Authorisation on European level and role of EFSA GMO Panel in food risk assessment

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efsa
European Food Safety Authority

ROUND TABLE:
„GMO IN FOOD PRODUCTION"
Opatija, Croatia
23rd of October 2014

www.efsa.europa.eu

OUTLINE

1. **EU legal framework and EFSA's remit in the GMO area**
2. Risk assessment of GMO applications
3. Guidance

GMO IN EUROPE

An organism is "genetically modified" if its genetic material has been changed in a way that does not occur under natural conditions through cross-breeding or natural recombination.

Defined by the European Union Directive 2001/18/EC (Art. 2)

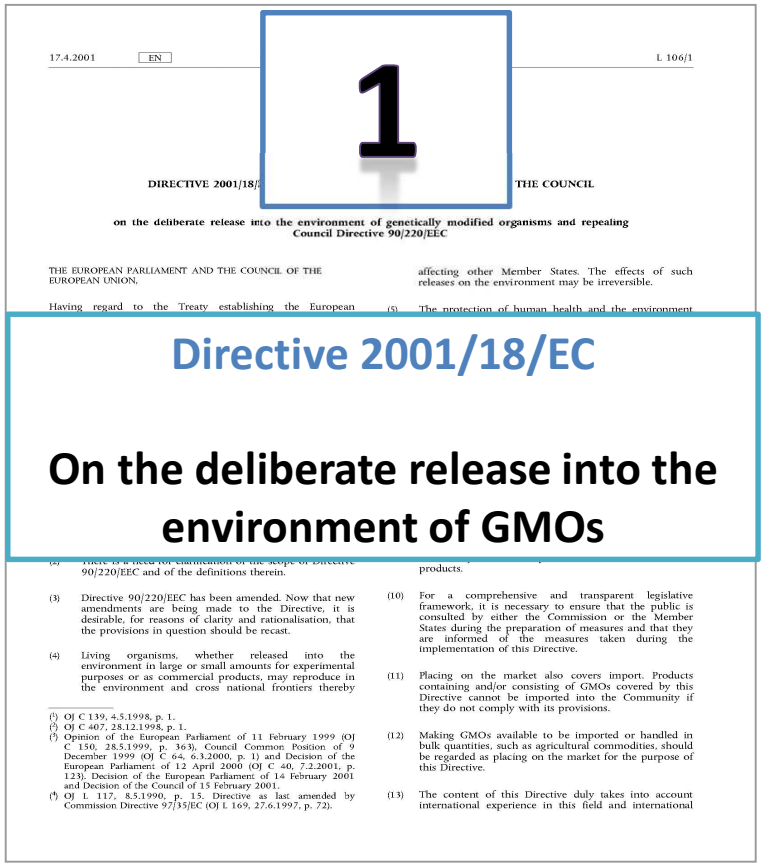
In the EU, products that are, contain, or are produced from Genetically Modified Organisms (GMOs) must have an authorisation prior to entering the market

THE REMIT OF EFSA

- EFSA is responsible to perform a **risk assessment of GMOs** with regard to **human and animal health** and **the environment**
- **What EFSA cannot do**
  - **Give authorisations** (for products such as GMOs, feed additives, food additives, pesticides etc)
  - **Be responsible for food safety legislation** (sampling, labelling or other risk management issues such as co-existence measures)
  - **Take charge of food safety/quality controls**

LEGAL FRAMEWORK FOR GMO RISK ASSESSMENT

EFSA's role is to carry out scientific Risk Assessment on GMOs under two regulatory frameworks:



17.4.2001 EN L 106/1

1

DIRECTIVE 2001/18/ THE COUNCIL

on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European

affecting other Member States. The effects of such releases on the environment may be irreversible.

(5) The protection of human health and the environment

90/220/EEC and of the definitions therein.

(3) Directive 90/220/EEC has been amended. Now that new amendments are being made to the Directive, it is desirable, for reasons of clarity and rationalisation, that the provisions in question should be recast.

(4) Living organisms, whether released into the environment in large or small amounts for experimental purposes or as commercial products, may reproduce in the environment and cross national frontiers thereby

products.

(10) For a comprehensive and transparent legislative framework, it is necessary to ensure that the public is consulted by either the Commission or the Member States during the preparation of measures and that they are informed of the measures taken during the implementation of this Directive.

(11) Placing on the market also covers import. Products containing and/or consisting of GMOs covered by this Directive cannot be imported into the Community if they do not comply with its provisions.

(12) Making GMOs available to be imported or handled in bulk quantities, such as agricultural commodities, should be regarded as placing on the market for the purpose of this Directive.

(13) The content of this Directive duly takes into account international experience in this field and international

(1) OJ C 139, 4.5.1998, p. 1.
(2) OJ C 407, 28.12.1998, p. 1.
(3) Opinion of the European Parliament of 11 February 1999 (OJ C 150, 28.5.1999, p. 363), Council Common Position of 9 December 1999 (OJ C 64, 6.3.2000, p. 1) and Decision of the European Parliament of 12 April 2000 (OJ C 40, 7.2.2001, p. 123). Decision of the European Parliament of 14 February 2001 and Decision of the Council of 15 February 2001.
(4) OJ L 117, 8.5.1990, p. 15. Directive as last amended by Commission Directive 97/35/EC (OJ L 169, 27.6.1997, p. 72).

