codex alimentarius commission

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS

WORLD HEALTH ORGANIZATION

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JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX AD HOC INTERGOVERNMENTAL TASK FORCE ON FOODS DERIVED FROM BIOTECHNOLOGY

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Proposed Draft Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Animals

Comments at Step 3, in response to Circular Letter CL 2006/27-FBT, by Argentina, Australia, Canada, European Community, Japan, Kenya, Mexico, New Zealand and the United States of America.

ARGENTINA

Argentina is very pleased with the outcome of this work, and compliments the Working Group for providing such an excellent document, which contains only a few sections with open options. Argentina has no comments for the most of the document which is under consensus; therefore, we are only providing comments on the bracketed sections and the expert consultation.

Paragraph 2: Issues that the guideline is not intended to address. This subject has motivated a lengthy debate in the Working Group. Except for this case, in every other occasion where a very controversial issue was raised, it was agreed to maintain the original wording of the plant guideline. Therefore, Argentina would like to suggest a consistent approach, and to adopt the third option for paragraph 2.

Nevertheless, if other members insist on a more detailed text, Argentina would be, in principle, willing to engage on discussing the fourth option to paragraph 2.

Paragraph 16: Unintended effects of random DNA insertion. The first sentence of the section between brackets is not deemed to be necessary, since the change of "metabolites patterns" will be necessarily due to the effects on gene expression listed in the previous sentence. Besides, the text can be misleading because the alteration of metabolite patterns can be interpreted to be a separate possible outcome, when it is a secondary consequence of gene expression effects. And it is not clear what exactly a "pattern of metabolites" is, and if there is actually any difference between a "new pattern" and a "changed pattern". In addition, the second sentence is quite an obvious example; and this level of exemplification has been avoided throughout the elaboration of the guideline. In conclusion, Argentina would like to propose to remove the text between brackets.

Paragraph 37, item C: information on DNA insertion. We consider that the proposed changes do not improve or add significant changes to the previous guidance. Since it is one of the working principles not to innovate from the plant guideline unless there is a significant issue, Argentina would like to propose to maintain the original text of the plant guideline for this item.

Paragraph 39, item D: gene expression under different typical husbandry conditions. The text proposed in brackets does not provide guidance on the rationale for deciding which cases merit the need of repeated expression studies, and the extent to which further studies of this kind are advised. Therefore, Argentina would not support the incorporation of this text unless a clear, scientifically sustained, alternative text is presented.

AUSTRALIA

Australia would like to expresses its sincere appreciation to the Government of Japan and the European Community for hosting the Working Group meetings, chaired by Japan and Australia, which developed the Proposed Draft Guideline for the Conduct of Food Safety Assessment of Food Derived from Recombinant-DNA Animals.

Australia considers the draft text developed by the Working Group will provide very useful general guidance to those evaluating the safety and nutritional aspects of foods derived from recombinant-DNA animals.

Australia is particularly supportive of the approach to food safety assessment, as outlined in the draft guideline (paragraph 7), which takes account of three key elements: the nature of the recombinant DNA construct and its expression products; the health of the recombinant DNA animal; and the composition of foods derived from the recombinant DNA animal. Australia believes this approach to be consistent with that recommended by the 2003 FAO/WHO Expert Consultation on the Safety Assessment of Foods Derived from Genetically Modified Animals, including Fish[1].

Australia is also supportive of the approach adopted by the Working Group to base the animal guideline closely on the plant guideline and to only deviate from the language in the plant guideline where it could be scientifically justified on the basis of biological differences between plants and animals. Australia believes this parsimonious approach provided for more focussed discussion in the Working Group, which greatly assisted the development of the current text.

Specific Comments on the Proposed Draft Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Animals

Paragraph 1

Australia notes that in initiating development of the animal guideline, the Task Force agreed that the initial work would be focussed on developing a guideline for recombinant-DNA animals in general. The general scope of the document is alluded to in the second sentence of paragraph 1, which states:

> *It addresses safety and nutritional aspects of foods consisting of, or derived from, **animals that have a history of safe use as sources of food**, and that have been modified by modern biotechnology to exhibit new or altered expression of traits.*

[1] FAO/WHO (2004) Report of the FAO/WHO Expert Consultation, Rome, 17-21 November 2003, FAO Food and Nutrition Paper 79.

