



# Updated EFSA Guidance Document for the Risk Assessment of GM plants and derived Food and Feed

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**GUIDANCE DOCUMENT  
OF THE SCIENTIFIC PANEL  
ON GENETICALLY MODIFIED  
ORGANISMS FOR THE RISK  
ASSESSMENT OF GENETICALLY  
MODIFIED PLANTS AND  
DERIVED FOOD AND FEED**

Adopted on 24 September 2004  
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May 2006

- Adopted on 24 September 2004
- Updated in December 2005 (PMEM)
- Published in May 2006
- Complemented in
  - December 2006 (Renewals)
  - March 2007 (Stacked events)

## Rationale

1. Science and technology evolves together with experience thus updates can always be expected. Role of Self Tasks.
2. Significant driver: The Commission wishes to build greater consensus (improve legal and scientific certainty) for applicants and to increase the overall transparency of the evaluation process. The guidance by EFSA was updated and adopted in 2008 to be used as a basis to draft legal texts in respect of the evaluation of GMOs.

Document launched for consultation in July until September 2008.

The document is now under final discussions at EC level with MS before it is presented for voting.

## Guidance Documents

- Stacked events (conventional crosses)
- Renewal dossiers
- Post Market Environmental Monitoring

## Self Tasks

- Animal feeding trials (published)
- **Antibiotic resistance marker genes in GM plants (published)**
- Field trial design and statistical analysis (published)
- Allergenicity
- **Interplay GMO and pesticide legislation**
- Selection of comparators

- Elaboration on principles and strategies for risk assessment of GMOs
- More details on required information in the various chapters
- Required information on stacked events incorporated into various chapters where appropriate
- Extended chapters on experimental design field trials and statistical analysis of results
- Reference to standardised protocols for toxicity testing of single compounds

- Details on performance of animal feeding trials with whole GM food/feed and conditions when needed
- Further details on nutritional assessment of GM food/feed
- Further precision of the final integrative risk characterisation of GM plants
- Introductory paragraphs in the various chapters to explain why information is required
- Per chapter summary of conclusions

## Risk Characterisation

- Chapter updated to improve the performance of the final risk characterisation
- How should the evidence collected from the molecular analysis, the comparative compositional analysis, the food and feed safety assessment and the e.r.a. be interpreted and considered in risk characterisation
- Issues to be considered:
  - Evaluation of the quality of results, lack of data
  - Application of extrapolation factors
  - Can threshold levels/safety limits be established
  - Identification of uncertainties
  - Long term impact on humans, animals and the environment

# Molecular Characterisation



- A clear description of the insert, including all information necessary to interpret molecular data: primer binding sites, restriction sites, probe locations
- Information on the safety of the source of the sequences intended to be inserted
- The requirement for the description of the helper plasmid (if used) has been reintroduced
- Southern analyses should cover the insert flanking regions
- The sequence similarity search for detection of interrupted host genes should also use databases containing sequences from other species than the transformed plant

- All sequences between stop codons, not limiting the length of the sequence should be considered when searching for new ORFs spanning the novel junctions
- Bioinformatics searches should be conducted on the possible new ORFs not just at the insert-genomic DNA junctions, but also at the junction sites arising due to internal rearrangements of the insert(s)
- Expression analysis of potential new ORFs identified at the junction sites created as a result of the genetic modification shall be provided only in cases when complementary information (e.g. potential for transcription/translation and similarity to known allergens/toxins) indicates a potential safety issue.

- Protein expression data from field trials (not glasshouse trials). The same material should be used as for compositional analysis.
- Developmental protein expression levels are not required in all cases (e.g. food-feed import and processing)
- On case-by-case basis data may be required on potential reduction of protein levels other than those intended (RNA techniques)
- RNA levels might be required on a case-by-case basis
- Multiple generation is now defined as five to demonstrate trait stability .

- Field Trials and Statistical Analysis
- Comparators and Comparative Analysis
- Toxicology and Nutrition
- Allergenicity

- Vegetatively propagated crops: conventional counterpart shall, in principle, be the non-GM isogenic variety used to generate the transgenic lines and with a history of safe use. In the case of crops that reproduce sexually, the conventional counterpart shall have a genetic background that is as close as possible to the GM plant and with a history of safe use.
- Null segregants when used with other non GM comparators are useful but cannot be considered as a non GM comparator with history of safe use.
- This is line with *Codex Alimentarius* Guidelines, 2003 where it is explained that for the foreseeable future, foods derived from modern biotechnology will not be used as conventional counterparts.
- Comparator Self Task due to report ca. March 2010.