Directive 2001/18/EC

On the deliberate release into the environment of GMOs

18.10.2003 EN L 268/1

2

REGULATION (EC) No 18 AND OF THE COUNCIL

on genetically modified food and feed

(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Com-

(4) Differences between national laws, regulations and administrative provisions concerning the assessment and authorisation of genetically modified food and feed may hinder their free movement, creating conditions of unequal and unfair competition

feed is an essential aspect of the internal market and contributes significantly to the health and well-being of citizens, and to their social and economic interests.

(2) A high level of protection of human life and health should be ensured in the pursuit of Community policies.

(3) In order to protect human and animal health, food and feed consisting of, containing or produced from genetically modified organisms (hereinafter referred to as genetically modified food and feed) should undergo a safety assessment through a Community procedure before being placed on the market within the Community.

(7) Feed consisting of or containing genetically modified organisms (GMOs) has so far been authorised, subject to the authorisation procedure provided by Council Directive 90/220/EEC of 23 April 1990 (5) and Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms (6); no authorisation procedure exists for feed produced from GMOs; a single, efficient and transparent Community authorisation procedure for feed consisting of, containing or produced from GMOs should be established.

(8) The provisions of this Regulation should also apply to feed intended for animals which are not destined for food production.

(1) OJ C 304 E, 30.10.2001, p. 221.
(2) OJ C 221, 17.9.2002, p. 114.
(3) OJ C 278, 14.11.2002, p. 31.
(4) Opinion of the European Parliament of 3 July 2002 (not yet published in the Official Journal), Council Common Position of 17 March 2003 (OJ C 113 E, 13.5.2003, p. 31), Decision of the European Parliament of 2 July 2003 (not yet published in the Official Journal) and Council Decision of 22 July 2003.

(5) OJ L 43, 14.2.1997, p. 1.
(6) OJ L 117, 8.5.1990, p. 15. Directive repealed by Directive 2001/18/EC.
(7) OJ L 106, 17.4.2001, p. 1. Directive as last amended by Council Decision 2002/811/EC (OJ L 280, 18.10.2002, p. 27).

Regulation (EC) No 1829/2003

On GM food and feed including derived products

NEW IMPLEMENTING REGULATION ON GM PLANT APPLICATIONS

novel elements in IR (EU) No 503/2013

- 90 day feeding study with whole food/feed mandatory for all single events
  - A review of this requirement is foreseen by 2016. The Commission will perform this review based on new scientific information such as the outcome of the EU project GRACE (GMO Risk Assessment and Communication of Evidence) (see Art. 12, IR 503/2013).
- re-sequencing of DNA inserts and their flanking regions in GM plants containing stacked events
  - To be compared with the nucleotide sequence of the respective single events
- Quantitative measurement of allergens in the frame of compositional analysis as referred to in relevant OECD documents

OUTLINE

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2. **Risk assessment of GMO applications**

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SCOPE OF GMO APPLICATIONS

Food

- GMO for food use
- Food containing or consisting of GMOs
- Food produced from or containing ingredients produced from GMO

Feed

- GMO for feed use
- Feed containing or consisting of GMOs
- Feed produced from GMOs

Deliberate release into the environment

- Import and processing
- Seeds and plant propagation material for cultivation

RISK ASSESSMENT PERFORMED BY

- **The GMO Panel (19 external experts)**
  - elaborates guidance documents
  - delivers scientific opinions on applications for market authorisation regarding GMOs
- **40 Ad-hoc experts** support the GMO Panel in **Working groups** (4 standing WG and several temporary WGs)
- **15 GMO Unit scientists** that provide support to the GMO Panel and its Working Groups
- **210 Member State experts** from 108 MS organisations and authorities comment on each application

EFSA GMO PANEL EXPERTISE

Ad-hoc experts in new techniques, microbiology

Ad-hoc experts in food sciences, animal pathology

Ad-hoc experts in pesticides, natural toxins, environmental monitoring

MOLECULAR CHARACTERISATION
- biochemistry
- molecular biology
- genetics
- plant breeding
- microbiology

FOOD FEED SAFETY
- toxicology
- immunology
- nutrition & animal feed
- food chemistry
- biotechnology

ENVIRONMENTAL RISK ASSESSMENT
- plant biology
- ecology
- agronomy
- entomology
- biometrics & statistics

GMO application
(via a Member State)

Applications of
GM plants with scope
cultivation:
One Member State
performs initial ERA

Scientific Opinion

All applications:
Consultation with all
Member States via GMO
EFSA net

RISK ASSESSMENT

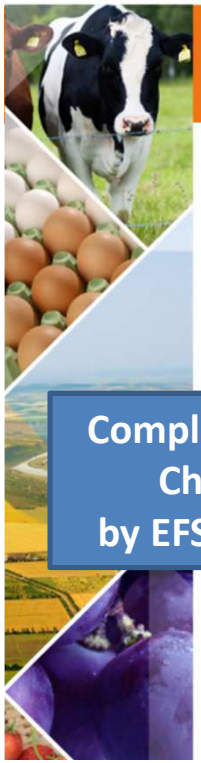
RISK MANAGEMENT

Public consultation

European Commission: draft
decision

Member States and European
Commission:
Decision to authorize or
not to authorize in Standing
Committee

