Fourth International Workshop on Regulatory Approaches for Animal Biotechnology

Codex Alimentarius

GUIDELINE FOR THE CONDUCT OF FOOD SAFETY ASSESSMENT OF FOODS DERIVED FROM RECOMBINANT-DNA ANIMALS

Session 4: Concepts in biotech regulatory approaches

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Abstract

- Introduction to the CAC/GL 68-2008 guideline
- General criteria and considerations
- Framework and elements of the guideline
- Final words

Introduction to the CAC/GL 68-2008 guideline

Codex Alimentarius - FAO- WHO

Codex *ad hoc* intergovernmental task force on food derived from biotechnology (TFFBT)

7 meetings hosted by Japan, 2000 – 2007.

Reference	Title	Committee
CXG 44-2003	Principles for the Risk Analysis of Foods Derived from Modern Biotechnology	TFFBT
CXG 45-2003	Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants	TFFBT
CXG 46-2003	Guideline for the Conduct of Food Safety Assessment of Foods Produced Using Recombiant-DNA Microorganisms	TFFBT
CXG 68-2008	Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Animals	TFFBT

Introduction to the CAC/GL 68-2008 guideline

CAC/GL 68-2008 - Recombinant DNA Animals guideline adopted in 2008

TFFBT was dissolved

Foods derived from modern biotechnology

Second edition

World Health Organization

Food and Agriculture Organization of the United Nations

Biotechnology

Biotechnology represents the refinement and extension of the way we produce natural resources for the purpose of human consumption. Today, it allows producers to obtain specific traits such as increased insect resistance or herbicide tolerance, in a controlled manner, making it possible to grow new plants and animals and create desirable, genetically modified food. However, biotechnology has also raised consumer concerns.

The role of Codex in Biotechnology

For many foods, the level of food safety generally accepted by society reflects the history of their safe consumption by humans. The hazards associated with foods are subjected to the Codex risk analysis process to assess potential risks and, if necessary, to develop approaches to manage these risks.

Codex role in biotechnology is primarily concerned with the risk assessment aspect of food safety. Risk assessment includes a safety assessment, which is designed to identify whether a hazard, nutritional or other safety concern is present, and if present, to gather information on its nature and severity. The safety assessment should include a comparison between the food derived from modern biotechnology and its conventional counterpart focusing on determination of similarities and differences. Codex has developed texts relevant to labelling of foods derived from modern biotechnology.

https://www.fao.org/fao-who-codexalimentarius/thematic-areas/biotechnology/it/

General criteria and considerations

Developed for Recombinant DNA animals used for food

Addresses only:

- safety of foods consisting of, or derived from, rDNA animals
- nutritional aspects

Out of scope:

- 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 and microorganisms.

General criteria and considerations

Applies for animals that have a history of safe use as sources of food, that have been modified by modern biotechnology

Developed primarily for animals bearing heritable recombinant-DNA constructs

Foods derived from animals bearing non-heritable constructs may require additional specific consideration

General criteria and considerations

In general, very similar approach and framework to plants guideline.

Identify and characterize intended and unintended effects, and evaluate their biological significance, in order to assess the safety of the novel traits.

Focuses on identify new or altered hazards (safety impacts) or nutritional concerns, and gather information on their character and severity.

General criteria and considerations

Comparative approach and substancial equivalence

- Safety assessment carried out to identify similarities and differences between the new food and its conventional counterpart.
- ***"Conventional Counterpart"*** **—** an animal breed with a known history of safe use as food from which the recombinant-DNA animal line was derived, as well as the breeding partners used in generating the animals ultimately used as food, and/or food derived from such animals.

Unintended effects and case by case assessments

- Unintended effects can result from the random insertion of DNA sequences into the animal genome, which may cause disruption or silencing of existing genes, activation of silent genes, or modifications in the expression of existing genes.

Stepwise approach and weight of evidence

- There is no a single test that can provide all the information needed, variety of data and information are necessary.
- These data and information, when considered in total, provide assurance that the food is unlikely to have an adverse effect on human health.

