: +81 3 5232 4027
Fax: +81 3 5232 4029
E-Mail: lois.ransom@dfat.gov.au

Mrs. Jenny Cupit
Director, Science Policy, Rural Policy and Innovation
Department of Agriculture, Fisheries and Forstry-Australia
GPO Box 858, Canberra, Act, 2601,
AUSTRALIA
Phone: +61 2 6272 4684
Fax: +61 2 6272 5926
E-Mail: jennifer.cupit@affa.gov.au

BELGIUM
BELGIQUE
BÉLGICA

Dr. Sébastien Jean Goux
Food Policy Officer
Division Denrées Alimentaires et Produits de Consommation
Direction Générale Animaux, Végétaux et Alimentation SPF Santé Publique, Sécuriré de la Chaîne alimentaire et Environnement
CAE Quartier Esplanade-11ème étage
Boulevard Pachéco 19 bte 5-1010 Bruxelles, 1010, BELGIUM
Phone: +32 2 210 48 46
Fax: +32 2 210 48 16
E-Mail: sebastien.goux@health.fgov.be

BRAZIL
BRÉSIL
BRASIL

Mr. Ricardo Oliva
Director of Foods and Toxicology
Brazilian Health Surveillance Agency
Ministry of Health
SEPN 515, Bloco B Ed. Ômega, 3 Andar, Brasilia - DF -, BRAZIL
Phone: +55 61 448 1102
Fax: +55 61 448 1224
E-Mail: RICARDO.OLIVA@anvisa.gov.br

Ms. Marilia Regini Nutti
Director
Embrapa Food Technology
Ministry of Agriculture, Livestock and Supply
Av das Americas 29 501, Rio de Janeiro - RJ-, BRAZIL
Phone: +55 21 2410 1350
Fax: +55 21 2410 1090
E-Mail: marilia@ctaa.embrapa.br

CANADA
CANADA
CANADÁ

Mr. Paul Mayers
Acting / Associate Director General
Food Directorate, Health Products and Food Branch, Health Canada
Building #7, Postal Locator 0701A5 Tunncy's Pasture, Ottawa, Ontario, K1A 0L2, CANADA
Phone: +1 613 952 3368
Fax: +1 613 957 1784
E-Mail: paul_mayers@hc-sc.gc.ca

Mr. Allan McCarville
Senior Advisor, Codex
Bureau of Food Regulatory, International and Interagency Affairs, Food Directorate, Health Products and Food Branch
Health Canada
Building #7, Room 2394 (0702C1) Tunney's Pasture, Ottawa, Ontario K1A 0L2, CANADA
Phone: +1 613 957 0189
Fax: +1 613 941 3537
E-Mail: allan_mccarville@hc-sc.gc.ca

Ms. Nora Nishikawa
A/Director
Office of Biotechnology
Canadian Food Inspection Agency
59 Camelot Drive Nepean, Ontario, K1A 0Y9, CANADA
Phone: +1 613 225 2342 (ext: 4185)
Fax: +1 613 228 6604
E-Mail: nnishikawa@inspection.gc.ca

Ms. Chris Moran
Technical Barriers and Regulations
Department of Foreign Affairs and International Trade, 125 Sussex Drive, CANADA
Phone: +1 613 944 4847
Fax: +1 613 944 0756
E-Mail: chris.moran@dfait-maeci.gc.ca

Dr. Mary Alton Mackey
President
Alton Mackey and Associates
Canadian Biotechnology Advisory Committee
379 Markland Drive, Etobicoke, Ontario, M9C ISI, CANADA
Phone: +1 416 626 2448
E-Mail: maryaltonmackey@sympatico.ca

CHINA
CHINE
CHINA

Mr. Guosheng Chen
Deputy Director, DVM
Division of Animal Epidemic Prevention and Supervision of National Animal Husbandry & Veterinary Service
Ministry of Agriculture
P. R. CHINA
Phone: +86 10 64194602
Fax: +86 10 64194623
E-Mail: Chengsh@cav.net.cn

Mr. Kegong Tian
Director of Department

National Veterinary Diagnostic Center
Ministry of Agriculture
P. R. CHINA

Mr. Xiaoguang Yang
Deputy Director General
Chinese Nutrition Society, Vice President
Slue Food and Notation
Consultation Committee, Vice President
China Center for Disease Control and Prevention
No.27 Nanwei Road Xuanwu District, Beijing, 100050, CHINA
Phone: +86 10 63012327
Fax: +86 10 63170894
E-Mail: xgyang@95777.com

Mr. Xu Hai Bin
Associate Professor
Department of Health Assessment
National Institute of Nutrition and Food Safety
China Center for Disease Control and Prevention
7 Pan Jia Yuan Nanli Chao YangDistricBeijing, 100021, P. R. CHINA
Phone: +86 10 87780694
Fax: +86 10 67711813
E-Mail: HbXu1231602@vip.sina.com

Dr. Dan-dan William Ho
Chemist
Government Laboratory of HongKong
P. R. CHINA

Ms. Christina Li
Chemist
Government Laboratory of HongKong
P. R. CHINA

Dr. Hiu Yeung Choi
Senior Medical Officer
Food and Environmental Hygiene Department of HongKong
P. R. CHINA

Ms. Chen Ying
Doctor
China Import and Export Commodity Inspection Technology Institute of AQSIQ
No.3 Gaobeidian North Road, Chaoyang Districl, Beijing, 100025, P.R. CHINA
Phone: +86 10 85753925
Fax: +86 10 85775789
E-Mail: yingchen72@yahoo.com.cn

Mr. Jiang Yuan
Director of Food Laboratory
Jiangsu Entry-Exit Inpection and Quarantine
1, Baixia Road, Nanjing, CHINA
Phone: +86 25 6644744 / 6649815
Fax: +86 25 6644744 / 6648977
E-Mail: jiango@yeah.net

REPUBLIC
RÉPUBLIQUE TCHÈQUE
REPÚBLICA CHECA

Dr. Jiří Ruprich
Head of Food Safety Division
National Institute of Public Health
Palackého 3a, 61242 Brno, CZECH REPUBLIC
Phone: +42 5 41211764
Fax: +42 5 41211764
E-Mail: jruprich@chpr.szu.cz

DENMARK
DANEMARK
DINAMARCA

Ms. Anne Christine Duer
Senior Adviser
Danish Veterinary and Food Administration
Moerkhoej Bygade 19, DK-2860, Soeborg, DENMARK
Phone: +45 33 95 60 00
Fax: +45 33 95 60 01
E-Mail: acd@fdir.dk

Mr. Jan Pedersen
Senior Scientist
Danish Veterinary and Food Administration
Moerkhoej Bygade 19, DK-2860, Soeborg, DENMARK
Phone: +45 33 95 60 00
Fax: +45 33 95 60 01
E-Mail: jp@fdir.dk

Mr. Bruno Sander Nielsen
Head of Division
Food and Research
Danish Agriculture Council
Axeltorv 3, 1609 Copenhagen, DENMARK
Phone: +45 3339 4267
Fax: +45 3339 4141
E-Mail: bsn@agriculture.dk

EGYPT
EGYPTE
EGIPTO

Mr. Mokhtar Omar
First Secretary
Embassy of the Arab Republic of Egypt
1-5-4 Aobadai, Meguro-ku, Tokyo, 153-0042, EGYPT
Phone: +81 3 3770 8022
Fax: +81 3 3770 8021
E-Mail: egyptemb@n.c.kcom.ne.jp
thinkmokh@yahoo.co.uk

FINLAND
FINLANDE
FINLANDIA

Dr. Leena Mannonen
Commercial Counsellor
Ministry of Trade and Industry
PO Box 32, FIN-00023 Government, FINLAND
Phone: +358 9 1606 3716
Fax: +358 9 1606 2670
E-Mail: leena.mannonen@ktm.fi

FRANCE
FRANCIA
FRANCIA

Christophe Lepretre
Ministère de l'Agriculture, de l'Alimentation, de la Peche et des Affaires Rurales DGAL
251, rue de Vaugirard, 75732 PARIS CEDEX 15, FRANCE
Phone: +33 1 4955 5010
Fax: +33 1 4955 5948
E-Mail: christophe.lepretre@agriculture.gouv.fr

Sophie Gallotti
AFSSA - DERN
27-31, boulevard du Général Leclerc, 94701 MAISONS-ALFORT, FRANCE
Phone: +33 1 4977 2628
Fax: +33 1 4977 1352
E-Mail: sophie.gallotti@afssa.fr

Emmanuelle Mollet
Ministère de l'Economie, des Finances et de l'Industrie DGCCRF 59, Boulevard Vincent Auríol, 75703 PARIS
CEDEX 13, FRANCE
Phone: +33 1 4497 2406
Fax: +33 1 4497 3037
E-Mail:emmanuelle.mollet@dgccrf.finances.go uv.fr

GERMANY
ALLEMAGNE
ALEMANIA

Dr. Maria Anna Schauzu
Scientific Director
Federal Institute of Risk Assessment
Thielallee 88-92, Berlin, D-14195, GERMANY
Phone: +49 30 8412 3758
Fax: +49 30 8412 3635
E-Mail: m.schauzu@bfr.bund.de