WORKING PROCEDURE



When scope includes CULTIVATION

Completeness Check by EFSA staff

Member State

Panel WG on food and feed safety

Panel WG on environmental risk assessment

Panel WG on molecular characterisation

GMO Panel Opinion

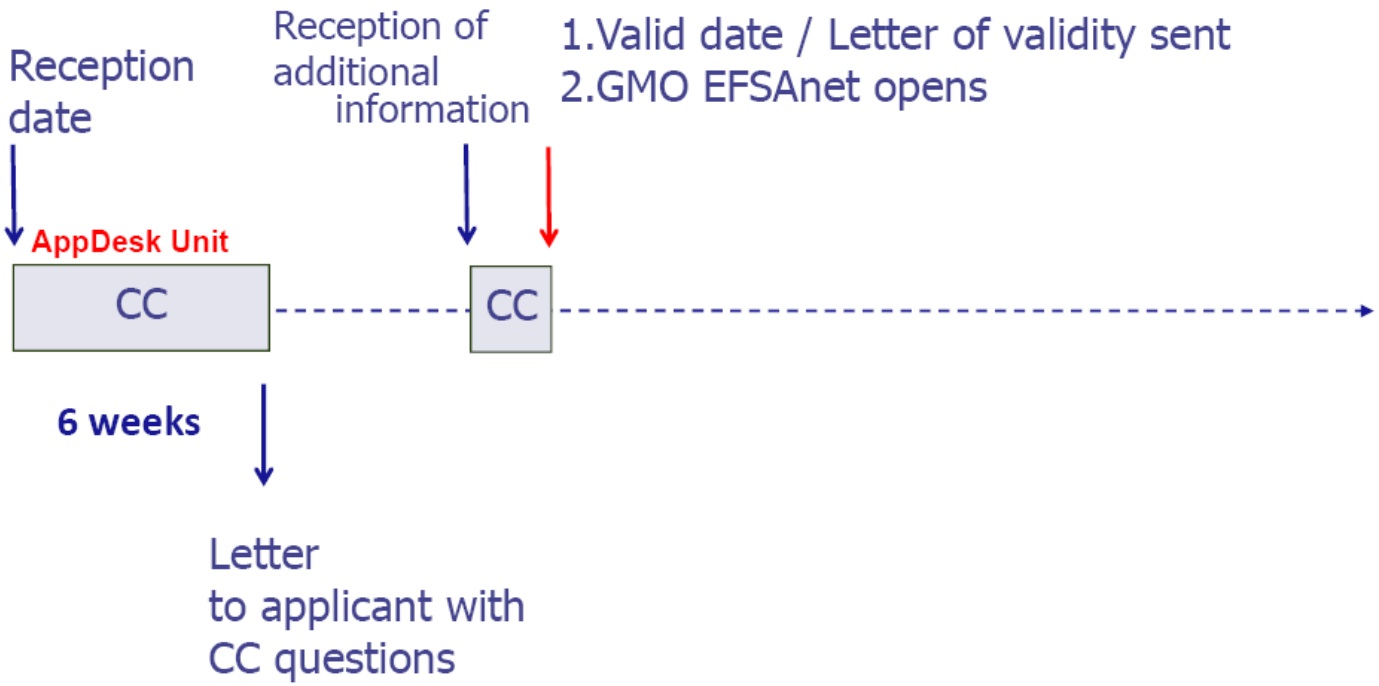
CC- check

Risk Assessment by a MS

by the GMO Panel

adopted

COMPLETENESS CHECK AND RA TIMELINE (6 MONTHS LEGAL DEADLINE + STOP CLOCK)