This wording is essentially identical to that in the plant guideline and is intended to cover the full gamut of animal species (both invertebrate and vertebrate) that are used as sources of food and which it is technically possible to modify using modern biotechnology. However, as written, Australia considers the wording of this sentence may be a bit vague, particularly in the animal context, and suggests that consideration be given to including a footnote to indicate that the guideline is intended to apply to both vertebrate and invertebrate species.

Paragraph 2

While Australia recognises that issues such as animal welfare, ethical, moral and socio-economic aspects, environmental considerations etc, may be important issues for governments to consider in relation to animal biotechnology, Australia does not believe it appropriate for such matters to be considered within the context of a food safety assessment, which is a science-based risk assessment exercise. Australia also notes that such issues are not addressed by the Principles for the Risk Analysis of Foods Derived from Modern Biotechnology[2], under which the proposed draft guideline would sit.

Australia therefore supports the inclusion of a paragraph within the proposed draft guideline which lists those issues that are not addressed by the guideline and has given consideration to the five options that are currently within square brackets in the document. Australia prefers the fourth option as listed in the document, namely:

> *2. This Guideline addresses only food safety and nutritional issues. It therefore does not address:*
> - *animal welfare;*
> - *ethical, moral and socio-economical aspects;*
> - *the safety of food derived from recombinant-DNA animals intended to be used [exclusively] for other purposes than food (e.g. pharmaceutical, xenotransplantation, or industrial uses);*
> - *environmental risks related to the environmental release of recombinant-DNA animals used in food production;*
> - *the safety of recombinant-DNA animals used as feed, or the safety of animals fed with feed derived from recombinant-DNA animals, plants or microorganisms.*

This option is preferred because the wording in the chapeau statement avoids the use of value-laden terms, and it is clear both what is within the scope of the guideline, and what is not.

In relation to the matters which are listed as not being addressed by the proposed draft guideline, Australia would support deletion of the third dot point relating to recombinant-DNA animals intended for purposes other than food. Australia recognises there may be legitimate circumstances in which a country may wish to apply a food safety assessment to such animals and therefore believes the proposed draft guideline will provide useful guidance in such circumstances.

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[2] CAC/GL 44-2003, paragraph 7.

Paragraph 31

Australia notes that in initiating development of the draft guideline the Task Force agreed that "*no new work would be commenced, at this stage, to address the food safety of cloned animals as such, while noting that the issue could be considered, if appropriate and to the extent necessary, during the process of developing a draft guideline for the food safety assessment of recombinant-DNA animals*."[3]

This matter was considered within the context of recombinant-DNA animals by the Working Group, where it was recognised it would be important to provide information on the various techniques and processes used to obtain the initial recombinant-DNA animal. Nuclear transfer or "cloning" has been given as an example of one of these techniques. Australia considers the issue of nuclear transfer has therefore been appropriately considered, and to the extent necessary, within the context of the recombinant-DNA animal guideline.

Paragraph 37(C)

The report of the Working Group states that "some participants have ongoing concerns about the draft text that describes the DNA sequence information required at various stages of the assessment process". The text referred to is contained within paragraph 37(C) of the proposed draft animal guideline, and the equivalent paragraph in the plant guideline is 30(C). The two paragraphs are identical except for the inserted text currently in square brackets (bolded below) which appears in the proposed draft animal guideline:

> *(C) [the organisation of the inserted genetic material at each insertion site including copy number and sequence data of the inserted**[, modified or deleted]** material and of the surrounding region, sufficient to identify any substances expressed as a consequence of the inserted material, or, where more appropriate/**[and if applicable]**, other information such as analysis of transcripts or expression products to identify any new substances that may be present in the food; and]*

As agreement could not be reached on modifications to this paragraph, and because of concerns expressed about the extent of sequence information required, it was decided to place the entire paragraph in square brackets.

Australia is mindful of the approach that was adopted by the Working Group to only deviate from the language contained within the plant guideline where it could be scientifically justified on the basis of differences between plants and animals. We have been unable to identify any difference between plants and animals that would justify more onerous requirements for sequence analysis in the case of recombinant DNA animals. Given this, Australia would suggest that the proposed text in square brackets (in bold above) be deleted and that the text of this paragraph remain identical to that in the plant guideline.