GREECE
GRÈCE
GRECIA

Mr. Anagnostou Konstandinos
Officer of the Directorate of Processing Standardization and Quality Control of Agri-food Products, Ministry of Agriculture of Greece
2 Acharnon Str., GR-10176, Athens, GREECE
Phone: +30 210 2124349
Fax: +30 210 5238337
E-Mail: ax2u049@minagric.gr

Mrs. Eirini Theodorakopoulou
Officer of the Directorate of Agricultural Policy
Ministry of Agriculture of Greece
5 Acharnon Str., GR-10176, Athens, GREECE
Phone: +30 210 2124114
Fax: +30 210 5249097
E-Mail: ax5u023@minagric.gr

HUNGARY
HONGRIE
HUNGRÍA

Dr. Diána Bánáti
Director General
Central Food Research Institute
P.O. Box 393, H-1537, Budapest, HUNGARY
Phone: +361 355 8991
Fax: +361 212 9853
E-Mail: d.banati@cfri.hu

INDONESIA
INDONÉSIE
INDONESIA

Dr. Joni Munarso
Senior Scientist
Indonesian Agricultural Postharvest Research Institute, JL. Ragunan 29A Pasarminggu, Jakarta, 12540, INDONESIA
Phone: +62 21 7820024
Fax: +62 21 7820024
E-Mail: jmunarso@yahoo.com

Mr. Ishaka H. Mustamin
Agricultural Attaché
Embassy of the Republic of Indonesia

2-9, Higashi-Gotanda, 5-Chome, Shinagawa-ku,
Tokyo, 141-0022, JAPAN
Phone: +81 3 3447 6364
Fax: +81 3 3447 6364
E-Mail: atanityo@cts.ne.jp

IRAN, ISLAMIC REPUBLIC OF
IRAN,RÉPUBLIQUE ISLAMIQUE DE
IRÁN,REPÚBLICA ISLÁMICA DEL

Dr. Behzad Ghareyazie
Director General
Agricultural Biotechnology Research Institute of Iran
P.O. Box 19835-175 Tabnak Ave., Tehran, IRAN
Phone: +98 261 2709485
Fax: +98 21 240 0568
E-Mail: ghareyazie@yahoo.com

IRELAND
IRELANDE
IRLANDA

Dr. Pat O'Mahony
Chief Specialist: Biotechnology
Food Safety Authority of Ireland
Abbey Court, Lower Abbey Street, Dublin 1, IRELAND
Phone: +353 1 817 1300
Fax: +353 1 817 1301
E-Mail: info@fsai.ie

ITALY
ITALIE
ITALIA

Dr. Eugenia Dogliotti
Istituto Superiore di Sanitā-Roma
Viale Regina Evena 239, 00161 Rome, ITALY
Phone: +39 06 43302580
Fax: +39 06 43302580
E-Mail: dogliott@iss.it

Dr. Giovanna Franciosa
Researcher
Istituto Superiore Sanitā
Viale Regina Elena 299, 00161 Rome, ITALY
Phone: +39 06 49902810
Fax: +39 06 49387101
E-Mail: francios@iss.it

Dr. Brunella Lo Turco
Segretario Generale
Comitato Nazionale Codex
Ministero delle Politiche Agricole
Via Sallustiana 10, ITALY
Phone: +39 06 46656512
Fax: +39 06 4880273
E-Mail: BLTURCO@tiscali.it

Dr. Alessandro Proposito
Agenzia delle Dogane
Laboratorie Chimico di Roma
Via Mario Carucci, 71-00143 Rome, ITALY
Phone: +39 06 50244106
Fax: +39 06 50957345
E-Mail: ALEXPROP@tin.it

JAPAN
JAPON
JAPÓN

Ministry of Foreign Affairs

Mr. Naohito Izumikawa
Official
Developing Economies Division
Economic Affairs Bureau
Ministry of Foreign Affairs
2-11-1 Shibakouen, Minato-ku, Tokyo, JAPAN
Phone: +81 3 6102 2229
Fax: +81 3 6402 2221
E-Mail: naohito_izumikawa@mofa.go.jp

Ministry of Health, Labour and Welfare

Dr. Akira Endou
Director-General for Department of Food, Safety, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare
1-2-2 Kasumigaseki, Chiyoda-ku, Tokyo, JAPAN
Phone: +81 3 3595 2326
Fax: +81 3 3503 7965

Mr. Sotarou Yoshioka
Director for Policy Planning Division
Department of Food Safety, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare
1-2-2 Kasumigaseki, Chiyoda-ku, Tokyo, JAPAN
Phone: +81 3 3595 2326
Fax: +81 3 3503 7965

Dr. Mitsuhiro Ushio
Director for International Food Safety Planning
Policy Planning Division
Department of Food Safety, Pharmaceutical and

Food Safety Bureau
Ministry of Health, Labour and Welfare
1-2-2 Kasumigaseki, Chiyoda-ku, Tokyo,
JAPAN
Phone: +81 3 3595 2326
Fax: +81 3 3503 7965
E-Mail: ushio-mitsuhiro@mhlw.go.jp

Dr. Hiroyuki Ota
Deputy Director for Standards Division
Department of Food Safety, Pharmaceutical and
Food Safety Bureau
Ministry of Health, Labour and Welfare
1-2-2 Kasumigaseki, Chiyoda-ku, Tokyo,
JAPAN
Phone: +81 3 3595 2341
Fax: +81 3 3501 4868
E-Mail: ota-hiroyuki@mhlw.go.jp

Mr. Katsutoshi Saruta
Deputy Director for Inspection and Safety
Division, Department of Food Safety,
Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare
1-2-2 Kasumigaseki, Chiyoda-ku, Tokyo,
JAPAN
Phone: +81 3 3595 2337
Fax: +81 3 3503 7964
E-Mail: saruta-katsutoshi@mhlw.go.jp

Dr. Akira Miki
Assistant Director for Inspection and Safety
Division, Department of Food Safety,
Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare
1-2-2 Kasumigaseki, Chiyoda-ku, Tokyo,
JAPAN
Phone: +81 3 3595 2337
Fax: +81 3 3503 7964
E-Mail: miki-akira@mhlw.go.jp

Dr. Hiroshi Umeda
Assistant Director for Office of Quarantine
Station Administration, Policy Planning
Division, Department of Food Safety,
Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare
1-2-2 Kasumigaseki, Chiyoda-ku, Tokyo,
JAPAN
Phone: +81 3 3595 2333
Fax: +81 3 3591 8029
E-Mail: umeda-hiroshi@mhlw.go.jp

Dr. Yoshiyuki Kanagawa
Chief
Policy Planning Division
Department of Food Safety, Pharmaceutical and
Food Safety Bureau
Ministry of Health, Labour and Welfare
1-2-2 Kasumigaseki, Chiyoda-ku, Tokyo,
JAPAN
Phone: +81 3 3595 2326
Fax: +81 3 3503 7965
E-Mail: kanagawa-yoshiyuki@mhlw.go.jp

Dr. Tamio Maitani
Director
Division of Foods
National Institute of Health Sciences
1-18-1 Kamiyoga, Setagaya-ku, Tokyo, 158-
8501, JAPAN
Phone: +81 3 3700 9348
Fax: +81 3 3700 9348
E-Mail: maitani@nihs.go.jp

Dr. Shigeki Yamamoto
Director
Division of Biomedical Food Research
National Institute of Health Sciences
1-18-1 Kamiyoga, Setagaya-ku, Tokyo, 158-
8501, JAPAN
Phone: +81 3 3700 9357
Fax: +81 3 3700 9406
E-Mail: syamamoto@nihs.go.jp

Dr. Shizunobu Igimi
Section Chief
Division of Biomedical Food Research
National Institute of Health Sciences
1-18-1 Kamiyoga, Setagaya-ku, Tokyo, 158-
8501, JAPAN
Phone: +81 3 3700 9164
Fax: +81 3 3700 9246
E-Mail: igimi@nihs.go.jp

Dr. Fumiko Kasuga
Section Chief
Division of Biomedical Food Research
National Institute of Health Sciences
1-18-1 Kamiyoga, Setagaya-ku, Tokyo, 158-
8501, JAPAN
Phone: +81 3 3700 9169
Fax: +81 3 3700 9527
E-Mail: kasuga@nihs.go.jp

Dr. Hiroshi Akiyama
Section Chief
Division of Foods
National Institute of Health Sciences
1-18-1 Kamiyoga, Setagaya-ku, Tokyo, 158-
8501, JAPAN
Phone: +81 3 3700 9397
Fax: +81 3 3707 6950
E-Mail: akiyama@nihs.go.jp

Dr. Kazuaki Miyagishima
Member of Food Sanitation
Council Associate Professor

Graduate School of Medicine, Kyoto University
Yoshida Konoe-cho, Sakyo-ku, Kyoto-shi,
Kyoto, 606-8501, JAPAN
Phone: +81 75 753 4464
Fax: +81 75 753 4466
E-Mail: miyagishima@pbh.med.kyoto-u.ac.jp

Dr. Atsuo Urisu
Member of Food Sanitation
Council Professor for Department of Pediatrics
Fujita Health University
The Second Teaching Hospital
3-6-10 Otoubashi, Nakagawa-ku, Nagoya-shi,
Aichi, JAPAN
Phone: +81 52 323 5670
Fax: +81 52 322 4734
E-Mail: urisu@fujita-hu.ac.jp