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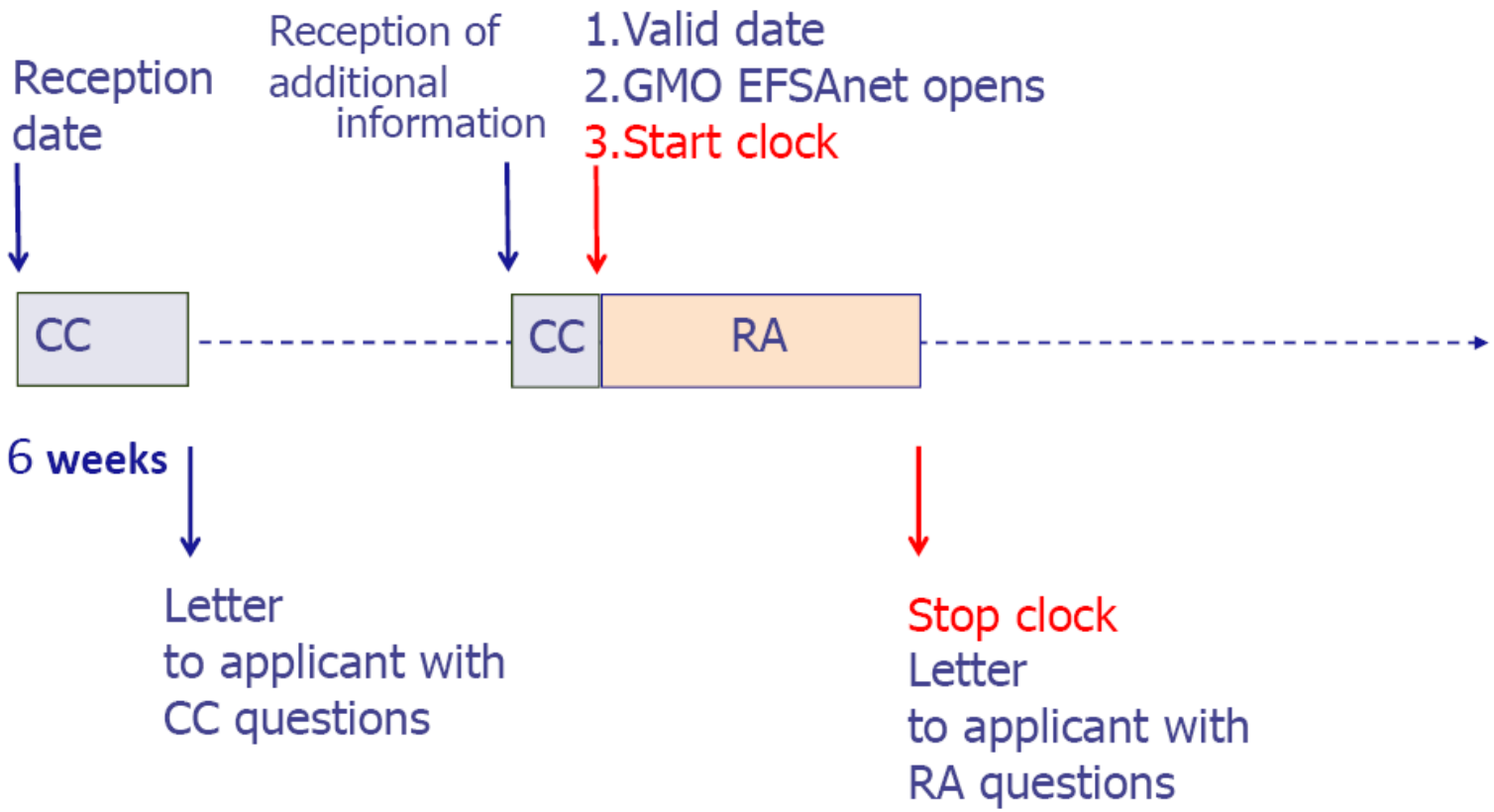
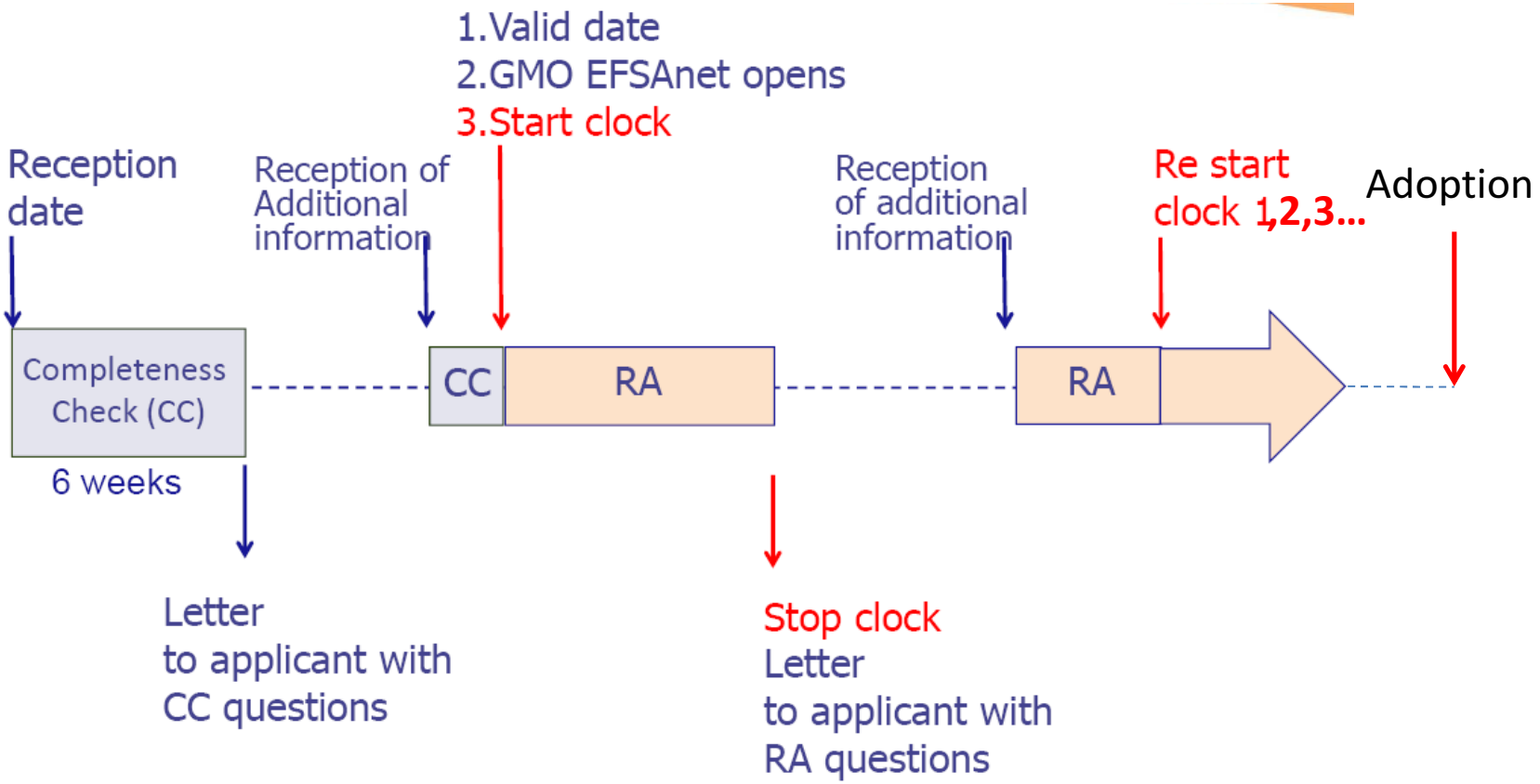


COMPLETENESS CHECK AND RA TIMELINE (6 MONTHS LEGAL DEADLINE + STOP CLOCK)