The objective of the Risk Assessment is to conclude that the GMA and the new foods derived from it, are as safe as and nutritious than the conventional counterpart.

Framework and elements of the guideline

In assessing the safety of food from recombinant-DNA animals, the approach should take into account:

- A) the nature of the recombinant-DNA construct and its expression product(s), if any;
- B) the health status of the recombinant-DNA animal; and
- C) the composition of foods produced from recombinant-DNA animals, including key nutrients.

Framework and elements of the guideline.

Stepwise information requirement:

- General description of the recombinant-DNA animal;
- Description of the recipient animal prior to the modification and its use as food or for food production;
- Description of the donor organism or other source(s) of the introduced recombinant-DNA;
- Description of the genetic modification(s) including the construct(s) used to introduce the recombinant-DNA;
- Description of the methods used to produce the initial recombinant-DNA animal (founder animal) and the processes to produce the recombinant-DNA animal ultimately used as food or for food production;
- Characterization of the genetic modification(s) in the recombinant-DNA animal ultimately used as food or for food production;

Framework and elements of the guideline.

Stepwise information requirement:

- Safety assessment:

  - Health status of the recombinant-DNA animal

  - Expressed substances (non-nucleic acid substances)

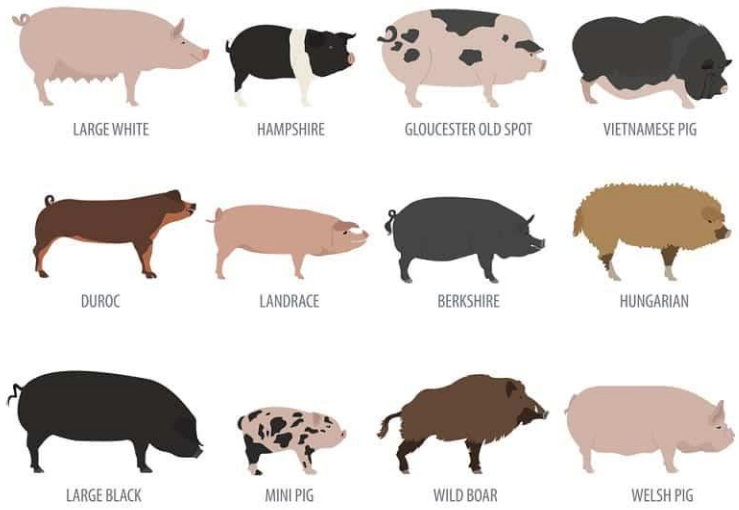
  - Compositional analyses of key components

  - Food storage and processing

  - Intended nutritional modification

- Other considerations.

General Description of the rDNA animal – Phenotypic and breeding information



- General description of the recombinant-DNA animal and its new traits.
- Description of the recipient animal prior to the modification and its use as food or for food production
- Description of the source(s) of the introduced recombinant-DNA
- <u>Description of the breeding process</u>