## **“Safety and Nutritional Assessment of Genetically Modified Plants and Derived Food and Feed: The role of animal feeding trials”**

Report of the EFSA GMO Panel Working Group on Animal Feeding Trials

Adopted by the EFSA GMO Panel on 12 September 2007



*Food and Chemical Toxicology*  
volume 46, supplement 1, March 2008, pages S1-S70

<http://www.efsa.europa.eu>

# Animal Feeding Trials with Whole GM Foods/Feed

- Case by case approach, hypothesis driven, not routinely required
- If molecular, compositional, phenotypic, agronomic and other analyses have demonstrated equivalence of the GM food/feed, animal feeding trials do not add to the safety assessment
- Minimising the use of experimental animals

- Performance of a 90-day rodent feeding study with whole GM food/feed can be used for reassurance of the performed risk assessment.
- This should be performed in case of extensive alterations in the composition of the GM food/feed or in case of indications for the occurrence of unintended effects based on evaluation of molecular, biochemical, compositional, and phenotypic and agronomic aspects.
- The limited sensitivity and specificity of the study prevents it from being used as the main test in the safety assessment. Thus, a case-by-case approach is recommended.



- Importance of at least two dose levels in the 90-day rodent feeding] study to allow for assessment of a dose-response relationship and the toxicological relevance of any observed difference(s) between groups
- Laboratory animal feeding studies with defined single substances should be conducted according to the OECD Guidelines for the Testing of Chemicals (OECD Test Guidelines) and in compliance with the principles of Good Laboratory Practice (GLP).
- Regarding the testing of GM foods and feeds, an adaptation of the existing OECD protocol for subchronic oral toxicity testing in rodents is recommended.

- Newly expressed protein: source and history of previous consumption molecular and biochemical characterisation search for homology with known toxic proteins resistance to proteolytic enzymes (e.g. pepsin) stability under expected treatment of the food/feed
- Unless reliable information is provided which demonstrates the safety of the newly expressed protein, the safety assessment of proteins with no history of safe use (for consumption as food) should normally include a repeated-dose toxicity test (normally 28 days) and not rely on acute toxicity testing.

- Stacks: The risk assessment of stacked events requires a case-by-case approach focused on the identification of potential interactions between the events. For example, The assessment of potential interactions between newly expressed proteins is foreseen at several places
- If the potential for interactions is identified, which may impact on food/feed safety specific studies including animal feeding trials with the whole GM food/feed may be required

- For the risk assessment of GM plants with an altered level of specific nutrients and GM plants intended to provide health benefits, existing reference values for acceptable or tolerable levels of intake of the specific substance(s), e.g. the Acceptable Daily Intake (ADI) or Tolerable Upper Intake Level (UL), should be taken into account
- If no such value has been derived, information for the toxicological and nutritional assessment has to be provided This may include comprehensive toxicological testing of the single substances, including studies in humans as well as bioavailability studies.
- Health, nutritional status and dietary practices of specific population(s) anticipated to consume the food should be considered in the assessment
- The Panel will consider the need for new guidance on this subject based on the experience from the evaluation of new products.

- The allergenicity section remains essentially unchanged
- Comments on allergenicity are not addressed in this report. The EFSA GMO Panel is currently working on a self task activity entitled "the assessment of allergenicity of GM foods/feed" where valid comments that are not addressed in Annex B, will be considered. The document produced by the self tasking Group will be available for public consultation during the course of 2009.

- Additional consultation on the environmental components of the risk assessment is foreseen (mandate from the Commission and GMO Panel Self Task)
- Will provide update on issues such as assessing potential long-term environmental effects of cultivation and potential risks to non-target organisms by traits such as insect-resistance in GM plants.

# Conclusions

- EFSA Guidance document continues to present a robust strategy for the risk assessment of GM plants and derived foods and feed
- Elaboration on the structure of the risk analysis process
- Description of the purposes of the different steps of risk assessment
- Further precision of requirements
- Specific guidance for field trial designs and statistical analysis of results
- Reference to existing test toxicological protocols
- Conditions and protocol for animal testing of whole GM Food/Feed
- International setting is important

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