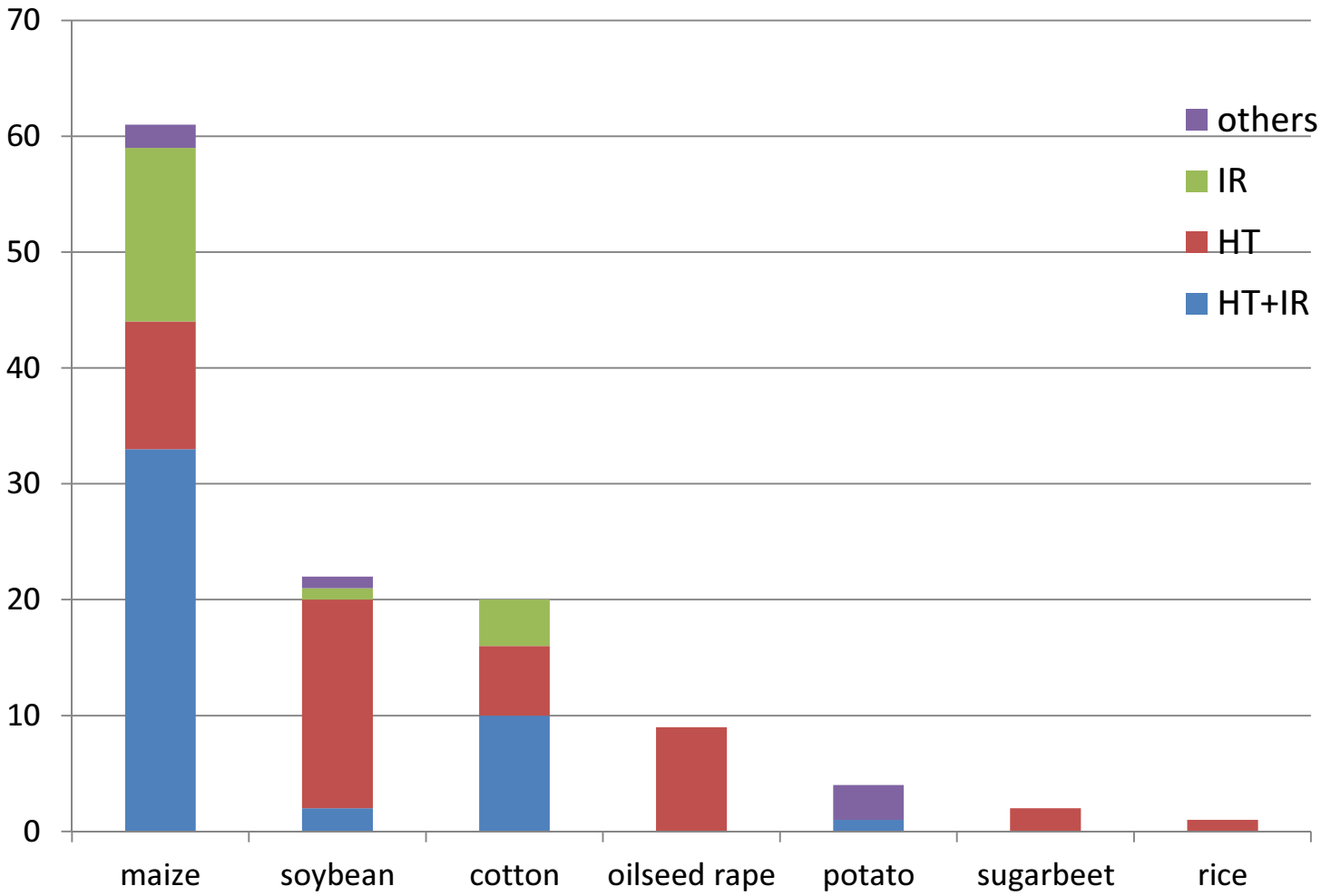
APPLICATIONS RECEIVED AND FINALISED

	GM Plants for food/feed use, including renewals (1829/2003/EC)		GM Plants release into environment (2001/18/EC)	
Year	**Received**	**Finalised**	**Received**	**Finalised**
2003 - 2009	**100 (includes 26 renewals)**	**37**	**15**	**12**
2010	**13**	**10**	**-**	**1**
2011	**14**	**9**	**-**	**-**
2012	**8**	**8**	**-**	**-**
2013	**9**	**12**	**2**	**-**
2014	**-**	**5**	**1**	**-**
Total 2003-2014	**144**	**81**	**18**	**13**

Withdrawn applications: under Regulation 1829/2003/EC**: 23**; under Directive 2001/18/EC: **2**

Ongoing applications: under Regulation 1829/2003/EC**: 40**; under Directive 2001/18/EC: **3**

DISTRIBUTION OF APPLICATIONS BY CROP AND TRAIT



OUTLINE

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THE PRINCIPLE LOGIC

COMPARATIVE APPROACH

Compare the GMO and derived products to their non-GM counterparts

Assessment of the identified differences regarding:

Environmental impact

Food/Feed safety

Nutritional impact

- **Intended effects**: those occurring because of the genetic modification
- **Unintended effects**: additional effects which were NOT the objective of the genetic modification

FOOD/FEED RISK ASSESSMENT OF GM PLANTS
SCIENTIFIC ISSUES

Molecular Characterisation

- Description of methods used for the genetic modification
- Source and characterisation of nucleic acid used for transformation
- Nature and source of vector(s) used
- Description of the traits introduced or modified
- Information on the sequences actually inserted/deleted (sequence of the insert(s) + flanking regions; copy number of insert)
- Information on the expression of the inserted/modified sequences (typically protein expression levels)
- Bioinformatic analysis to
  - identify ORFs
  - Identify homology to toxins and allergens
  - Support problem formulation for HGT
- Genetic and phenotypic stability

FOOD/FEED RISK ASSESSMENT OF GM PLANTS
SCIENTIFIC ISSUES

Food and Feed safety

- Compositional and agronomic assessment
- Toxicological assessment
- Allergenicity assessment
- Nutritional assessment

ERA and PMEM

- Several issues including:
  Persistence and invasiveness,
  Gene flow
  Non-Target Organisms

FOOD/FEED RISK ASSESSMENT OF GM PLANTS
ALLERGENICITY

Allergenicity assessment → Is the novel protein allergenic?