Paragraph 63

Australia notes this paragraph was modified to make it more relevant to the animal context and supports the amended wording, as drafted by the Working Group. However, to improve clarity Australia would propose that the final sentence of this paragraph be modified to read:

> "***The safety assessment should take the potential for these alterations into account, and*** *where such alterations are identified, consideration should be given to the potential impacts on human health using conventional procedures for establishing safety*."

[3] ALINORM 06/29/34, paragraph 17.

Paragraphs 64-67

Australia recalls the lengthy debate on the issue of antibiotic resistance genes during the elaboration of the plant guideline and therefore would strongly support retaining the language in paragraphs 64-67, as currently drafted (and which is identical to that in the plant guideline). To modify the text as currently drafted in the animal guideline would introduce an inconsistency between the animal and plant guidelines, which in Australia's view would be difficult to justify on scientific grounds, given that antibiotic resistance genes are currently being safely used in both animal and plant biotechnology. Australia also notes that a number of questions on marker and reporter genes have been posed by the Working Group for consideration by an expert consultation and therefore considers it would be premature to discuss the issue of antibiotic resistance genes, or any modifications to paragraphs 64-67, until scientific advice has been received from the expert consultation.

Minor comments

Australia has noted a number of minor typographical errors which escaped the editing process following the Working Group meetings, and these are listed below for reference:

- Paragraph 4, third line – "……*counterpart having a history* ~~***or***~~ ***of*** *safe use, …..*"
- Paragraph 15, line 8-9 – "*Unintended effects in recombinant-DNA* ***animals*** *may also arise……*"
- Paragraph 24, point E) – "*history of safe use for* ~~***food***~~ *consumption as food*."
- Paragraph 35, third line – "*….information on how the animals breed and* ***grows*** *its….*"
- Paragraph 39, point A) – "*….or whether significant* ***rearrangements*** *have occurred…..*"

CANADA

Canada would like to thank Australia and Japan for co-chairing the working group meetings to develop the Proposed Draft Guideline for the Conduct of Food Safety Assessment for Foods Derived from Recombinant-DNA Animals. We are pleased to provide the following comments on Codex Circular Letter CL 2006/27-FBT.

General Comments

Canada supports the approach taken to keep the scope of the proposed draft guideline science-based and focussed on aspects related to assessing the safety of food derived from recombinant-DNA (rDNA) animals. Canada also supports the use of *Codex Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants* (CAC/GL 45-2003) as a model for the proposed draft rDNA animal guideline and to modify the text taking into account the differences between plants and animals. In this regard, we agree with the approach to safety assessment outlined in the proposed draft guideline, which takes into account the following three elements: the nature of the rDNA construct and its expression products; the health of the rDNA animal; and the composition of foods derived from the rDNA animal. We believe this approach is consistent with the recommendations of the 2003 FAO/WHO Expert Consultation on the Safety Assessment of Foods Derived from Genetically Modified Animals, including Fish.

With respect to safety considerations related to cloned animals, Canada is of the view that this issue has been appropriately considered by the working group and is adequately reflected in the proposed draft guideline. We note that paragraph 31 of the proposed draft guideline calls for the provision of information related to the techniques and processes used to obtain the initial rDNA animal, nuclear transfer being listed as an example of such a technique.

Overall, we believe the text developed by the working group provides very useful guidance for evaluating the safety and nutritional aspect of foods derived from rDNA animals. We support the work that has been accomplished by the working group and are looking forward to further contributing to the advancement of this important initiative.

Specific Comments on the Proposed Draft Guideline

Section 1 -

Canada notes that the proposed draft guideline is being developed to provide science-based guidance regarding the food safety assessment of foods derived from rDNA animals consistent with *Codex Principles for the Risk Analysis of Foods Derived from Modern Biotechnology* (CAC/GL 44-2003). Although we acknowledge the importance of considerations such as animal welfare, ethics, moral and socio-economical aspects, as well as environmental risks, Canada does not believe these issues fall within the scope of the proposed draft rDNA animal guideline.

Canada notes the extensive discussions of the working group regarding the development of the various text options for paragraph 2, and would support the inclusion of a paragraph that clearly outlines the issues the proposed draft guideline does and does not intend to address.

Canada prefers the fourth option of the five options proposed for paragraph 2. We believe that both the chapeau statement and the bullets of the fourth option state clearly and in a concise fashion what is included, and what is not included, in the scope of the proposed draft guideline.