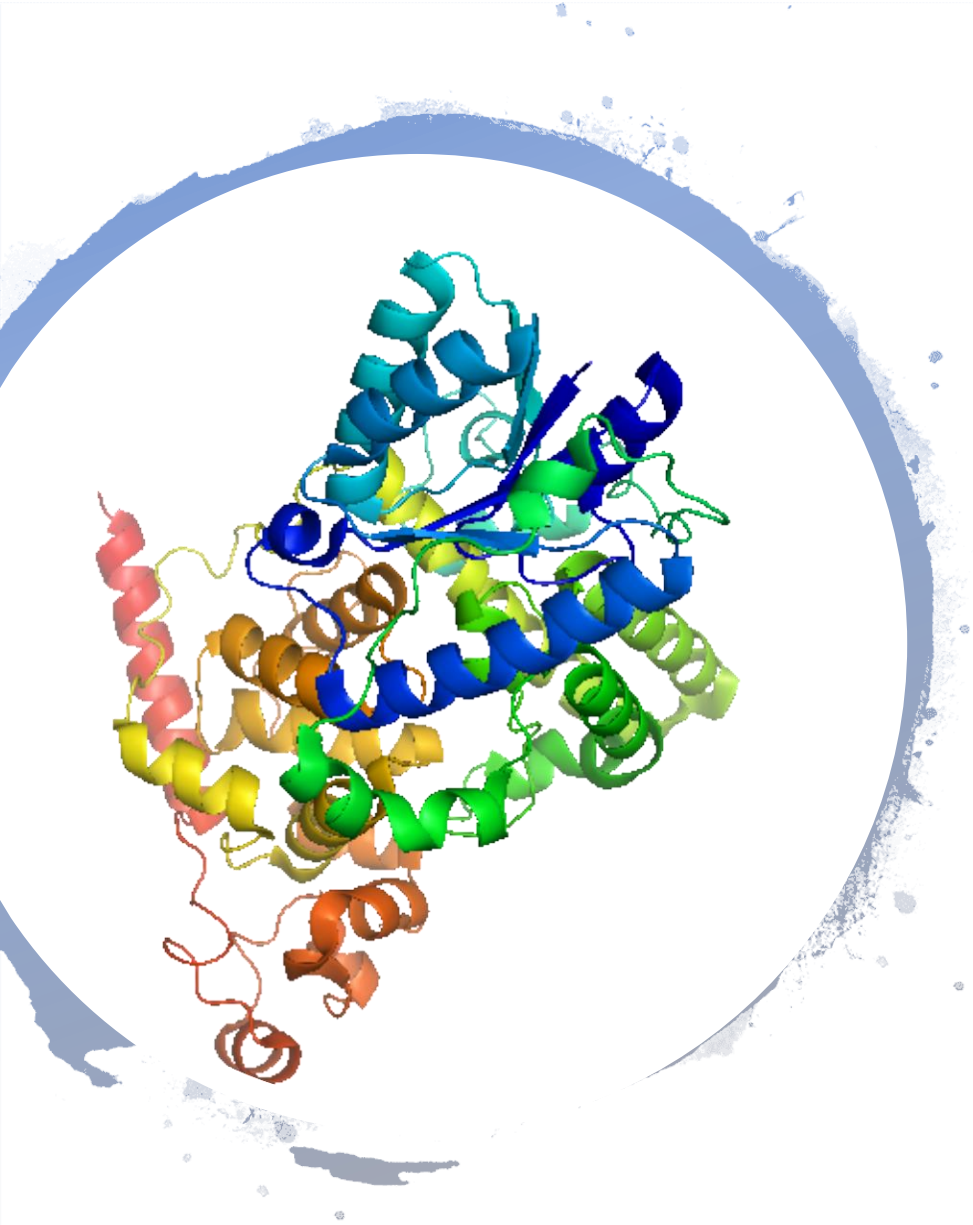
  - Information on how the initial recombinant-DNA animal leads to the production of the animal ultimately used as food or for food production

Molecular and biochemical characterization

- Characterization of the genetic modification(s) in the recombinant-DNA animal ultimately used as food or for food production
- Information on the DNA insertions into the animal genome: Genetic construction; No. of insertion sites; No. of copies and sequences;
- Information of novel substances: level and site of expression, biological function