Allergenicity assessment → Is the GM plant more allergenic than the comparator?

weight-of-evidence approach, since no single definitive test available

Novel protein:

- Amino acid sequence homology comparison with known allergens
- Pepsin resistance and other in vitro digestibility tests

Whole food/feed (if it is an allergenic crop)

- IgE-binding assays with human sera from allergic individuals
- Analytical methodologies, e.g. proteomics, mass spectrometry to detect level of known allergens

QUESTIONS?

Thank you!

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RENEWAL OF AUTHORIZATION OF GM PLANT PRODUCTS - BACKGROUND

- Food/feed products derived from GM plants authorised under Regulation (EC) No 1829/2003 are valid for 10 years

- After 10 years these products can be renewed under articles 11 and 23 of Regulation (EC) No 1829/2003

- The first authorisations for placing on the EU market of GM plant products will start expiring from 2014 onward.

RENEWAL OF AUTHORIZATION OF GM PLANT PRODUCTS

No specific guidance document for the renewal of such products in accordance with Articles 11 and 23 of Regulation (EC) No 1829/2003 is available.

Self-tasking Working Group established to develop a new Guidance Document for the risk assessment of renewals of existing GM plants authorised under Regulation (EC) No 1829/2003.

RENEWAL GUIDANCE – TERMS OF REFERENCE

- To prepare a Guidance Document for the risk assessment of the renewal of authorizations of existing GM plants authorized under Regulation (EC) No 1829/2003

- To consult the public in the frame of a public consultation

- To finalize the new Guidance considering the relevant comments gathered from the public consultation by 25th March 2015

RENEWAL GUIDANCE - LEGAL FRAMEWORK

Regulation (EC) 1829/2003: Articles 11 and 23

The application shall be accompanied by the following:

a) A copy of the authorisation for placing the food/feed on the market

a) A report on the results of the monitoring, if so specified in the authorization

a) Any other new information which has become available with regard to the evaluation of the safety in the use of the food/feed and the risks of the food/feed to the consumer or the environment

GMO RISK ASSESSMENT

Risk assessment methodology and principles

- Science-based
- Step-by-step principle (tiered approach)
- Comparative approach
- Case-by-case principle

POST MARKET ENVIRONMENTAL MONITORING (PMEM)

PMEM is compulsory if living GMOs are placed on the market, e.g. for cultivation

- To identify the occurrence of adverse effects of GM plants that were **not anticipated** in the ERA (general surveillance)

- To confirm the assumptions of the ERA = to assess whether **anticipated** effects related to cultivation of a GM crop occur (Case-Specific Monitoring)

- **EFSA's Guidance on PMEM (2011**)

POST MARKET ENVIRONMENTAL MONITORING (PMEM)

PMEM reports are submitted by the applicant on a yearly basis

EFSA evaluates these reports , for cultivation dossiers, since 2010

- 2009 and 2010 PMEM reports on MON810 maize

  Cultivated in Czech Republic, Poland, Portugal, Romania, Slovakia and Spain

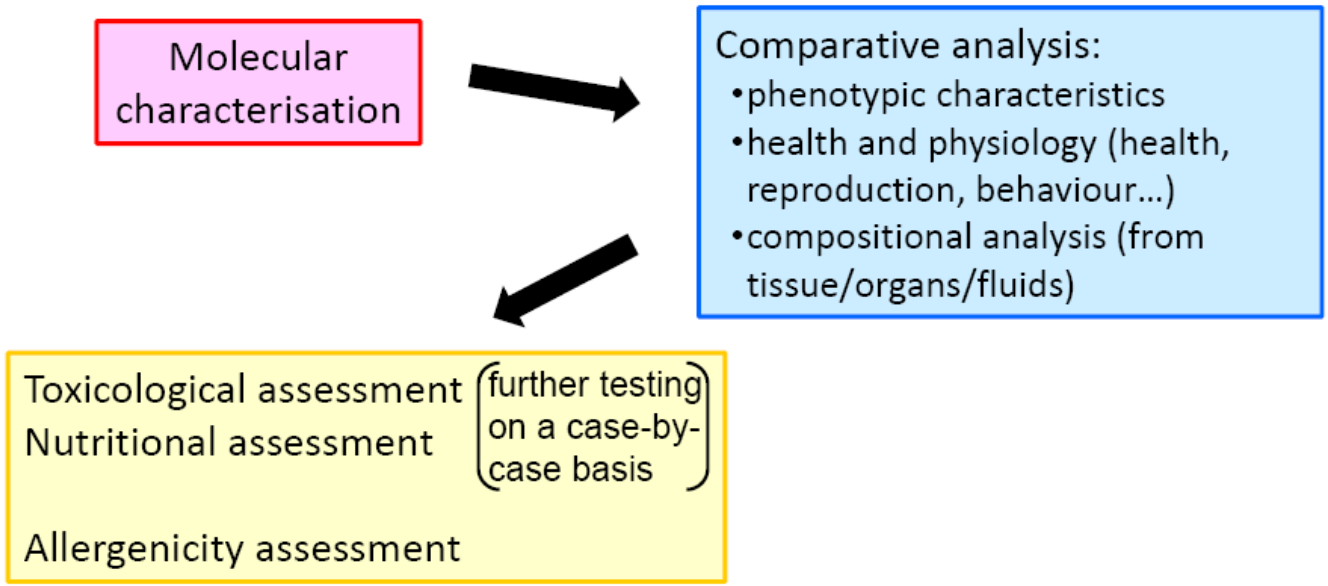
- 2010 and 2011 PMEM reports on Amflora potato