Ministry of Economy, Trade and Industry

Mr. Norihiro Kushida
Assistant Director, Bio-Industry Division
Ministry of Economy, Trade and Industry
1-3-1 kasumigaseki, Chiyoda-ku, Tokyo,
JAPAN
Phone: +81 3 3501 8625
Fax: +81 3 3501 0197
E-Mail: kushida-norihiro@meti.go.jp

Ministry of Agriculture, Forestry and Fisheries

Mr. Jun Koda
Director for International Standardization Office
Standards and Labelling Division
General Food Policy Bureau
Ministry of Agriculture, Forestry and Fisheries
1-2-1 Kasumigaseki, Chiyoda-ku, Tokyo, 101-8950, JAPAN
Phone: +81 3 5512 1571
Fax: +81 3 3501 0580
E-Mail: zyun_kohda@nm.maff.go.jp

Ms. Takako Kimura
Section Chief, International
Standardization Office
Standards and Labelling Division
General Food Policy Bureau
Ministry of Agriculture, Forestry and Fisheries
1-2-1 Kasumigaseki, Chiyoda-ku, Tokyo, 101-8950, JAPAN
Phone: +81 3 5512 1571
Fax: +81 3 3501 0580
E-Mail: takako_kimura@nm.maff.go.jp

Mr. Tadayoshi Sueguchi
Section Chief Deputy Director
Biotechnology Safety Division
Agriculture, Forestry and Fisheries
Research Council Secretariat
Ministry of Agriculture, Forestry and Fisheries
1-2-1 Kasumigaseki, Chiyoda-ku, Tokyo, 101-8950, JAPAN
Phone: +81 3 3501 3780
Fax: +81 3 3502 4028
E-Mail: stada@s.affrc.go.jp

Dr. Masakatsu Yanagimoto
Director
Applied Microbiology Division
National Food Research Institute
Independent Administrative Institution
2-1-12 Kannondai, Tsukuda, Ibaraki, 305-8642, JAPAN
Phone: +81 29 838 8013
Fax: +81 29 838 7996
E-Mail: yanagmt@nfri.affrc.go.jp

Dr. Kenji Isshiki
Associate Director for Research
National Food Research Institute,
Independent Administrative Institution
2-1-12 Kannondai, Tsukuda, Ibaraki, 305-8642, JAPAN
Phone: +81 29 838 8067
Fax: +81 29 838 7996
E-Mail: isshiki@nfri.affrc.go.jp

Dr. Akihiro Hino
Head of Molecular Engineering Lab.,
National Food Research Institute,
Independent Administrative Institution
2-1-12 Kannondai, Tsukuda, Ibaraki, 305-8642, JAPAN
Phone: +81 29 838 8079
Fax: +81 29 838 7996
E-Mail: akihino@nfri.affrc.go.jp

Mr. Makoto Endou
Assistant Director
Consumer Consulting Division
Center for Food Quality, Labeling and Consumer Services
1-21-2 Kitafukuro-cho, Saitama City, Saitama, 330-9731, JAPAN
Phone: +81 48 600 2357
Fax: +81 48 600 2377

Mr. Hideo Kuribara
Section Chief of Technical Research Division
Center for Food Quality, Labeling and Consumer Services

1-21-2 Kitafukuro-cho, Saitama City, Saitama, 330-9731, JAPAN
Phone: +81 48 600 2365
Fax: +81 48 600 2377

Dr. Keiji Kainuma
Senior Adviser
Ministry of Agriculture, Forestry and Fisheries
1-2-1 Kasumigaseki, Chiyoda-ku, Tokyo, 100-8950, JAPAN
Phone: +81 3 3501 3780
Fax: +81 3 3502 4028

Technical Advisers

Mr. Tetsuhiko Okajima
Technical Adviser
Japan Food Industry Center
Sankaido Building 7th FL., 9-13 Akasaka 1-chome, Minato-ku, Tokyo, 107-0052, JAPAN
Phone: +81 3 3591 2524
Fax: +81 3 3591 3011
E-Mail: jdpa@mx1.alpha-web.ne.jp

Mr. Masahiko Karasawa
Technical Adviser
Japan Food Industry Center
Sankaido Building 7th FL., 9-13 Akasaka 1-chome, Minato-ku, Tokyo, 107-0052, JAPAN
Phone: +81 3 5215 3535
Fax: +81 3 5215 3537
E-Mail: masahiko_karasawa@ajinomoto.com

Mr. Yasuyuki Nagara
Technical Adviser
Japan Food Industry Center
Sankaido Building 7th FL., 9-13 Akasaka 1-chome, Minato-ku, Tokyo, 107-0052, JAPAN
Phone: +81 3 3593 0661
Fax: +81 3 3593 0780
E-Mail: jafix@titan.ocn.ne.jp

Mr. Hiroshi Watanabe
Technical Advisor
Japan Food Industry Center
Sankaido Building 7th FL., 9-13 Akasaka 1-chome, Minato-ku, Tokyo, 107-0052, JAPAN
Phone: +81 3 3224 2366
Fax: +81 3 3224 2398
E-Mail: Hiroshi.Watanabe@jp.nestle.com

Mr. Tadashi Hirakawa
Director
Japan Bioindustry Association
2-26-9 Hatchobori, Chuo-ku, Tokyo, 104-0032, JAPAN
Phone: +81 3 5541 2731
Fax: +81 3 5541 2737
E-Mail: hirakawa@jba.or.jp

Ms. Yoshiko Sassa
Manager
Life & Bio Plaza 21
2-26-9 Hatchobori, Chuo-ku, Tokyo, 104-0032, JAPAN
Phone: +81 3 5541 2790
Fax: +81 3 5541 5143
E-Mail: sassa@life-bio.or.jp

KOREA, REPUBLIC OF
CORÉE, RÉPUBLIQUE DE
COREA, REPÚBICA DEL

Dr. Mun Gi Sohn
Deputy Director
Korea Food and Drug Administration
#5, Nokbun-dong, Eunpyung-gu, Seoul, 122-704,
KOREA
Phone: +82 2 380 1733
Fax: +82 2 388 6392
E-Mail: mgsohn@kfda.go.kr

Ms. Sun-Hee Park
Senior Researcher
Food Microbiology Division
Food Evaluation Department
Korea Food & Drug Administration
#5, Nokbun-dong, Eunpyung-gu, Seoul, 122-704,
KOREA
Phone: +82 2 380 1683
Fax: +82 2 382 4982
E-Mail: shp5538@hanmail.net
shp1023@kfda.go.kr

Dr. Soon Ho Lee
Researcher
Food Microbiology Division
Food Evaluation Department
Korea Food & Drug Administration
#5, Nokbun-dong, Eunpyung-gu, Seoul, 122-704,
KOREA
Phone: +82 2 380 1682
Fax: +82 2 382 4892
E-Mail: Leesh13@kfda.go.kr

Miss Jeong-Mi Hong
Researcher
Food Sanitation Council

Ministry of Health and Welfare
1 Jungan-dong, Kwacheon City, Kyunggi-do, KOREA
Phone: +82 2 503 7557
Fax: +82 2 504 1456
E-Mail: codexkorea@kfda.go.kr

Miss Hyang Ki Lee
Vice President
Food & Research
Consumers Union of Korea
Hannam-dong 272-1, Youngsan-gu, Seoul, 140-885, KOREA
Phone: +82 2 794 7081
Fax: +82 2 798 6564
E-Mail: Hanggeena@hotmail.com

Mr. Taek-Ryoun Kwon
Research Scientist
National Institute of Agricultural Biotechnology, RDA
249, Seodun-dong, Suwon-shi, 441-707, KOREA
Phone: +82 31 299 1704
Fax: +82 31 299 1692
E-Mail: trkwon@rda.go.kr

Mr. Soon-Wo Kwon
Research Scientist
Division of Biotechnology Planning and Coordination
Research Management Bureau
Rural Development Administration
250 Seodun-dong, Suwon-shi, 441-707, KOREA
Phone: +82 31 299 2965
Fax: +82 31 299 2968
E-Mail: swkwon@rda.go.kr

MEXICO
MEXIQUE
MÉXICO

Mr. Samuel Ibarra Vargas
Director of Legal Affairs
Intersecretariat Commission on Biosafety and Genetically Modified Organisms (CIBIOGEM)
Leibnitz #14,6 Piso, Col. Anzures, 11590, MEXICO
Phone: +52 55 52039678
Fax: +52 55 52039678
E-Mail: samuelbarra@prodigy.net.mx
cibiogem@cibiogem.gob.mx

Mrs. Elvira Gutiérrez Espinosa
Sanitary Standardization Director
International Commerce
Health Ministry
Monterrey 36, 06010, MEXICO
Phone: +52 55 5552082810
Fax: +52 55 5552080915
E-Mail: eespinossa@yahoo.com.mx

Mr. Jorge Ruiz Ascencio
Vice President, International Relations
CONMEXICO
Calderon de la Barca 118, Polanco, 11500, MEXICO
Phone: +52 55 5281 2215
E-Mail: conmex1@prodigy.net.mx

NETHERLANDS
PAYS-BAS
PAÍSES BAJOS

Mrs. Sandra Ciere-Koolhaas
Senior Policy Officer Biotechnology and Food
Department of Food and Veterinary Affairs
Ministry of Agriculture, Nature Management and Fisheries
P.O. Box 20401, 2500 EK The Hague, THE NETHERLANDS
Phone: +31 70 378 4039
Fax: +31 70 378 6141
E-Mail: s.ciere@vva.agro.nl