In addition, Canada would support the deletion of the third bullet of paragraph 2 relating to rDNA animal intended for purposes other than food use. This is in recognition that there may be legitimate circumstances under which the guidance provided in the proposed draft guideline could be used to conduct a food safety assessment of foods derived from such animals.

Sections 2, 3, 4, 5 and allergenicity annex -

As indicated in our general comments, Canada is of the view that the proposed draft rDNA animal guideline should be modeled on the one adopted for rDNA plants and should differ from it solely where aspects specific to recombinant-DNA animals and/or biological differences with recombinant-DNA plants are identified and can be scientifically justified.

Canada thus supports text identical to that of the rDNA plant guideline for paragraphs 16, 30C, 37C, 39D of the proposed draft rDNA animal guideline. Similarly, we believe that the text related to the use of antibiotic resistance marker genes and that of the allergenicity assessment annex should be consistent with that contained in the rDNA plant guideline.

EUROPEAN COMMUNITY

The European Community and its Member States (ECMS) would like to thank the Working Group and its Australian and Japanese Chairs for the excellent work resulting in the proposed draft guideline for the Conduct of Food Safety Assessment of Foods Derived from recombinant-DNA animals.

The ECMS are of the view that the Working Group has reached in its two sessions a large measure of agreement on contentious issues such as the role of the health status of the r-DNA animal in the overall food safety assessment, the assessment of possible toxicity or bioactivity and the potential effects on food storage and hygiene.

However, a number of other key issues remain in dispute, notably the role of "other legitimate factors", whether the guidelines should cover "non-heritable constructs" and the presence of antibiotic marker genes in recombinant-DNA animals. In this respect, the ECMS would like to make the following general comments.

1. "Other legitimate factors"

The EC and all its Member States are of the view that issues such as ethical, animal welfare and socio-economic considerations are legitimate factors that need to be taken into account by Codex Members in the decision-making process on recombinant-DNA animals. Accordingly, the ECMS would like to support the second of the four options put forward in section 1 of the draft guideline.

2. Recombinant DNA animals developed for pharmaceutical and other non-food uses

The ECMS are of the opinion that the guidelines should not address the food use of animals developed for pharmaceutical or other non-food uses. This is motivated by the real concerns over safety, the residual value of such animals compared to their primary use and the small numbers of animals likely to be concerned and the consumer image problems. The EC could accept that the bullet point making reference to these animals is deleted from the document, since it does not represent a legitimate factor to be given due consideration in the decision making on food derived from recombinant-DNA animals.

If the bullet point was nevertheless maintained, the acceptance of the word "exclusively" in the second line of the bullet point could inadvertently open the door to the inclusion of rDNA animals "partially" developed for pharmaceutical reasons in the scope of the draft guideline. Therefore the ECMS would argue to delete the word "exclusively" from the bullet point if it was maintained.

3. Inclusion of "non-heritable constructs"

The ECMS have continued to argue for careful consideration of the opportunity to include "non-heritable constructs" in the scope of the guideline to be developed, i.e. these constructs need to be a focus of particular attention in the risk assessment exercise or even excluded altogether until more is known about their implications.

Accordingly, the ECMS continue to argue that there should be a further expert consultation on these constructs and that the expert consultation should not only look at any specific safety concerns but also explain their role and potential of this technology in the development of rDNA animals.

4. Antibiotic Resistance Marker Genes

The current text discourages such genes and encourages alternatives. Nonetheless, it does not close the door to their use, provided the appropriate procedures are followed. Conversely, the EC has argued that such genes should be excluded, pointing to the clear signals in this regard from the 2003 WHO/FAO Expert Consultation. Moreover, the need for such marker genes is increasingly considered *dépassé* by the biotech industry and there is a general consensus that if the mistakes of the GM plant authorisations were to be avoided, such technology such be avoided in the case of rDNA animals

5. DNA sequence information to be provided to support the safety assessment

The ECMS are of the view that the sequence information of the inserted genetic material at each insertion site including the surrounding region is a prerequisite to conduct a proper safety assessment of the recombinant-DNA animal ultimately used for food production. Such information is necessary in order to carry out the comprehensive molecular and biochemical characterisation of the genetic modification required in paragraph 36 of the draft guideline.