  Cultivated in Czech Republic, Germany and Sweden

- just received : 2012 PMEM report on MON810

GUIDANCE FOR THE RA OF FOOD AND FEED FROM GM ANIMALS (2011)

- EFSA has no applications for GM animals market release
- Upon request of the European Commission
- Issues on animal health and welfare also covered
- Scope: animals bred for food and feed use with heritable genetic modifications



GUIDANCE FOR THE ENVIRONMENTAL RISK ASSESSMENT (ERA) OF GM ANIMALS (2013)

- Based on Directive 2001/18
- Scope: fish, insects, mammals and birds
- Deliberately released for food/feed and non- food/feed purposes
- Experimental releases not covered

NEW IMPLEMENTING REGULATION ON GM PLANT APPLICATIONS FOR FOOD AND FEED USE

Regulation (EU) No 503/2013 on applications for authorisation of genetically modified food and feed in accordance with Regulation (EC) No 1829/2003

- Mandatory from 8 December 2013
- Defined the scientific information requirements to be provided in applications for GM food and feed under Regulation (EC) No 1821/2003
- The EFSA Guidance for risk assessment of food and feed from GM plants (2011) is only in place for applications submitted before 8/12/2013
- Reflects the EFSA GD to a large extent but contains additional mandatory elements

APPLICATIONS UNDER 1829/2003

Number of applications under 1829/2003	118
Number of ongoing applications	42 (3 for cultivation)
Applications with drawn by applicant	26 (11 for cultivation)

HERBICIDE TOLERANCE: GENES AND TRAITS

Gene	Product	HT	Mode of action	Origin
cp4-epsps	EPSPS	Glyphosate	Tolerant form of EPSPS, insensitive to Glyphosate	*Agrobacterium tumefaciens*
mepsps	EPSPS	Glyphosate	Tolerant form of EPSPS, insensitive to Glyphosate	*Zea mais*
gat	glyphosate N-acetyltransferase enzyme	Glyphosate	Acetylation, detoxifies glyphosate	*Bacillus licheniformis*
gox	Glyphosate oxidase	Glyphosate	Degrades glyphosate into aminomethylphosphonic acid (AMPA) and glyoxylate	*Ochrobactrum anthropi*
pat	phosphinothricin N-acetyltransferase enzyme	Glufosinate	Acetylation of glufosinate (phosphinothricin) herbicides	*Streptomyces viridochromogenes*

HERBICIDE TOLERANCE: GENES AND TRAITS

Gene	Product	HT	Mode of action	Origin
dmo	dicamba mono-oxygenase enzyme	Dicamba	Uses dicamba as substrate in an enzymatic reaction	*Streptomyces viridochromogenes*
ahas	acetohydroxyacid synthase	Imidazolinone	Tolerant form of AHAS, insensitive to imidazolinone	*Arabidopsis thaliana*
als	modified acetolactate synthase (ALS)	chlorimuron and thifensulfuron	Tolerant form of ALS insensitive to acetohydroxyacid inhibiting herbicides	*Glycine max* or *Zea mais*
aad	aryloxyalkanoate dioxygenase 1 (AAD-1) protein	2,4D	detoxifies 2,4-D herbicide	*Sphingobium herbicidovorans*
hppd	modified p-hydroxyphenylpyruvate dioxygenase (HPPD) enzyme	Isoxaflutole (IFT)	Tolerant form of HPPD, insensitive to isoxaflutole	*Pseudomonas fluorescens*
avhppd				*Avena sativa*

INSECT RESISTANCE: GENES AND TRAITS

Protein class	Target organisms	Mode of action	Genes	Origin
Cry1	Lepidoptera	• Following ingestion, proteins are proteolytically processed into active fragments • Active fragments bind to receptors in the mid-gut epithelium of target insects • Receptor binding is followed by the formation of pores in epithelial membranes which leads to cell lysis and death	*Cry1A.105* *Cry1Ab* *Cry1Ac* *Cry1F*	*Bacillus thuringiensis*
Cry2	Lepidoptera/diptera		*Cry2Ab2* *Cry2Ae*	
Cry3	Coleoptera		*Cry3.1Ab* *Cry3A* *Cry3Bb1*	
Cry34	Coleoptera		*Cry34Ab1*	
Cry35	Coleoptera		*Cry35Ab1*	
Vip3A	Lepidoptera		*Vip3Aa20*	