Ms. Lysanne Van Der Lem
Policy Officer Biotechnology and Food
Food and Nutrition Division
Ministry of Health, Welfare and Sports
P.O. Box 20350, 2500 EJ The Hague, THE NETHERLANDS
Phone: +31 70 340 54 47
Fax: +31 70 340 55 54
E-Mail: l.vd.lem@minvws.nl

Mr. G. De Rooij
Main Board for Arable Products
P.O. Box 29739, 2502 LS The Hague, THE NETHERLANDS
Phone: +31 70 370 8324
Fax: +31 70 370 8444
E-Mail: g.de.rooij@hpa.agro.nl

Mrs. J.A.G. Van De Wiel
Head Safety Assessment of Novel Foods
Health Council of the Netherlands
P.O. Box 16052, 2500 BB The Hague, THE NETHERLANDS
Phone: +31 70 340 5825
Fax: +31 70 340 7523
E-Mail: jag.van.de.wiel@gr.nl

NEW ZEALAND
NOUVELLE-ZÉLANDE
NUEVA ZELANDIA

Dr. Paul Dansted
Senior Advisor (Technical Policy)
New Zealand Food Safety Authority
PO Box 2835, Wellington, NEW ZEALAND
Phone: +64 4 463 2500
Fax: +64 4 463 2566
E-Mail: paul.dansted@nzfsa.govt.nz

NORWAY
NORVÈGE
NORUEGA

Mrs. Solbjørg Hogstad
Adviser
Section for Food Quality and Consumer Affairs
Department for Food Additives, Contaminants, Food Labelling, and Quality
Norwegian Food Control Authority
P.O. Box 8187 Dep, N-0034 OSLO, NORWAY
E-Mail: solbjorg.hogstad@snt.no

Mr. Thor Jan Schiøth
Adviser
Section for Scientific, International and Legal Affairs, Department for Food Control and Coordination
Norwegian Food Control Authority
P.O. Box 8187 Dep, N-0034 OSLO, NORWAY
E-Mail: thor-jan.schioth@snt.no

Mr Ingolf R. Nes
Professor, Laboratory of Microbial Gene Technology
Department of Chemistry and Biotechnology
Agricultural University of Norway
P.O. Box 5051
N-1432 ÅS, Norway
e-mail: ingolf.nes@ikb.nlh.no

PHILIPPINES
PHILIPPINES
FILIPPINAS

Jim Tito B. San Agustin
Foreign Service Officer / Principal Assistant
Office of the Undersecretary for International Economic Relations
Department of Foreign Affairs
2330 Roxas Boulevard, Pasay City, PHILIPPINES
Phone: +63 682 834 3033
Fax: +63 682 834 1451
E-Mail: jbsanagustin@dfa.gov.ph

SINGAPORE
SINGAPOUR
SINGAPUR

Dr. Siang Thai Chew
Deputy Director (Veterinary Public Health)
Food and Veterinary Administration
Agri-Food and Veterinary Authority
51 Jalan Buroh, SINGAPORE, 619495
Phone: +65 6267 0826
Fax: +65 6265 0784
E-Mail: chew_siang_thai@ava.gov.sg

Mr. Teck Heng, Leslie Phua
Head (Microbiology and Molecular Biology Branches)
Veterinary Public Health Laboratory Division
Food and Veterinary Administration
Agri-Food and Veterinary Authority
51 Jalan Buroh, SINGAPORE, 619495
Phone: +65 6267 0823
Fax: +65 6265 0784
E-Mail: phua_teck_heng@ava.gov.sg

Ms. Huay Leng Seah
Head
Food Control Division
Food and Veterinary Administration
Agri-Food and Veterinary Authority
5 Maxwell Road, #18-00, Tower Block, MND Complex, SINGAPORE, 69110
Phone: +65 6325 5480
Fax: +65 6324 4563
E-Mail: seah_huay_leng@ava.gov.sg

SOUTH AFRICA
AFRIQUE DU SUD
SUDÁFRICA

Ms. Wilna Jansen van Rijssen
Deputy Director : Food Control
Department of Health
Private Bag X828, 0001 Pretoria, SOUTH AFRICA
Phone: +27 12 312 0154
Fax: +27 12 312 3162
E-Mail: vrijsw@health.gov.za

SPAIN
ESPAGNE
ESPAÑA

Dr. Dolores Chiquero Sánchez
Jefe de Servicio de Desarrollo Alimentario
Subd. Gral. Planificación Alimentaria. D.G.A.
Ministerio de Agricultura, Pesca y Alimentación
Pº Infanta Isabel, 1, 28071-MADRID, SPAIN
E-Mail: mchiquer@mapya.es

Dr. Isabel Bombal Díaz
Jefe de Sección, Técnico
Subd. Gral. Planificación Alimentaria. D.G.A.

Ministerio de Agricultura, Pesca y Alimentación
Pº Infanta Isabel, 1, 28071-MADRID, SPAIN
E-Mail: ibombald@mapya.es

Dr. Pilar Contreras Gordo
Técnico Superior
Subdirección General de Gestión de Riesgos Alimentarios
Agencia Española de Seguridad Alimentaria.
(Mº de Sanidad y Consumo)
Pº del Prado, 18-20, 28071-MADRID, SPAIN
E-Mail: mcontreras@msc.es

SWEDEN
SUÈDE
SUECIA

Mr. Christer Andersson
Toxicologist
Toxicology Division
Research and Development Department
National Food Administration
Box 622 SE-751 26 Uppsala, SWEDEN
Phone: +46 18 17 57 64
Fax: +46 18 10 58 48
E-Mail: chan@slv.se

Dr. David Carlander
Senior Administrative Officer
Food Division
Ministry of Agriculture, Food and Fisheries
SE-103 33 Stockholm, SWEDEN
Phone: +46 8 405 2134
Fax: +46 8 20 64 96
E-Mail: david.carlander@agriculture.ministry.se

SWITZERLAND
SUISSE
SUIZA

Dr. Martin Schrott
Staff Scientist
Division Food Science
Swiss Federal Office of Public Health
CH-3003 Berne, SWITZERLAND
Phone: +41 31 322 69 89
Fax: +41 31 322 95 74
E-Mail: martin.schrott@bag.admin.ch

Dr. Stefanie Kramer-Jutant
Regulatory Affairs
Nestec Ltd.
Avenue Nestlé 55 CH-1800 Vevey,
SWITZERLAND
Phone: +41 21 924 42 10
Fax: +41 21 924 45 47
E-Mail: stephanie.Kramer-Jutant@nestle.com

THAILAND
THAÏLANDE
TAILANDIA

Prof. Pakdee Pothisiri
Deputy Permanent Secretary (Health Services Support Cluster), Office of the Permanent Secretary, Ministry of Public Health
Tiwanond Rd. Nouthaburi, 11000, THAILAND
Phone: +66 2 590 1015
Fax: +66 2 590 1136
E-Mail: ppakdee@health.moph.go.th

Dr. Chanin Charoenpong
Senior Food Expert
Food Control Division
Food and Drug Administration
Ministry of Public Health
Tiwanond Rd., Nouthaburi, 11000, THAILAND
Phone: +66 2 590 7030
Fax: +66 2 590 7177
E-Mail: chanin@fda.moph.go.th

Mrs. Darunee Edwards
Deputy Director
National Center for Genetic Engineering and Biotechnology
113 Phaholyothin Rd., Klong 1, Klong Luang
Pathumthane, 12120, THAILAND
Phone: +66 2 564 6700 (ext: 3163)
Fax: +66 2 564 6701
E-Mail: dedwards@biotec.or.th

Mrs. Oratai Silapanapaporn
Assistant Director
Office of Commodity and System Standards
National Bureau of Agricultural Commodity and Food Standards
Ministry of Agriculture and Cooperatives
Rajadamnern Nok Avenue, Bangkok, 10200, THAILAND
Phone: +66 2 280 3905
Fax: +66 2 280 1542
E-Mail: oratais@tisi.go.th

Mr. Sommart Prapertchob
Vice Chairman
Food Processing Industry Club

The Federation of Thai Industries
THAILAND
Phone: +66 2 657 8125
Fax: +66 2 657 8382
E-Mail: sommart.prapertchob@th.nestle.com

UNITED KINGDOM
ROYAUME-UNI
REINO UNIDO

Dr. Clair Baynton
Head of Novel Foods Branch 1
Food Standards Agency
Aviation House, 125 Kingsway, London, WC2B 6NH, UNITED KINGDOM
Phone: +44 20 7276 8566
Fax: +44 20 7276 8564
E-Mail: clair.baynton@foodstandards.gsi.gov.uk

UNITED STATES OF AMERICA
ETATS-UNIS D'AMÉRIQUE
ESTADOS UNIDOS DE AMÉRICA

Delegate

Mr. L. Robert Lake
Director
Office of Regulations and Policy
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration (HFS-004)
5100 Paint Branch Parkway, College Park, MD 20740, USA
Phone: +1 301 436 2379
Fax: +1 301 436 2637
E-Mail: Robert.Lake@cfsan.fda.gov

Alternate Delegate

Dr. Sally L. McCammon
Science Advisor to the Administrator
Animal and Plant Health Inspection Service
U.S. Department of Agriculture
4700 River Road (Unit 98) Riverdale, MD 20737, USA
Phone: +1 301 734 5761
Fax: +1 301 734 5992
E-Mail: Sally.L.McCammon@usda.gov

