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Comparative Risk Assessment Strategies for Food and Feed derived from Genetically Modified Plants and Future Challenges

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On the occasion of EFSA's 10 Year Anniversary
Challenging boundaries in risk assessment – sharing experiences , 7th – 8th November 2012 , Parma, Italy

First Generation of GM Plants with Agronomical Traits

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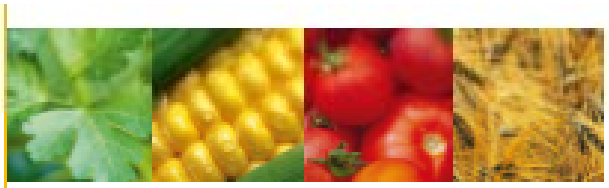
- Improved disease resistance (viruses, fungi)
- Improved pest resistance (lepidoptera, beetles)
- Tolerance for herbicides (glyphosate, glufosinate)
- Combined herbicide tolerance/ pest resistance (stacks)

- Main Commercial Crops:

Soybean, Maize, Rapeseed, Cotton

EFSA Guidance for GM Plants and derived Food and Feed



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
First, edited version of 8 November 2004

March 2005

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- Adopted on 24 September 2004,
- Updated in December 2005 (PMEM)
- Complemented in
  - December 2006 (Renewals)
  - March 2007 (Stacked events)
- Updated
  - May 2008, for Public Consultation,
  - May 2011 final version

DRAFT COMMISION REGULATION

Draft

COMMISSION REGULATION

on

implementing rules concerning applications for authorisation of genetically modified food and feed in accordance with Regulation (EC) No 1829/2003 of the European Parliament and of the Council and amending Regulations No (EC) 641/2004 and (EC) No 1981/2006

EC Regulation 1829/2003 (1)

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Comparative Approach

Compare the GMO and derived products to the

(non-GM) conventional counterpart

and assess the identified differences

Conventional counterpart = a similar food or feed produced without the help of genetic modification and for which there is a well-established history of safe use

EC Regulation 1829/2003 (2)

- Traditionally cultivated crops are well known and have gained a history of safe use for the environment, consumers and animals.

- These crops can serve as a *baseline* for the environmental and food/feed safety assessment

- *Concept of Substantial Equivalence, Concept of Familiarity,, Comparative Safety Assessment.*

Identification of Differences between the GMO, its Comparator and Commercial Varieties

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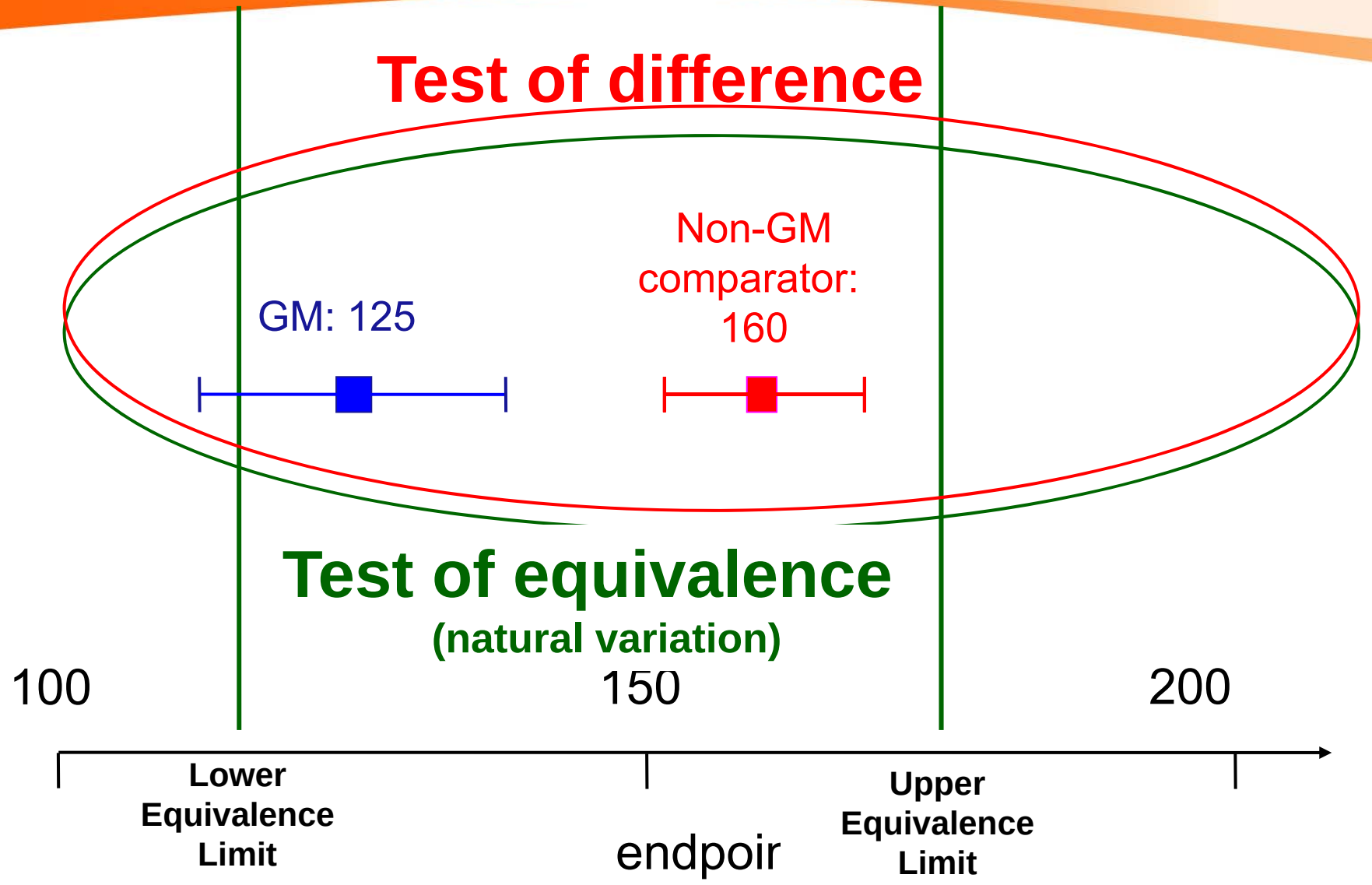
1. Test of Difference:

