codex alimentarius commission

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS

WORLD HEALTH ORGANIZATION

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Agenda Item 3 **CX/FBT 07/7/3 Add.1**
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JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX *AD HOC* INTERGOVERNMENTAL TASK FORCE ON FOODS DERIVED FROM BIOTECHNOLOGY

Seventh Session

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SUMMARY OF THE REPORT OF THE FAO/WHO EXPERT CONSULTATION ON THE SAFETY ASSESSMENT OF FOODS DERIVED FROM RECOMBINANT-DNA ANIMALS

Submission from FAO and WHO

Background

1. The Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) convened the Joint Expert Consultation on the Safety Assessment of Foods Derived from Recombinant-DNA Animals on 26 February - 2 March 2006, at the Headquarters of WHO, Geneva, Switzerland.

2. The objective was to provide scientific advice to FAO/WHO and their Member States on two sets of questions regarding: i) marker and reporter genes; and ii) non-heritable applications[1]. The Codex *ad hoc* Intergovernmental Task Force on Foods Derived from Biotechnology had specifically requested advice on these questions. The Consultation built upon the conclusions and recommendations of the Joint FAO/WHO Expert Consultation on the Safety Assessment of Foods Derived from Genetically Modified Animals, including Fish (FAO/WHO 2004).

3. This Working Document provides the conclusions and recommendations of the Expert Consultation as presented in Annex. The full report of the Expert Consultation is available from the websites of WHO and FAO as follows:

WHO: http://www.who.int/foodsafety/biotech/meetings/animals_2007/en/index.html
FAO: http://www.fao.org/ag/agn/agns/biotechnology_expert_2007_en.asp

[1] ALINORM 07/30/34 Appendix II

ANNEX

Conclusions of the Expert Consultation

1. Marker and reporter genes

- ***What developments have occurred in the development and use of reporter and selectable marker genes?***

  - At least three major types of marker genes are used to screen and/or select for the success of introduction of foreign DNA into animal cells.

  - Most of the representatives of these 3 classes of markers were developed as basic research tools. At this time, there is insufficient information on the food safety of recombinant-DNA animals with these markers genes. Nevertheless, information from other species can be used as a starting point for further research on the safety aspects of marker genes

  - Marker genes for both positive and negative selection will become increasingly important in combination with nuclear transfer from somatic cells or pluripotent cells in the generation of recombinant-DNA food animals.

- ***Are there non-antibiotic resistance marker or reporter genes that have been demonstrated to be safe to humans in food products, and if so, what are they?***

  - Although many non-antibiotic resistance marker or reporter genes exist, few are currently used for producing recombinant-DNA animals intended for food.

  - Experience on the utility, stability and performance of these marker genes is available from studies of animal models in the laboratory. However, the limited number of studies that has been performed on the safety of non-antibiotic marker genes in recombinant-DNA food animals, has yielded inconclusive results.

- ***When removal of specific DNA sequences is desired, are reliable and safe techniques available to do this on a routine basis?***

  - Site-specific recombination systems can provide a functional means for removing marker genes provided measures are taken to minimize off-target effects.

  - Only limited scientific information relevant to food safety aspects of site-specific excision systems used in food animals is available.

2. Non-heritable applications

- ***Are there relevant differences from a food safety perspective between animals with heritable and non-heritable traits, and if so what are they?***

  - The differences in food consumption hazards posed by recombinant-DNA animals are a function of (a) the integration status (and origin and composition of sequences) of the construct, not its heritability, and (b) excipient effects, which need to be evaluated in recombinant-DNA animals with non heritable constracts (NHC).

  - There are no qualitative differences between heritable or non-heritable constructs regarding the nature of the hazards and risks when the constructs are chromosomally integrated.

  - Quantitative differences in the safety of foods derived from recombinant-DNA animals containing heritable or non-heritable recombinant-DNA constructs may arise from the expression pattern and amount of the construct, not its heritability.

  - The potential for horizontal gene transfer to occur is a function of whether the recombinant-DNA construct is integrated into the genome of the recipient cells or maintained episomally, and not of the heritability of the construct. Episomal recombinant-DNA (heritable and non-heritable) may be more readily transferred or taken up than integrated recombinant-DNA by bacteria or somatic cells of animals or humans consuming food products derived from recombinant-DNA animals. This may pose animal health risks, but the degree to which such potential horizontal gene transfer poses human health risks via food consumption risks is not clear.