Therefore, bullet C in paragraph 37 of the draft guideline should read as follows:

C) the organization of the inserted genetic material at each insertion site including copy number and sequence data of the inserted, modified or deleted material and of the surrounding region, sufficient to identify any substances expressed as a consequence of the inserted material, and, if applicable, other information such as the analysis of transcripts or expression products to identify any new substances that may be present in food; and

Finally, the ECMS would like to support the two questions on non-heritable constructs and marker and reporter genes to be put forward to a WHO/FAO for an expert consultation.

The ECMS will make further detailed comments to the wording of the draft guideline when it is discussed.

JAPAN

Japan generally supports the proposed draft Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant DNA Animals, and is pleased to submit the following specific comments.

SECTION 1

Paragraph 2

Japan prefers the **Option 4** as it fully describes the items which this Guideline is not expected to cover in accordance with the “Scope and Definitions” of the “Principles for the Risk Analysis of Foods Derived from Modern Biotechnology”.

Also, we’d like to propose to delete **[exclusively]** in the Option 4. We believe that recombinant DNA animals developed for the purposes other than food should be assessed for its safety as food in the different framework with special attention, and should not be included in this Guideline.

SECTION 4

Paragraph 27

It is not clear what kind of information should be provided if the recombinant-DNA was synthesized and it is not from a known natural source (subparagraph A)). Therefore, we would like to suggest re-drafting the paragraph 27 as follows;

27. Information should be provided:

A) If derived from another organism:
i. ~ viii.

B) If the recombinant-DNA was synthesized and it is not from a known natural source:
items i. ~ viii. listed in A) as appropriate.

Paragraph 37 C)

We would like to suggest to delete the outmost square brackets and to keep the sentence identical to the Plant Guideline since there is no scientific justification for our deviating from the Plant Guideline at this point. The subparagraph C) would read;

> *C) ~~[~~the organization of the inserted genetic material at each insertion site including copy number and sequence data of the inserted ~~[, modified or deleted]~~ material and of the surrounding region, sufficient to identify any substances expressed as a consequence of the inserted material, or, where more appropriate ~~/[and, if applicable]~~, other information such as analysis of transcripts or expression products to identify any new substances that may be present in the food; and~~]~~*

Paragraph 39 D)

We would like to propose to delete the square brackets and keep the sentence "it may be necessary …… under more than one typical husbandry condition" as it is.

Health Status

Paragraph 42

A) Add the item "**resistance to diseases**" after "growth and development" since it is one of the essential indicators to compare the health status of the animals.

Paragraph 60 (editorial)

To delete the second "appropriate" from the text as it seems redundant.

KENYA

We find the proposed draft generally acceptable. However, we wish to make the following comments and proposals:

Scope, Paragraph 2, (page 5)

1. We propose that the first option of paragraph 2 be adopted with the addition of a bullet between bullet one and two to include:
"Ethical, moral and socioeconomic aspects"

Paragraph 2, 3rd line (page 5)

2. The word "[exclusively]"in the first option should be retained. This will ensure focus is on safety assessment of products used for human consumption.

Paragraph 4, 3rd line (page 6)

4. The word "or" in the paragraph be replaced with the word "of". The paragraph to read: "…. counterpart having a history **of** safe use"

Section 4, paragraph 23, 5th line, brackets (page 11)

5. The abbreviations "TSE" be written in full i.e. "transmissible spongiform encephalopathy"

Section 4, paragraph 37C (page 14)

6. In order to ensure consistency within paragraph 37, we propose that the words "[modified or deleted]" be deleted

7. Considering that the words "if applicable and appropriate" have the same implication, we prefer that the words "if applicable" be deleted.

8. We therefore propose that the statement reads as follows:

“The organization of the inserted genetic material at each insertion site including copy number and sequences data of the **inserted** material and of the surrounding region, sufficient to identify any substances expressed as a consequence of the inserted material, or, where more **appropriate**, other information such as analysis of transcripts or expression products to identify any new substances that may be present in the food; and”

Section 4, paragraph 39D (page 15),

9. We propose the adoption of the last statement:
“It may be necessary to examine the expression of new traits under more than one typical environmental conditions” because;
Environmental conditions such as feeding, climate, disease management, confinement and others can have a major influence on the expression intensity of traits. The expression of a trait is as a result of genotype and environment interactions

MEXICO

Scope

We need to note that while the scope of this document does not include cloning, the safety aspects of such techniques will have to be considered in future work.