To verify whether the GMO is different from the non-GM comparator (identification of possible hazard)

2. Test of Equivalence:

To verify whether the identified difference(s) ‘fall’ within natural variation ranges of reference (commercial) varieties

EFSA Approach for Difference and Equivalence Testing in Field Trials



Data Requirements for the Risk Assessment of GM Plants and Derived Food/Feed

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- Genetic modification and its consequences
- Agronomic, morphological and compositional characteristics of the GM plant and it products
- Potential (long term) toxicity and allergenicity of the GM plant and its products
- Influence of processing
- Nutritional impact and dietary intake

Toxicological and Allergenicity Assessment

- Assessment of newly or differently expressed proteins
- Assessment of possible new constituents
- Assessment of possible alterations in content of natural constituents
- Assessment of the whole GM food/feed,
- An integrated, weight-of-evidence approach for allergenicity assessment (EFSA, Codex Task Force for Biotechnology)
- OECD Guidelines and protocols for testing recommended

Animal Testing of Whole GM Food/Feed

WHEN TESTING OF WHOLE GM FOOD/FEED IN ANIMALS?

– In case of indications or remaining uncertainties for the potential occurrence of unintended effects

- In case of relevant differences identified by molecular, compositional, phenotypic, or agronomic analyses
- In case of stacks with interacting proteins

Hypothesis-driven approach (not routine)

Difficulties with Animal Feeding Trials with Whole (GM) Foods/Feed

- Natural bulkiness of food
- Effects on satiety
- Need to maintain nutritional balance
- Limit of dietary administration in order to prevent dietary imbalance
- Matrix effects

Whole Food and Feed Testing in Laboratory Animals

"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

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

Guidance on conducting repeated-dose 90-day oral toxicity study in rodents on whole food/feed

EFSA Scientific Committee

European Food Safety Authority (EFSA), Parma, Italy

EFSA Journal 2011;9(12):2438

EFSA Guidance for Performing Animal feeding Trials with Whole (GM) Food/Feed

- Animals should be housed ***as pairs*** and not singly
- Use of a *randomised block design* (further increase in power)
- The number of treatment groups may be reduced
- Full range of observations as described in the OECD Guideline 408
  - food/feed intake, growth, haematology, blood clinical biochemistry ,urinalysis, gross necropsy and histopathology, immune and hormonal parameters, gut eco-system parameters (case-by-case)
- Documented statistical methodology

RAPIDLY EVOLVING NEW BREEDING TECHNOLOGIES

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1. ZINC FINGER NUCLEASE TECHNOLOGY
   (ZFN-1, ZFN-2 and ZFN-3)
2. OLIGONUCLEOTIDE DIRECTED MUTAGENESIS (ODM)
3. CISGENESIS/INTRAGENESIS
4. RNA-DEPENDENT DNA METHYLATION
   (RdDM)
5. GRAFTING ON GM ROOTSTOCK
6. AGRO-INFILTRATION
7. REVERSE BREEDING
8. SYNTHETIC BIOLOGY

Questions of the Commission

1. Need for new guidance or update of the existing EFSA guidance on risk assessment of products obtained by the new breeding techniques?