- ***Are there specific food safety questions (e.g. with regard to types of vectors) that should be considered relative to the assessment of safety of foods from animals containing heritable and non-heritable traits?***

  - Quantitative differences in the safety of foods derived from recombinant-DNA animals containing heritable or non-heritable recombinant-DNA constructs may arise from the extent to which the vectors may contain viral sequences. In this case, recombination with endogenous viral sequences could result in health risks to the recombinant-DNA animals. The degree to which these animal health risks pose human food consumption risks is a function of, among other things, the host range of the resulting recombined viruses.

Recommendations

1. Marker and reporter genes

- The continued validation and development of gene excision systems is strongly encouraged to allow the controlled removal of specific DNA sequences in recombinant-DNA animals. This is in line with the outcome of the 2004 FAO/WHO expert consultation which recommended avoiding the use of unnecessary DNA sequences in the gene construct, including marker genes (FAO/WHO, 2004).
- Further research with focus on studies relevant to food from recombinant-DNA animals is needed to evaluate the safety of non-antibiotic resistance marker genes and gene excision systems.
- It is desirable to develop novel non-antibiotic resistance markers that facilitate efficient positive and negative selection of transgenic cells.
- To minimize the potential for off-target effects, recombinant-DNA animals intended for food use should be free of the introduced gene excision system.

2. Non-heritable applications

- Some potential animal health hazards associated with the use of viral sequences were identified, including the potential for recombination and subsequent expression, altered pathogenicity, and reverse transcription of RNA viral sequences. These issues should comprise the basis of a guideline on the safe use of virally-derived vectors for non-heritable applications for animal health and production. The recent developments on nonviral episomal vectors provide a means to overcome many of the concerns associated with viral-based vector systems. These guidelines should take into account the principles of guidelines developed for human gene therapy. A suitable venue for developing such a guideline would be the OIE.
- In order to minimize the likelihood of an adverse event posing an animal health risk to recombinant-DNA animals *via* horizontal gene transfer to prokaryotic organisms, the coding region(s) of the genes in recombinant-DNA constructs that are integrated into the recombinant-DNA animal's genome should contain introns. (Bacteria do not contain the cellular machinery to splice out introns and therefore would not be able to produce a functional product should horizontal gene transfer occur.)
- Care should also be taken that the health of the recombinant-DNA animal is not compromised in the course of developing a safe food product. The animal health issues should form the basis of a guideline on the health of recombinant-DNA animals similar to the one being developed for animal clones by OIE. A suitable venue for developing such a guideline would be the OIE.
- Further direct research should be encouraged to help elucidate whether food safety hazards are affected by
  a. potential horizontal gene transfer to prokaryotic or eukaryotic cells
  b. recombinant-DNA made with viral sequences that are part of NHCs (e.g., viral recombination).
- Because recombinant-DNA animals containing NHCs may have an increased inter-animal variance in the expression products of the recombinant-DNA constructs, there is a need to establish a guideline on statistically appropriate sampling strategies for assessing potential exposure and risks from eating food derived from recombinant-DNA animals with NHCs. Appropriate venues for

creating such guidelines would be international standard setting bodies with interests in animal health and food safety (e.g. FAO, WHO, OIE).

- A comprehensive publicly available database should be established and maintained by appropriate international intergovernmental organizations such as FAO/WHO on all reported results arising from consumption of food derived from recombinant-DNA organisms, including the results of any subsequent investigations of those reports.
- A comprehensive publicly available database should be established and maintained by relevant international organizations such as OIE on the methods of introducing heritable and non-heritable recombinant-DNA constructs into animals, accompanied by a full bibliography.
- It would not be inappropriate to use the principles and methods outlined in the Draft Guideline[2] applied to assessing the food safety of recombinant-DNA animals, with the added caveats regarding excipients and episomes, for assessing animal health and food safety of animals bearing NHCs for production or other purposes to assess the food safety of animals treated with recombinant-DNA vaccines.
- Given the complexity and importance of the animal health and food safety issues raised by recombinant-DNA vaccines, these issues should be considered by a joint FAO/WHO/OIE expert group.

[2] Proposed Draft Guideline for the Conduct of Food Safety Assessment of Foods Derived From Recombinant-DNA Animals is currently being elaborated at Steps 3 and 4 of the Codex process (see ALINORM 07/30/34)