Mexico considers option 5 to be the most appropriate for, while animal welfare and environmental aspects are legitimate, they fall outside the scope of a guideline intended to assess the safety of recombinant-DNA animals to be used for human consumption.

Definitions

No comments

Introduction to food safety assessment

We consider that the square brackets in paragraph 16 should be deleted because of the relevance of the unintended effects that could occur (and therefore be assessed) through changes in metabolic pathways.

With regard to paragraph 37, the Delegation of Mexico considers that the full molecular characterization of the inserted material, copy number, insertion site, transcripts and expressed material should be provided, so this information can be used to predict possible activation or silencing of genes, as well as changes in metabolic pathways or synthesis of toxic compounds that could affect the safety of foods derived from recombinant-DNA animals. We therefore request the removal of the opening and closing square brackets in subparagraph C.

We also request that the second square bracket *[, modified or deleted]* be removed, for if we know what genetic material has been modified or deleted, we will know the possible modifications to gene expression patterns not necessarily in the vicinity of the insertion, it being well known that in eukaryotic organisms many genetic controls are conducted up to a distance of 10 000 bp, because of DNA topology and folding patterns and possible consequences for food safety. Finally, we kindly request that the term "*and, if applicable*" be adopted, as we consider this less discretionary than "*where more appropriate*".

The proposed text would therefore read:

C) the organization of the inserted genetic material at each insertion site including copy number and sequence data of the inserted, modified or deleted material and of the surrounding region, sufficient to identify any substances expressed as a consequence of the inserted material and, if applicable, other information such as analysis of transcripts or expression products to identify any new substances that may be present in the food; and…

With regard to paragraph 39, we suggest removing the square brackets in subparagraph D.

With regard to paragraph 65 (Use of antibiotic resistance marker genes), we wish to point out that it is not possible to discount the probability of horizontal gene transfer, as recent research has shown that the transfer of mammal genes to pathogenic intestinal micro-organisms does occur (Williams et al 2006), as does the transfer of bacterial genes to human pathogens such as amoebas (Loftus, 2005). The Delegation of Mexico therefore suggests the inclusion of a footnote **12 bis** mentioning the cited bibliography reporting the latest research on horizontal gene transfer. The citations to be included in the proposed footnote are as follows:

- *Keeling Patrick J. , Gertraud Burger, Dion G. Durnford, B. Franz Lang, Robert W. Lee, Ronald E. Pearlman, Andrew J. Roger and Michael W. Gray. 2005. The tree of eukaryotes. Trends in Ecology and Evolution 20(12) 670-676.*
- *Loftus Brendan, Iain Anderson, Rob Davies, U. Cecilia M. Alsmark[3], John Samuelson, Paolo Amedeo, Paola Roncaglia, Matt Berriman, Robert P. Hirt, Barbara J. Mann, Tomo Nozaki, Bernard Suh, Mihai Pop, Michael Duchene, John Ackers, Egbert Tannich, Matthias Leippe[1], Margit Hofer, Iris Bruchhaus, Ute Willhoeft, Alok Bhattacharya, Tracey Chillingworth, Carol Churcher, Zahra Hance, Barbara Harris, David Harris, Kay Jagels, Sharon Moule, Karen Mungall, Doug Ormond, Rob Squares, Sally Whitehead, Michael A. Quail, Ester Rabbinowitsch, Halina Norbertczak, Claire Price, Zheng Wang, Nancy Guillén[1], Carol Gilchrist, Suzanne E. Stroup[5], Sudha Bhattacharya, Anuradha Lohia, Peter G. Foster, Thomas Sicheritz-Ponten, Christian Weber, Upinder Singh, Chandrama Mukherjee, Najib M. El-Sayed, William A. Petri, Jr, C. Graham Clark, T. Martin Emble, Bart Barrell, Claire M. Fraser and NeilHall. 2005. The genome of the protist parasite Entamoeba histolytica. Nature **433**, 865-868(24 February 2005) .*

With regard to assessment of possible allergenicity (paragraphs 52 and 53), we know that by expressing a new protein, genetically modified foods potentially generate an immunological response, which is why the allergenic effect has been identified as one of the hazards to be assessed. While certain transgenes can provoke activation of the immunological system, there is reason to believe that other transgenes could provoke other types of effects on the immunological system. It is therefore advisable to include studies on indicators of the functioning of the immunological system; the findings could serve to complement the assessment.