2. Risks that these new techniques could pose, irrespective of whether or not they fall under the GMO legislation?

   – *Compare plants obtained by the new techniques with plants obtained by conventional plant breeding or with genetic modification (transgenesis).*

Cisgenesis/Intragenesis

- ***Cisgenesis:***
  - Genetic modification of an organism with a gene from a ***crossable*** organism (same species or closely related)
  - Cisgenic plants do not contain any parts of transgenes or **foreign** sequences
- ***Intragenesis:***
  - Similar to cisgenesis, but new combinations of DNA-elements from the same species are possible
    - Novel hazards
- *Similar methods are used as for transgenesis (Agrobaterium, electroporation, bolistics)*

Issues with Cisgenesis, Intragenesis

- No linkage drag with cisgenesis and intragenesis compared to conventional breeding (rec DNA transfer methods)
- No ***foreign*** transgenes inserted
- Alterations at the insertion site and elsewhere (gene disruptions, deletions, rearrangements) are comparable with conventional breeding
- History of safe use and consumption may be available for the inserted gene(s) and expressed products
- Greater consumers acceptance?

Conclusions Risk Assessment of Cisgenic and Intragenic plants and derived /food/feed

- EFSA Guidance Documents for Food/Feed Risk Assessment and for the Environmental Risk Assessment developed for transgenic (GM) plants apply also to Cisgenic/Intragenic Plants

- **Data requirements can be reduced** where there is familiarity with the donor and/or recipient plants

  –Less data on toxicity and consumption of newly expressed proteins (history of safe use)

  –Less data for the environmental risk assessment

- **EFSA Opinion Cisgenesis/Intragenesis,** EFSA Journal 2012;10(2):2561

Safety Assessment of Plants Developed Using Zinc Finger Nucleases –3 or other Site Directed Nucleases-3

Zinc Finger Nuclease–3
artificial restriction enzyme

- Zinc finger nucleases **target** insertion of DNA sequences into a ***pre-defined region*** of the genome
- Specific zink finger DNA binding domains combined with cleavage domain of a bacterial restriction endonuclease (*Fok*I)
- Repair mechanisms via non homologous end joining (NHEJ) or via homologous recombination (HR) using donor DNA templates
- Hazards from random integration are *decreased* compared to transgenesis

Zinc Finger Nuclease 3 and other Site-Directed Nucleases with similar function

- EFSA Guidance Documents for Food/Feed Risk Assessment and for the Environmental Risk Assessment developed for transgenic plants are applicable for SDN-3 plants
- The targeted insertion of DNA by SDN-3 techniques can diminish hazards associated with the disruption of genes and/or regulatory elements:
- Flexibility in data requirements may be considered
- EFSA Opinion (2012) in press

GM Crops with altered composition (Processing , Nutrient Deficiencies, Health)

Soybean	enriched omega-3 fatty acids
Soybean	increased oleic acid/decreased linoleic acid
Potato	high amylopectin content
'Golden' rice	containing β-carotene
Rice	fortified with iron
	lower allergen content
Tomato	β-carotene / lycopene enriched
Lupin	higher methionine levels
Maize	higher levels of lysine
	detoxification of mycotoxins
Sweet potato	enhanced β-carotene
	higher protein content
Cassava	detoxification of cyanogens
Kidney beans	lower levels of lectins
Alfalfa	transgenic phytase, P-availability
Rape seed	vitamin E enriched

Need for an Adapted Risk ssessment?

- Extensive compositional alterations
- Suitable comparators may not be available
- A Comprehensive Risk assessment per se is needed
  - based on the characteristics of the product
  - Novelty is the trigger

- EFSA TENDER “Review of the strategies for the comprehensive food and feed safety and nutritional assessment of GM plants *per se*”

General Considerations of an Assessment of GM foods/feeds per sé

- NOVEL FOOD APPROACH---PRODUCT BASED

- **History of organism(s) and of safe use**
- **Genetic modification characteristics**
- **Compositional analysis**
- **Toxicological and allergenicity assessment**
- **Nutritional Assessment**
- **Dietary exposure**

CONCLUSIONS

- The Comparative Risk Assessment Strategy for GM plant derived Food/Feed as developed by EFSA is robust and guarantees a high level of safety for consumers and animals

- Data requirements for the risk assessment of GM plants and derived Food/Feed Products obtained by some of the new breeding technologies, may be further *specified and reduced* compared to requirements for transgenic plants

- Development of a Comprehensive Risk Assessment Strategy for GM plant derived food/feed is needed for new GM crops with a substantially altered composition; product characteristics and novelty are leading principles

Acknowledgements

- EFSA GMO Panel members
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- Scientific Committee and Working Group members “Guidance on 90-day Feeding Trials with Whole Food or Feed