Government Advisors

Mr. Man K. Cho
International Trade Specialist
Chemicals, Pharmaceuticals & Biotechnology Division
U.S. Department of Commerce, International Trade Administration
14th & Constitution Avenue, NW, Washington, DC 20230, USA
Phone: +1 202 482 0131
Fax: +1 202 482 2565
E-Mail: Man_Cho@ita.doc.gov

Dr. James Maryanski
Biotechnology Coordinator
Office of Plant and Dairy Foods and Beverages
U.S. Food and Drug Administration (HFS-400)
5100 Paint Branch Parkway, College Park, MD 20740, USA
Phone: +1 301 436 1715
Fax: +1 301 436 2637
E-Mail: James.Maryanski@cfsan.fda.gov

Dr. H. Michael Wehr
Special Assistant to the Director
Office of Constituent Operations
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration (HFS-550)
5100 Paint Branch Parkway, College Park, MD 20740, USA
Phone: +1 301 436 1725
Fax: +1 301 436 2618
E-Mail: Mwehr@cfsan.fda.gov

Mr. Richard White
Office of the U.S. Trade Representative
Executive Office of the President
600 17th Street, NW, Washington, DC 20508, USA
Phone: +1 202 395 9582
Fax: +1 202 395 4579
E-Mail: Rwhite@ustr.gov

Mr. Bobby Richey
Director
Food Safety and Technical Services
International Trade Policy
Foreign Agricultural Service
U.S. Department of Agriculture
1400 Independence Ave, SW, Washington, DC 20250, USA
Phone: +1 202 720 1301
Fax: +1 202 690 0677
E-Mail: richeyb@fas.usda.gov

Mr. Tetsuo Hamamoto
Agricultural Specialist
U.S. Embassy, Tokyo
1-10-5 Akasaka, Minato-ku, Tokyo, 107-8420,

JAPAN
Phone: +81 3 3224 5000
Fax: +81 3 3589 0793

Non Government Advisors

Mr. Jeffrey Barach
National Food Processors Association
1350 I Street, NW, Washington, DC 20005, USA
Phone: +1 202 639 5955
Fax: +1 202 639 5991
E-Mail: jbarach@nfpa-food.org

Mr. Terry Francl
American Farm Bureau Federation
U.S. Grains Council Biotechnology Advisory Team
225 Touhy Avenue, Park Ridge, IL 60068, USA
Phone: +1 847 685 8769
Fax: +1 847 685 8969
E-Mail: Terry@fb.org

Mr. James Stitzlein
Vice Chairman
National Grain and Feed Association
Food Safety Committee, Consolidated Grain and Barge Co.
5848 Old Route 54 New Berlin, IL 62670, USA
Phone: +1 217 483 3980
E-Mail: stitziej@egb.com

UNITED NATIONS AND SPECIALIZED UN AGENCIES

Food and Agriculture Organization of the United Nations (FAO)
Organization des Nations Unies Pour L'Alimentation et L'Agriculture
Organizacion de las Naciones Unidas Para la Agricultura Y la Alimentacion

Ezzeddine Boutrif
Senior Officer, Food Quality and Standards Service
Food and Nutrition Division
Economic and Social Department
Food and Agriculture Organization of the United Nations
Via delle Terme di Caracalla, 00100, Rome, ITALY
Phone: +39 06 5705 6156
Fax: +39 06 5705 4593
E-Mail: ezzeddine.boutrif@fao.org

Mr. Teiji Takahashi
Director FAO Liaison Office in Japan
Liaison Office in Japan
FAO
Yokohama International Centre Minato Mirai
Nishiku, JAPAN
Phone: +81 45 222 1101
Fax: +81 45 222 1103
E-Mail: teiji.takahashi@fao.org

World Health Organization (WHO)
Organisation Mondiale de la Sante (OMS)
Organizacion Mundial de la Salud (OMS)

Dr. Jørgen Schlundt
Director
Food Safety Department
WHO (World Health Organization)
World Health Organization 20 Ave Appia, CH-1211
Geneva, SWITZERLAND
Phone: +41 22 791 34 45
Fax: +41 22 791 48 07
E-Mail: schlundtj@who.int

Ms. Cristina Tirado
Food Safety Regional Adviser
Food Safety
World Health Organization (WHO)
World Health Organization, European Center for Environment and Health, Via Francesco Crispi, 10, 00187 Rome, ITALY
Phone: +39 06 4877525
Fax: +39 06 4877599
E-Mail: cti@who.it

INTERNATIONAL INTERGOVERNMENTAL ORGANIZATIONS

European Community (EC)

Mr. Patrick Deboyser
Head of "Food Law & Biotechnology"
Health & Consumer Protection DG
European Commission
F-101 9-38 Rue Be La Loi 200 Brussels, 1049, BELGIUM
Phone: +32 2 295 1529
Fax: +32 2 295 1735
E-Mail: patrick.oeboyser@cec.eu.int

Mr. Kari Töllikkö
Principal Administrator
Council of the European Union
Rue de la Loi 175, B-1048 Brussels, BELGIUM
Phone: +32 2 285 7841
Fax: +32 2 285 6198
E-Mail: kari.tollikko@consilium.eu.int

World Trade Organization (WTO/OMC)

Mr. João Magalhães
Counsellor
Agriculture and Commodities Division

World Trade Organization (WTO)
Rue de Lausanne 154, CH-1211 Geneva 21,
SWITZERLAND
Phone: +41 22 739 50 10
Fax: +41 22 739 57 60
E-Mail: joao.magalhaes@wto.org

INTERNATIONAL NON GOVERNMENTAL ORGANIZATIONS

the 49th Parallel Biotechnology Consortium(49P)

Prof. Philip L. Bereano
Co - Director
the 49th Parallel Biotechnology Consortium
3807 S. McClellan St., Seattle, WA 98144, USA
Phone: +1 206 543 9037
Fax: +1 206 543 8858
E-Mail: pbereano@u.washington.edu

Biotechnology Industry Organization (BIO)

Dr. Michael J. Phillips
Executive Director for Food and Agriculture
Biotechnology Industry Organization
1225 Eye Street N.W., Suite 400, Washington D.C.,
20005, USA
Phone: +1 202 962 9200
Fax: +1 202 962 9201
E-Mail: mphillips@bio.org

Dr. Warren M. Strauss
Global Regulatory Director
Monsanto Company
635 13th Street, N.W., Washington, D.C., 20004,
USA
Phone: +1 202 383 2845
Fax: +1 202 383 2840
E-Mail: warren.m.strauss@monsanto.com

Consumers International (CI)

Dr. Michael Hansen
Senior Research Associate
Consumers Union of U.S.
101 Truman Ave. Yonkers, NY 10703, USA
Phone: +1 914 378 2452
Fax: +1 914 378 2928
E-Mail: hansmi@consumer.org

Samuel J. Ochieng
Chief Executive, Head of Delegation
Consumer Information Network
Solai Plaza, Off Kamunde Road Kariobangi
3rd Floor, Room 305, P.O. Box 7569, 00300,
Nairobi,
KENYA
Phone: +254 2 781131
Fax: +254 2 797944
E-Mail: cin@insightkenya.com

Mr. Toshiki Mashimo
Permanent Member of Steering Committee
Consumers Union of Japan
2F Asaga Building, 1-10-16, Meguro-Honcho
Meguro-ku, Tokyo, 152-0002, JAPAN
Phone: +81 3 3711 7766
Fax: +81 3 3715 9378
E-Mail: nishoren@jca.apc.org

Council for Responsible Nutrition (CRN)

Mr. Eddie F. Kimbrell
13209 Moss Ranch Lane, Fairfax, VA, 22033,
USA
Phone: +1 703 631 9187
Fax: +1 703 631 3866
E-Mail: edkim@aol.com

European Association for Bioindustries (EUROPABIO)

Naohiro Hoko
Regulatory Affairs Manager
Syngenta Japan K.K.
21F Triton Square Office Tower X, 1-8-10 Harumi
Chuoh-ku Tokyo, 104-6021, JAPAN
Phone: +81 362 213 834
Fax: +81 362 213 898
E-Mail: naohiro.hoko@syngenta.com

Grain and Feed Trade Association (GAFTA)

Ms. Hannah Highfill
The Grain and Food Trade Association
GAFTA House, 6 Chapel Place, Rivington Street, London EC2A 3SH, UNITED KINGDOM
Phone: +44 20 7814 9666
Fax: +44 20 7814 8383

Mr. Paul Green
The Grain and Food Trade Association
GAFTA House, 6 Chapel Place, Rivington Street, London EC2A 3SH, UNITED KINGDOM

Phone: +44 20 7814 9666
Fax: +44 20 7814 8383

Greenpeace International (GREENPEACE)

Mr. Bruno Heinzer
GREENPEACE
Postfach, CH-8031 Zurich, SWITZERLAND
Phone: +41 1 447 4141
Fax: +41 1 447 4199
E-Mail: bheinzer@ch.greenpeace.org

International Association of Consumer Food Organizations (IACFO)

Mr. Junichi Kowaka
Director
Japan Offspring Fund
2-5-2 Kojimachi, Chiyoda, Tokyo, 102-0083, JAPAN
Phone: +81 3 5276 0256
Fax: +81 3 5276 0259
E-Mail: jof@nifty.ne.jp