We consider it appropriate for risk assessments to consider aspects relating to nutritional modifications, bioavailability of nutrients and alteration in the stability of selected toxicants.

We have no comments to make on the proposed approach for assessing allergenicity, as it works for assessing the potential allergenicity of transgenic proteins expressed in genetically modified plants and we consider it remains valid for new proteins expressed in transgenic animals.

NEW ZEALAND

New Zealand believes that the working group, co-chaired by Japan and Australia, has made excellent progress in developing a draft guideline as a basis for discussion by the Task Force.

New Zealand supports the general approach outlined in paragraph 7, which includes molecular considerations, the health status of the animal and the composition of the food.

New Zealand believes that the Task Force's instruction to the working group, to use the plants document as a model, and strong adherence to this principle by the working group, facilitated the development of the draft guidelines. New Zealand believes that the document should only depart from the wording used in the plant guideline where the biological differences between plants and animals require a different approach.

New Zealand's only specific comment pertains to paragraph 2, in which New Zealand sees no technical justification for departing from the paragraph 2 of the plants guideline. Therefore, New Zealand prefers option 3:

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

However, New Zealand acknowledges the keen interest of some delegations in elaborating this paragraph beyond that in the plant guideline. If the Task Force were to adopt more complex language, New Zealand's preference would be for option 4, with the deletion of bullet point 3.

- *the safety of food derived from recombinant-DNA animals intended to be used [exclusively] for other purposes than food (e.g. pharmaceutical, xenotransplantation,or industrial uses);*

New Zealand supports the primary intent of the 3rd bullet point, which is the exclusion of pharmaceutical, industrial and xenotransplantation products from the scope of the guideline. However, this exclusion is already implicit in the plants document and we see no need to deviate from the text in the plants document.

Importantly, the wording of the 3rd bullet point also excludes food from the scope of the document if the animal from which it is derived was modified for purposes other than food. This additional exclusion is inconsistent with the plant document. New Zealand believes that there are no biological differences between plants and animals that justify this departure from the plants guideline.

Additionally, New Zealand notes that there is already an accepted practice of deriving pharmaceutical and industrial products from food-producing plants and animals that have not been modified. Examples include: thyroxine from animal thyroid glands; adrenocorticotrophic hormone (ACTH) from animal pituitary glands used to treat rheumatic disorders such as arthritis and rheumatic heart disease; thrombin from beef blood used as a clotting agent in several types of surgery and dentistry; lactoferrin and lactose from cows' milk, which are used in a range of pharmaceutical and nutraceutical applications; bioethanol from sugarcane.

Given appropriate safeguards, such as a safety assessment guided by the draft animals document, New Zealand believes that there is no need to treat rDNA animals differently from conventional crops and animals.

UNITED STATES OF AMERICA

The United States would like to thank the European Community and the Government of Japan for hosting physical Working Group meetings to develop a Proposed Draft Guideline for the Conduct of Food Safety Assessment of Food Derived from Recombinant-DNA Animals (the Draft rDNA Animals Guideline). The U.S. would also like to extend its appreciation to Drs. Marion Healy (Australia) and Tamami Umeda (Japan), co-chairs, for their tireless and expert work throughout these sessions. In addition, the U.S. would like to express its gratitude to the entire Working Group for the constructive and collegial spirit that was present at both Working Group meetings. The U.S. believes that these three factors contributed to generating a high quality document for the Task Force to consider in its next meeting.

GENERAL COMMENTS

General, High-Level Nature of Document: The United States believes that the Draft rDNA Animals Guideline provides a useful, science-based approach for evaluating the safety of any foods derived from recombinant-DNA animals. The U.S. believes that the maximum utility of such a document comes from keeping its focus at a sufficiently general level that it can serve as a resource for all of the elements common to any recombinant-DNA animal. Were the document to become more specific on any one point, it would likely become trapped by considerations of species-specific issues, and could thereby lose its utility as an overarching guide to evaluate the food safety of products from rDNA animals.