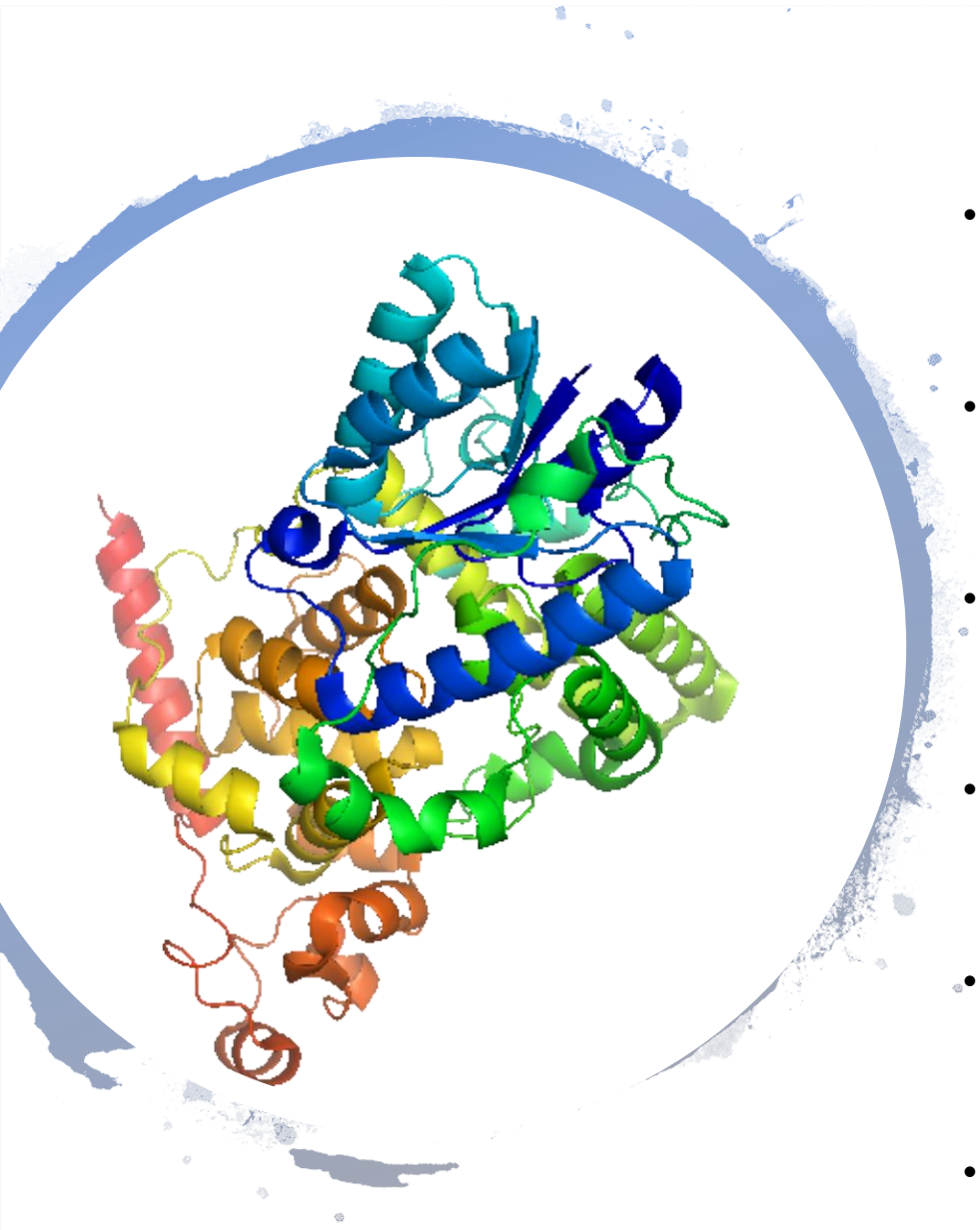
Animal health status

- Animals that have a history of safe consuption generally do not contain genes encoding for toxic substances.
- Therefore, animal health status is an excellent indicator of a potencial safe consumption.
- Compare the health status and performance indicators of the rDNA animal and the conventional counterpart, taking into account the development phase.