Ms. Natsuko Kumasawa
Japan Offspring Fund
2-5-2 Kojimachi, Chiyoda, Tokyo, 102-0083, JAPAN
Phone: +81 3 5276 0256
Fax: +81 3 5276 0259
E-Mail: natsuko@japan.email.ne.jp

Ms. Satoko Endo
Japan Offspring Fund
2-5-2 Kojimachi, Chiyoda, Tokyo, 102-0083, JAPAN
Phone: +81 3 5276 0256
Fax: +81 3 5276 0259
E-Mail: satoko.endo@japan.email.ne.jp

Ms. Yumiko Hayasaka
Japan Offspring Fund
2-5-2 Kojimachi, Chiyoda, Tokyo, 102-0083, JAPAN
Phone: +81 3 5276 0256
Fax: +81 3 5276 0259
E-Mail: jof@nifty.ne.jp

Miss Rorie Sasaki
Japan Offspring Fund
2-5-2 Kojimachi, Chiyoda, Tokyo, 102-0083, JAPAN
Phone: +81 3 5276 0256
Fax: +81 3 5276 0259
E-Mail: jof@nifty.ne.jp

Mr. Takashi Takeda
Japan Offspring Fund
2-5-2 Kojimachi, Chiyoda, Tokyo, 102-0083, JAPAN
Phone: +81 3 5276 0256
Fax: +81 3 5276 0259
E-Mail: jof@nifty.ne.jp

International Alliance of Dietary/Food Supplement Associations (IADSA)

Ms. Kaori Nakajima
IADSA - International Alliance of Dietary / Food Supplement Associations
Rue de L' Association 50, 1000 Brussels, BELGIUM
Phone: +32 2 2091155
Fax: +32 2 2233064
E-Mail: SECRETARIAT@iadsa.be

International Cooperative Alliance (ICA)

Ms. Hisako Nakazawa
Quality Control
Consumers Co-operative Tokyo
4-1-3 Shakuji-machi, Nerima-ku, Tokyo, 177-8511, JAPAN
Phone: +81 3 3904 1352
Fax: +81 3 5393 5619
E-Mail: hisako_nakazawa@coopnet.or.jp

Mr. Tatsuhito Kasamatsu
Merchandise Testing Center
Consumers Co-operative Kobe
1-3-23 Okamoto, Higashinada-ku, Kobe, Hyogo-pre, 668-0072, JAPAN
Phone: +81 78 453 0116
Fax: +81 78 453 0185
E-Mail: t.kasamatsu@clubAA.com

Ms. Ryoko Shimizu
Organization for the Policy Making by Citizen's Sector
Seikatsu Club Consumers' Cooperative Union
4-1-5 Akazutsumi, Setagaya-ku, Tokyo, 056-0044, JAPAN
Phone: +81 3 3325 7861
Fax: +81 3 3325 7955
E-Mail: BYR17071@nifty.ne.jp

Ms. Etsuko Kondou
Planning Department
Seikatsu Club Consumers' Cooperative Union
Sigma Higashi-Shinjuku Building, 6-24-20

Shinjuku, Shinjuku-ku, Tokyo, 160-0022, JAPAN
Phone: +81 3 5258 1883
Fax: +81 3 5285 1839
E-Mail: etsuko.kondou@s-club.coop

Mr. Shuichi Watanabe
Safety Policy Service
Japanese Consumers' Co-operative Union
CO-OP PLAZA, 3-29-8, Shibuya, Shibuya-ku, Tokyo, 150-8913, JAPAN
Phone: +81 3 5778 8109
Fax: +81 3 5778 8008
E-Mail: shuuichi.watanabe@jccu.coop

Mr. Hiroshi Suzuki
Safety Policy Service
Japanese Consumers' Co-operative Union
CO-OP PLAZA, 3-29-8, Shibuya, Shibuya-ku, Tokyo, 150-8913, JAPAN
Phone: +81 3 5778 8109
Fax: +81 3 5778 8008
E-Mail: hiroshi.suzuki@jccu.coop

Mr. Kazuo Onitake
Safety Policy Service
Japanese Consumers' Co-operative Union
CO-OP PLAZA, 3-29-8, Shibuya, Shibuya-ku, Tokyo, 150-8913, JAPAN
Phone: +81 3 5778 8109
Fax: +81 3 5778 8008
E-Mail: kazuo.onitake@jccu.coop

International Council of Grocery Manufacturers Associations (ICGMA)

Dr. Mark Nelson
Vice President, Scientific and Regulatory Policy
Scientific and Regulatory Policy
ICGMA-International Council of Grocery Manufacturers Associations
1010 Wisconsin Ave, NW, Suite 900,
Washington, DC, 20007, USA
Phone: +1 202 337 9400
Fax: +1 202 337 4508
E-Mail: mnelson@gmabrands.com

Institute of Food Technologists (IFT)

Robert V. Conover
Assistant General Counsel
Kikkoman Foods, Inc.
Six Comers Road, P.O. Box 69, Walworth, WI 53184
Phone: +262 275 1651
Fax: +262 275 9452
E-Mail: roconover@kikkoman.com

International Glutamate Technical Committee(IGTC)

Dr. Robert G. Bursey
Director Regulatory Affairs
1120 Connecticut Avenue, NW, Suite 416
Washington, DC 20036, USA
Phone: +1 202 457 0284
Fax: +1 202 457 0107
E-Mail: burseyb@ajiusa.com

International Life Sciences Institute (ILSI)

Mr. Fumitake Fukutomi
ILSI Japan
Kojimachi R.K. Bldg, 2-6-7, Kojimachi
Chiyoda-ku, Tokyo, 102-0083, JAPAN
Phone: +81 3 5215 3535
Fax: +81 3 5215 3537
E-Mail: ffukutomi@ilsijapan.org
Dr. Shogo Kurasawa
ILSI Japan
Kojimachi R.K. Bldg, 2-6-7, Kojimachi
Chiyoda-ku, Tokyo, 102-0083, JAPAN
Phone: +81 3 5215 3535
Fax: +81 3 5215 3537
E-Mail: ilsijapan@ilsijapan.org

Mr. Shoei Hashimoto
Suntory Ltd.
1-2-3, Motoakasaka, Minato-ku, Tokyo, 107-8430, JAPAN
Phone: +81 3 3470 1137
Fax: +81 3 5770 0965
E-Mail: Shoei_Hashimoto@suntory.co.jp

Dr. Takashi Sasaki
Meiji Institute of Health Science
540 Naruda, Odawara Kanagawa, 250-0862, JAPAN
Phone: +81 465 37 3661
Fax: +81 465 36 2776
E-Mail: TAKASHI_SASAKI@MEIJI-MILK.COM

Dr. Zenta Takatsu
Morinaga Milk Industry Co., Ltd.
5-1-83, Higashihara, Zama-shi Kanagawa, 228-

8583, JAPAN
Phone: +81 462 52 3056
Fax: +81 462 52 3049
E-Mail: z_takatu@morinagamilk.co.jp

International Soft Drinks Council (ISDC)

Dr. Shuji Iwata
Head of Delegation
International Soft Drinks Council (ISDC)
International Soft Drinks Council c/o National Soft Drink Association 1101, 16th Street, NW
Washington, D.C., 20036, USA
Phone: +1 202 463 6790
Fax: +1 202 463 8172
E-Mail: isdc@nsda.com

Mr. Yasuharu Gotoh
Delegate
International Soft Drinks Council (ISDC)
International Soft Drinks Council c/o National Soft Drink Association 1101, 16th Street, NW
Washington, D.C., 20036, USA
Phone: +1 202 463 6790
Fax: +1 202 463 8172
E-Mail: isdc@nsda.com

International Union of Biological Sciences(IUBS)

Prof. Darryl R.J. Macer
IUBS Bioethics Program Director
Institute of Biological Sciences
University of Tsukuba
Tsukuba Science City, 305-8572, JAPAN
Phone: +81 298 53 4662
Fax: +81 298 53 6614
E-Mail: macer@sakura.cc.tsukuba.ac.jp

Dr. Minakshi Bhardwaj
Institute of Biological Sciences
Tsukuba Science City, 305-8572, JAPAN
Phone: +81 298 53 4662
Fax: +81 298 53 6614
E-Mail: bminakshi@hotmail.com

Ms. Makina Kato
Institute of Biological Sciences
Tsukuba Science City, 305-8572, JAPAN
Phone: +81 298 53 4662
Fax: +81 298 53 6614
E-Mail: MAKINCHO@aol.com

Mrs. Eiko Suda
Eubios Ethics Institute
P.O. Box 125, Tsukuba Science City, 305-8691, JAPAN
Phone: +81 298 53 4662
Fax: +81 298 53 6614
E-Mail: fwhv4551@mb.infoweb.ne.jp

Dr. Uwe Serdult
Professor, Dept. of Political Science
University of Zurich, Karl Schmid-str. 4, Zurich, CH-8006, SWITZERLAND
Phone: +41 1 634 3848
Fax: +41 1 634 4925
E-Mail: serduelt@pwi.unizh.ch

SECRETARIAT

Joint FAO/WHO Secretariat

Ms. Selma H. Doyran
Food Standards Officer
Joint FAO/WHO Food Standards Programme
Food and Nutrition Division
Food and Agriculture Organization of the United Nations
Viale delle Terme di Caracalla, 00100 Rome, ITALY
Phone: +39 06 5705 5826
Fax: +39 06 5705 4593
E-Mail: selma.doyran@fao.org