Relationship to rDNA Plant Guideline: The United States strongly supports the decision of the working group to use the Guideline for the Conduct of Food Safety Assessment of Food Derived from Recombinant-DNA Plants (rDNA Plant Guideline) as the model for the Draft rDNA Animals Guideline. The United States also strongly supports the decision of the working group to deviate from the rDNA Plant Guideline only when changes are justified based on the underlying biological differences between plants and animals. Given the need for these documents to serve as general resources for assessing the safety of foods derived from a wide range of species of plants and animals, the U.S. believes that this approach is appropriate and commends the Working Group for adopting it.

Underlying Scientific Approach to Assessing the Safety of Food from rDNA Animals: The United States strongly supports the food safety assessment approach outlined in Paragraph 7 of the Draft Guideline. The three elements presented in this approach are mutually reinforcing and combine to form a comprehensive, science-based approach to assessing the safety of foods from rDNA animals.

SPECIFIC COMMENTS ON THE TEXT

Paragraph 2

The United States supports the fourth option for paragraph 2, with the deletion of the third bullet point in that option. The United States believes that the purpose of the rDNA Animals Guideline is to address food safety issues according to the Principles for the Risk Analysis of Foods Derived from Modern Biotechnology, and that the fourth option makes that point most succinctly. The United States does not believe that it is the role of the Task Force to make statements or express opinions on the importance, legitimacy, or need for other bodies or instruments to address non-food-safety-related factors associated, or potentially associated, with rDNA animals, and therefore would not support the first two options for paragraph 2.

The United States supports the deletion of the third bullet point of the fourth option for two reasons:

- First, the U.S. believes that the approach presented in the Draft Guideline document accommodates the safety of any rDNA construct and its potential expression product(s) regardless of its intended final use. A related point is that in some cases, expressed substances can be used for multiple purposes, only one of which might be for food use. For example, avidin, a major component of hen eggs, is consumed as food, but may be used as a post-harvest insecticide, and has been the subject of clinical trial as a cancer chemotherapeutic agent. Were it to be expressed in, for example, the milk of dairy mammals, the safety assessment would be the same regardless of its intended use.
- Second, maintaining the approach of deviating from the rDNA Plant Guideline only when justified by differences between plants and animals, the U.S. notes that the rDNA Plant Guideline did not include such exemption.

Therefore, the United States supports Paragraph 2 to read as follows:
"*This Guideline addresses only food safety and nutritional issues. It therefore does not address:*

- *animal welfare;*
- *ethical, moral and socio-economical aspects;*
- *environmental risks related to the environmental release of recombinant-DNA animals used in food production;*
- *the safety of recombinant-DNA animals used as feed, or the safety of animals fed with feed derived from recombinant-DNA animals, plants or microorganisms."*

Paragraph 37(C)

Consistent with the approach of deviating from the rDNA Plant Document only when justified by differences between plants and animals, the United States supports maintaining Paragraph 37 C as it is in the rDNA Plant document. The United States therefore supports deleting the text in square brackets (in bold below).

> *(C) [the organization of the inserted genetic material at each insertion site including copy number and sequence data of the inserted* ~~***[, modified or deleted]***~~ *material and of the surrounding region, sufficient to identify any substances expressed as a consequence of the inserted material, or, where more appropriate/* ~~***[and if applicable]***~~*, other information such as analysis of transcripts or expression products to identify any new substances that may be present in the food; and]*

Paragraph 39 (D)

Again, consistent with deviating from the rDNA Plant Guideline only when justified by differences between plants and animals, the United States opposes inclusion of the bracketed text in Paragraph 39D (in bold below), and supports maintaining the text of this paragraph as it is in the plant guideline.

> *(D) demonstrate whether the newly expressed trait(s) are expressed as expected in the appropriate tissues in a manner and at levels that are consistent with the associated regulatory sequences driving the expression of the corresponding gene.* ~~***[It may be necessary to examine the expression of the new traits under more than one typical husbandry condition]***~~*;*

The U.S. also notes that Paragraph 54 effectively addresses the issue of possible husbandry effects on food from the rDNA animal: "… it may be necessary to make comparisons between products from rDNA animals and appropriate conventional counterparts raised under more than one set of typical husbandry conditions."

Paragraphs 63 and 64-67

The United States supports the comments provided to the Secretary by Australia in its letter dated 8 September, 2006, regarding paragraphs 63 and 64-67.