Assessment of Potencial Toxicity and Bioactivity

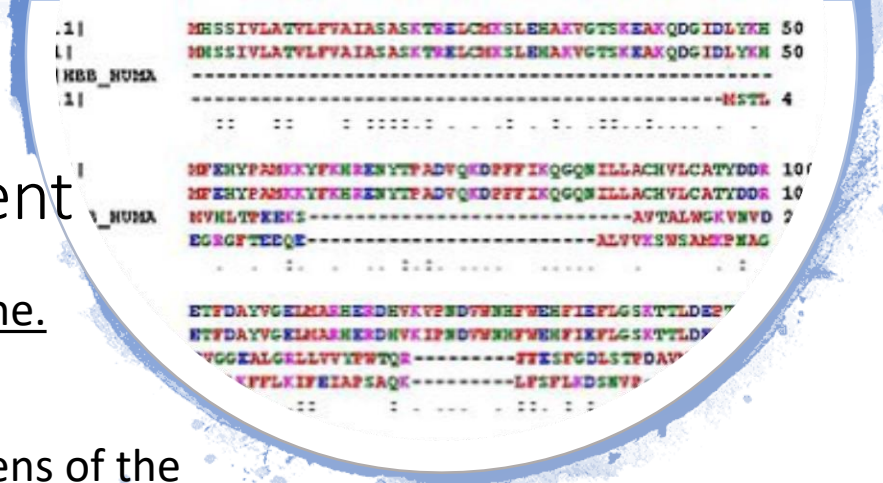
- Novel substances expressed might be evaluated for potencial toxicity or bioactivity (may be active in humans).
- Determination of toxicological potential based on the "weight of evidence".
- If there is a history of safe consumption, it is NOT necessary to conduct toxicological studies.



Assessment of Potencial Toxicity and Bioactivity

- Identification of known toxins in donor and recipient species.
- Identification of new toxins encoded by the transgenes.
- Similarity of expression products with known toxins (Bioinformatics).
- Thermal stability and resistance to gastric and intestinal model systems.
- Acute toxicology tests in animals, of the novel proteins with no history of consumption.
- Health status of the rDNA animal, potential dietary exposure to the substance and bioactivity in humans.

Allergenicity Assessment



- <u>Same process to plant guideline.</u>
- Identification of known allergens of the donor and recipient species.
- Identification of potential new allergens encoded by the transgenes.
- Similarity of expression products with known allergens (Bioinformatics: a window of 80 amino acids is compared).
- Other evidence: molecular weight (10-7 kDa), expression levels in food, resistance to processing (heat or others in vitro digestibility, glycosylation, IgE assays with serum from sensitive patients (if applicable).

Compositional analysis

- rDNA animal composition and conventional counterpart.
- Conventional counterpart ideally be matched in housing and husbandry conditions, breed, age, sex, parity, lactation, or laying cycle (where appropriate), but in practice may be not possible.
- May need more than one comparator
- Key components are compared: nutrients, antinutrients, allergens, toxicans (rare).

Compositional analysis

- When there are statistically significant differences, patterns of changes are analyzed.
- Take into account that the number of samples may be limited and there is likely to be large variation between animals.
- Evaluate that difference in the context of the natural variability of the species (if available)
- When the mean values are not included in the ranges of the comparisons made and the bibliography, it has to be verified that the statistical differences are not biologically relevant.

Intended Nutritional Modification

- When the nutritional profile is intentionally modified and not comparable with conventional foods
- Or changes in the bioavailability of nutrients are expected, feeding trials with the whole food may be requested.
- Nutritional value, nutrient bioavailability, and safety are compared.
- Use conventional foods whose nutritional composition is closer, as appropriate comparator.
- For specific population subgroups, additional nutritional assessments may be necessary.

Other considerations

- Potential for altered accumulation or distribution of xenobiotics (e.g. veterinary drug residues, metals), which may affect food safety, and potential of increased risk of zoonoses by microbes

- Use of antibiotic resistance marker genes: Gene transfer from animals and their food products to gut microorganisms or human cells

Final words

To date, there have not been many cases of application of the guide.

General assessment criteria and approaches are similar of those in Plants guideline.

Some specific provision in animal guideline: health status, bioactivity assessment, definition of conventional counterpart, breeding process and other considerations.

Thank you very much!

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