Mr. Yoshihide Endo
Food Standards Officer
Food and Nutrition Division
Food and Agriculture Organization of the United Nations
Viale delle Terme di Caracalla, 00100 Rome, ITALY
Phone: +39 06 5705 4796
Fax: +39 06 5705 4593
E-Mail: yoshihide.endo@fao.org

Dr. Yasuhisa Nakamura
Scientist, Food Safety Department
WHO
20 Avenue Appia CH-1211 Geneva 27, SWITZERLAND
Phone: +41 22 791 4324
Fax: +41 22 791 4807
E-Mail: nakamuray@who.int

Japanese Secretariat

Mr. Toshiro Nakagaki
Director

Standards Division
Department of Food Safety, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare
1-2-2 Kasumigaseki, Chiyoda-ku, Tokyo, JAPAN
Phone: +81 3 3595 2146
Fax: +81 3 3595 2251
E-Mail: codexj@mhlw.go.jp

Mr. Hideki Ito
Deputy Director
Policy Planning Division
Department of Food Safety, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

Dr. Atsushi Ichinose
Deputy Director
Policy Planning Division
Department of Food Safety, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

Mr. Fumihiko Okada
Section Chief
Policy Planning Division
Department of Food Safety, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

Mr. Tetsuya Taniguchi
Section Chief
Policy Planning Division
Department of Food Safety, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

Mr. Yusuke Hoshi
Policy Planning Division
Department of Food Safety, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

Mr. Satoru Tomonaga
Policy Planning Division
Department of Food Safety, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

Mr. Tatsuo Hasebe
Policy Planning Division
Department of Food Safety, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

Ms. Rie Hatanaka
Policy Planning Division
Department of Food Safety, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

Mr. Tetsuo Odaira
Deputy Director
Office of Health Policy on Newly Developed Foods Department of Food Safety, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

Mr. Yuji Kitayama
Section Chief
Office of Quarantine Station Administration
Department of Food Safety, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

Mr. Hideki Shingai
Office of Quarantine Station Administration
Department of Food Safety, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

Mr. Naohisa Kondo
Office of Quarantine Station Administration
Department of Food Safety, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

Mr. Hiroaki Noguchi
Office of Quarantine Station Administration
Department of Food Safety, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

Mr. Nobutaka Hoshikawa
Deputy Director
Standards Division
Department of Food Safety, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

Mr. Nobuo Uemura
Deputy Director
Standards Division
Department of Food Safety, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

Mr. Yasunori Yoshida
Deputy Director
Standards Division
Department of Food Safety, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

Mr. Hidefumi Miyoshi
Section Chief
Standards Division
Department of Food Safety, Pharmaceutical and

Food Safety Bureau
Ministry of Health, Labour and Welfare

Dr. Eiichi Yokota
Section Chief
Standards Division
Department of Food Safety, Pharmaceutical and
Food Safety Bureau
Ministry of Health, Labour and Welfare

Mr. Takahiro Inoue
Section Chief
Standards Division
Department of Food Safety, Pharmaceutical and
Food Safety Bureau
Ministry of Health, Labour and Welfare

Mr. Hirotada Nagai
Standards Division
Department of Food Safety, Pharmaceutical and
Food Safety Bureau
Ministry of Health, Labour and Welfare

Dr. Toshitaka Higashira
Standards Division
Department of Food Safety, Pharmaceutical and
Food Safety Bureau
Ministry of Health, Labour and Welfare

Mr. Yuki Iwama
Standards Division
Department of Food Safety, Pharmaceutical and
Food Safety Bureau
Ministry of Health, Labour and Welfare

Mr. Takayuki Okubo
Standards Division
Department of Food Safety, Pharmaceutical and
Food Safety Bureau
Ministry of Health, Labour and Welfare

Ms. Michiyo Takabayashi
Standards Division
Department of Food Safety, Pharmaceutical and
Food Safety Bureau
Ministry of Health, Labour and Welfare

Mr. Mitsuo Yoshida
Deputy Director
Inspection and Safety Division
Department of Food Safety, Pharmaceutical and
Food Safety Bureau
Ministry of Health, Labour and Welfare

Mr. Mitsumasa Yamauchi
Section Chief
Inspection and Safety Division
Department of Food Safety, Pharmaceutical and
Food Safety Bureau
Ministry of Health, Labour and Welfare

Mr. Nobuaki Yamagata
Inspection and Safety Division
Department of Food Safety, Pharmaceutical and
Food Safety Bureau
Ministry of Health, Labour and Welfare

Mr. Shotaro Aratsu
Inspection and Safety Division
Department of Food Safety, Pharmaceutical and
Food Safety Bureau
Ministry of Health, Labour and Welfare

Dr. Hiroki Tanabe
Inspection and Safety Division
Department of Food Safety, Pharmaceutical and
Food Safety Bureau
Ministry of Health Labour and Welfare

Ms. Yuko Kumagai
Deputy Director
International Affairs Division
Ministry of Health, Labour and Welfare

Appendix II

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

(At Step 8 of the Procedure)

SECTION 1 – SCOPE

1. This Guideline supports the Principles for the Risk Analysis of Foods Derived from Modern Biotechnology and addresses safety and nutritional 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 may 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. 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

[1] The microorganisms included in these applications are bacteria, yeasts, and filamentous fungi. (Such uses could 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 Joint FAO/WHO Expert 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.

assessments that have been conducted have focused primarily on the absence of properties associated with pathogenicity in these microorganisms and the absence of reports of adverse events attributed to ingestion of these microorganisms, rather than evaluating the results of prescribed studies. Further, many foods contain substances that would be considered 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. 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; and

   D) issues specific to the use of the recombinant-DNA microorganism in food production, including its genetic stability, potential for gene transfer, colonization of the gastrointestinal tract and persistence[4] therein, interactions that the recombinant-DNA microorganism may have with the gastrointestinal flora or the mammalian host, and any impact of the recombinant-DNA microorganism 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. 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.

8. 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, 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. When conducting a comparison of a recombinant-DNA microorganism or a food produced using recombinant-DNA microorganism with their respective conventional counterparts, any

[4] Persistence connotes survival of microorganisms in the gastrointestinal tract longer than two intestinal transit times (International Life Science Institute, *The safety assessment of viable genetically modified microorganisms used as food,* 1999, Brussels; the Joint FAO/WHO Expert Consultation on Foods Derived from Biotechnology- *Safety assessment of foods derived from genetically modified microorganisms*, 24-28 September, 2001, Geneva, Switzerland).

identified differences should be taken into account, whether they are the result of intended or unintended effects. Due consideration should be given to the interactions of the recombinant-DNA microorganism with the food matrix or the microflora and to the safety of any newly-expressed protein(s) and secondary metabolic products. 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.

SECTION 2 – DEFINITIONS

9. 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 techniques including recombinant deoxyribonucleic acid (DNA) and direct injection of nucleic acid into cells or organelles.

"**Conventional Counterpart**"[5] – means:

- a microorganism/strain with a known history of safe use in producing and/or processing the food and related to the recombinant-DNA strain. 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

10. 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.

11. 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, any effects on the safety of the food should be examined.

12. 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

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

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.

13. 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 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 food. 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.

14. 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, taking into account available information regarding the donor and the characterization of the modified genetic material and the gene product. 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.

15. 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 produced using 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*[6].

16. 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 and the food produced using recombinant-DNA microorganism relative to its conventional counterpart. This concept is used to identify for evaluation similarities and differences between a recombinant-DNA microorganism used in food processing as well as the food produced using the recombinant-DNA microorganisms and their respective conventional counterparts as defined in paragraph 9. It aids in the identification of potential safety and nutritional issues and is considered the most appropriate strategy to date for safety assessment of foods produced using recombinant-DNA microorganisms. The safety assessment carried out in this way does not imply absolute safety of the new

[6] The concept of *substantial equivalence* as described in the Joint 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.

product; rather, it focuses on assessing the safety of any identified differences so that the safety of the recombinant-DNA microorganism and the food produced using recombinant-DNA microorganism can be considered relative to their respective conventional counterparts.

Unintended Effects

17. 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. 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 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.

18. 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.

19. 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.

20. 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.

21. 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

22. 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: assessment of potential toxicity and other traits related to pathogenicity;

    b. compositional analyses of key components;

    c. evaluation of metabolites;

    d. effects of food processing;

    e. assessment of immunological effects;

    f. assessment of viability and residence of microorganisms in the human gastrointestinal tract;

    g. antibiotic resistance and gene transfer; and

    h. nutritional modification.

23. In certain cases, the characteristics of the microorganisms and/or the foods produced/processed using these microorganisms may necessitate generation of additional data and information to address issues that are unique to the microorganisms and/or food products under review.

24. 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.

25. 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 immuno-compromised individuals, infants, and the elderly. The expected endpoint of such an assessment will be a conclusion regarding whether the new food and/or microorganisms are as safe as the conventional counterparts taking into account dietary impact of any changes in nutritional content or value. Where the microorganism is likely to be viable upon ingestion, its safety should be compared to a conventional counterpart taking into account residence of the recombinant-DNA microorganism in the gastrointestinal tract, and where appropriate, interactions between it and the gastrointestinal flora of mammals (especially humans) and

impacts of the recombinant-DNA microorganism on the immune system. 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 to protect the health of consumers and if so to make well-informed and appropriate decisions in this regard.

SECTION 4- GENERAL CONSIDERATIONS

Description of the Recombinant-DNA Microorganism

26. 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 nature of the organism or food produced using the organism being submitted for safety assessment. Recombinant-DNA microorganisms used in food production or contained in food, should be conserved as stock cultures with appropriate identification using molecular methods, and preferably, in established culture collections. This may facilitate the review of the original safety assessment. Such stock cultures should be made available to regulatory authorities upon request.

Description of the Recipient Microorganism and its Use in Food Production

27. 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, antibiotic resistance 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, antibiotics, antibiotic resistance factors or other factors related to pathogenicity, or immunological impact, and information about the genetic stability of the microorganism;

    D) history of safe use in food production or safe consumption in food; and

    E) information on the relevant production parameters used to culture the recipient microorganism.

28. 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 including, as appropriate, the presence of mobile DNA elements, i.e. insertion sequences, transposons, plasmids, and prophages.

29. 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(s)

30. 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 organism, 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 organism's genotype and phenotype relevant to its safety including any known toxins, antibiotics, antibiotic resistance factors or other factors related to pathogenicity, or immunological impact; and

    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).

Description of the Genetic Modification(s) Including Vector and Construct

31. Sufficient information should be provided on the genetic modification(s) to allow for the identification of all 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.

32. The description of the strain construction process should include:

    A) information on the specific method(s) used for genetic modification;

    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 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.

33. 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)

34. 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 preferably limited to the sequences necessary to perform the intended functions.

35. 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 organisation of the modified genetic material at each insertion site including the copy number and sequence data of the inserted, modified, or deleted material, plasmids or carrier DNA used to transfer the desired genetic sequences, and the surrounding sequences. This will enable the identification of any substances expressed as a consequence of the inserted, modified or deleted material;

    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

    E) particular reference to any sequences known to encode, or to influence the expression of, potentially harmful functions.

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

    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).

37. In addition, information should be provided:

    A) to demonstrate whether the arrangement of the modified genetic material has been conserved[7] or whether significant rearrangements have occurred after introduction to the cell and propagation

[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

of the recombinant strain to the extent needed for its use(s) in food production, including those that may occur during its storage according to current techniques;

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 more 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

38. The safety assessment of the modified microorganism should be performed on a case by case basis depending on the nature and extent of the introduced changes. 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. Effects of the recombinant-DNA microorganism on the food matrix should be considered as well. If the characterisation of the food indicates that the available data are insufficient for a thorough safety assessment, properly designed animal or *in vitro* studies with the recombinant-DNA microorganism and/or the food produced using it could be considered necessary.

Expressed Substances: Assessment of Potential Toxicity and Other Traits Related to Pathogenicity

39. 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, if necessary, 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.

40. 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 and compared to a conventional counterpart. All quantitative measurements should be analysed using appropriate statistical techniques. Current dietary exposure and possible effects on population sub-groups should also be considered.

- In the case of proteins, the assessment of potential toxicity should take into account the structure

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 in a manner to enable verification of the genetic stability.

and function of the protein and 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 studies[9] may be carried out in cases where the protein is present in the food, but is not closely 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.

41. 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

42. Analyses of concentrations of key components[10] 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

43. 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 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).

44. 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

[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.

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.

Effects of Food Processing

45. 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

46. 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 the Annex to this guideline.

47. Genes derived from known allergenic sources should be assumed to encode an allergen and be avoided unless scientific evidence demonstrates otherwise. The transfer of genes from organisms 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.

48. Recombinant-DNA microorganisms that remain viable in foods may interact with the immune system in the gastrointestinal 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 Gastrointestinal Tract

49. In some foods produced using recombinant-DNA microorganisms, ingestion of these microorganisms and their residence[11] 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.

50. 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 (or residence time) of the microorganism alone and within the respective food matrix in the digestive tract and the impact on the intestinal microflora in appropriate systems. The nature of intended and unintended effects of genetic modification and the degree of differences from the conventional counterpart will determine the extent of such testing.

[11] 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. Whether the genetically modified microorganism is established in the gastrointestinal tract or not, the possibility remains that it might influence the microflora or the mammalian host (Joint FAO/WHO Expert Consultation on Foods Derived from Biotechnology – *Safety assessment of foods derived from genetically modified microorganism*, 24-28 September, 2001, Geneva, Switzerland).

Antibiotic Resistance and Gene Transfer

51. 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 in which antibiotic resistance is encoded by transmissible genetic elements should not be used where such strains or these genetic elements are present in the final food. Any indication of the presence of plasmids, transposons, and integrons containing such resistance genes should be specifically addressed.

52. 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.

53. 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.

54. 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;
- where the recombinant-DNA microorganism will remain viable in the gastrointestinal tract, genes should be avoided in the genetic construct that could provide a selective advantage to recipient organisms to which the genetic material is unintentionally transferred; and
- sequences that mediate integration into other genomes should be avoided in constructing the introduced genetic material.

Nutritional Modification

55. 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 nutritional 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.

56. 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.

57. 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.

58. 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.

59. 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 food.

Review of Safety Assessments

60. 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.

Annex

Assessment of Possible Allergenicity (Proteins)

Section 1 – Introduction

1. All newly expressed proteins[1] produced by recombinant-DNA microorganisms 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 produced by recombinant-DNA microorganisms, 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 by recombinant-DNA microorganisms. 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 immunological effects, paragraph 47 of the Draft Guideline for the Conduct of Food Safety Assessment of Foods Produced using Recombinant-DNA Microorganisms. 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 produced using recombinant-DNA microorganisms, information should describe any reports of allergenicity associated with the donor organism. Allergenic sources of genes would be defined as those organisms for which reasonable evidence of IgE mediated oral, respiratory or contact allergy is available. Knowledge of the source of the introduced protein allows the identification of tools and relevant data to be considered in the allergenicity assessment. These include: the availability of sera for screening purposes; documented type, severity and frequency of allergic reactions; structural characteristics and amino acid sequence; physicochemical and immunological properties (when available) of known allergenic proteins from that source.

Section 3.2 – Amino Acid Sequence Homology

8. The purpose of a sequence homology comparison is to assess the extent to which a newly expressed protein is similar in structure to a known allergen. This information may suggest whether that protein has an allergenic potential. Sequence homology searches comparing the structure of all newly expressed proteins with all known allergens should be done. Searches should be conducted using various algorithms such as FASTA or BLASTP to predict overall structural similarities. Strategies such as stepwise contiguous identical amino acid segment searches may also be performed for identifying sequences that may represent linear epitopes. The size of the contiguous amino acid search should be based on a scientifically justified rationale in order to minimize the potential for false negative or false positive results[2]. Validated search and evaluation procedures should be used in order to produce biologically meaningful results.

9. IgE cross-reactivity between the newly expressed protein and a known allergen should be considered a possibility when there is more than 35% identity in a segment of 80 or more amino acids (FAO/WHO 2001) or other scientifically justified criteria. All the information resulting from the sequence homology comparison between the newly expressed protein and known allergens should be reported to allow a case-by-case scientifically based evaluation.

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

11. A negative sequence homology result indicates that a newly expressed protein is not a known allergen and is unlikely to be cross-reactive to known allergens. A result indicating absence of significant sequence homology should be considered along with the other data outlined under this strategy in assessing the allergenic potential of newly expressed proteins. Further studies should be conducted as appropriate (see also sections 4 and 5). A positive sequence homology result indicates that the newly expressed protein is likely to be allergenic. If the product is to be considered further, it should be assessed using serum from individuals sensitized to the identified allergenic source.

Section 3.3 – Pepsin Resistance

12. Resistance to pepsin digestion has been observed in several food allergens; thus a correlation exists between resistance to digestion by pepsin and allergenic potential[3]. 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

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

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

allergenic. The establishment of a consistent and well-validated pepsin degradation protocol may enhance the utility of this method. However, it should be taken into account that a lack of resistance to pepsin does not exclude that the newly expressed protein can be a relevant allergen.

13. Although the pepsin resistance protocol is strongly recommended, it is recognized that other enzyme susceptibility protocols exist. Alternative protocols may be used where adequate justification is provided[4].

Section 4 – Specific Serum Screening

14. For those proteins that originate from a source known to be allergenic, or have sequence homology with a known allergen, testing in immunological assays should be performed where sera are available. Sera from individuals with a clinically validated allergy to the source of the protein can be used to test the specific binding to IgE class antibodies of the protein in *in vitro* assays. A critical issue for testing will be the availability of human sera from sufficient numbers of individuals[5]. In addition, the quality of the sera and the assay procedure need to be standardized to produce a valid test result. For proteins from sources not known to be allergenic, and which do not exhibit sequence homology to a known allergen, targeted serum screening may be considered where such tests are available as described in paragraph 17.

15. In the case of a newly expressed protein derived from a known allergenic source, a negative result in *in vitro* immunoassays may not be considered sufficient, but should prompt additional testing, such as the possible use of skin test and *ex vivo* protocols[6]. A positive result in such tests would indicate to 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.

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.

[4] Reference to Joint FAO/WHO Expert Consultation (2001).

[5] According to the Report of the Joint 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] Reference to Joint FAO/WHO Expert Consultation (2001) on description of ex vivo.