NUTRITIONAL MODIFICATION: GENES AND TRAITS

Gene(s)	Product	Mode of action	Origin	Trait (crop)
truncated intron of *FAD2-1A*, 5' UTR of *FATB1-A*	Sense RNA	Silencing the genes for delta-12 desaturase and palmitoyl acyl carrier protein thioesterase	*Glycine max*	High oleic acid content and decrease in polyunsaturated fatty acids (soybean)
gm-fad2-1	Sense RNA	Silencing the gene 1 for omega-6 desaturase	*Glycine max*	High oleic acid content (soybean)
Pj.D6D, Nc.Fad3	Δ6 desaturase, Δ15 desaturase	Desaturation of certain endogenous fatty acids	*Primula juliae, Neurospora crassa*	Produces omega-6 fatty acids (soybean)
cordapA	Lysine-insensitive dihydrodipicolinate synthase	Elimination of the lysine feedback inhibition of the lysine biosynthetic pathway	*Corynebacterium glutamicum*	High lysine content (maize)

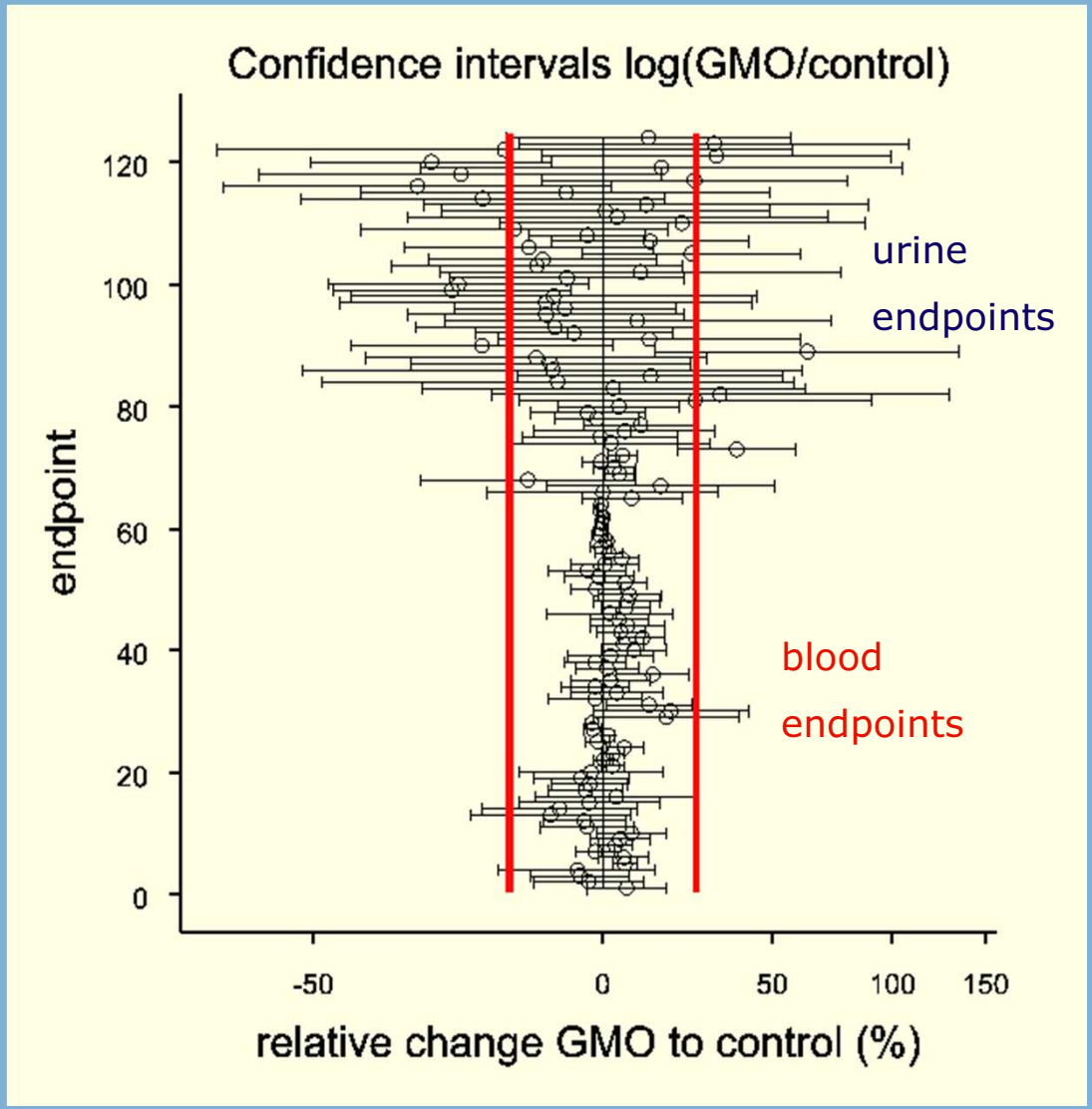
OTHER GENES AND TRAITS

Gene(s)	Product	Mode of action	Origin	Trait (crop)
anti *gbss*	antisense RNA	silencing the gene for granule bound starch synthase	*Solanum tuberosum*	Amylose-free starch (for industrial applications, potato)
amy797E	alpha-amylase	hydrolysis of starch into dextrins, maltose and glucose	*Thermococcales* (Archea)	thermostable alpha-amylase (for ethanol production, maize)
f3'5'h	flavonoid 3'5' hydroxylase	biosynthesis of delphinidin-based pigments	*Petunia* x *hybrida*	Mauve colour (carnation)
Dfr	dihydroflavonol 4-reductase	biosynthesis of delphinidin-based pigments	*Viola hortensis*	Mauve colour (carnation)

MON 863,
- **124 endpoints (blood and urine chemistry) in 90-day rat study**

Note logarithmic scale

Example limits at -20% (4/5) and +25% (5/4)



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Types of possible outcomes

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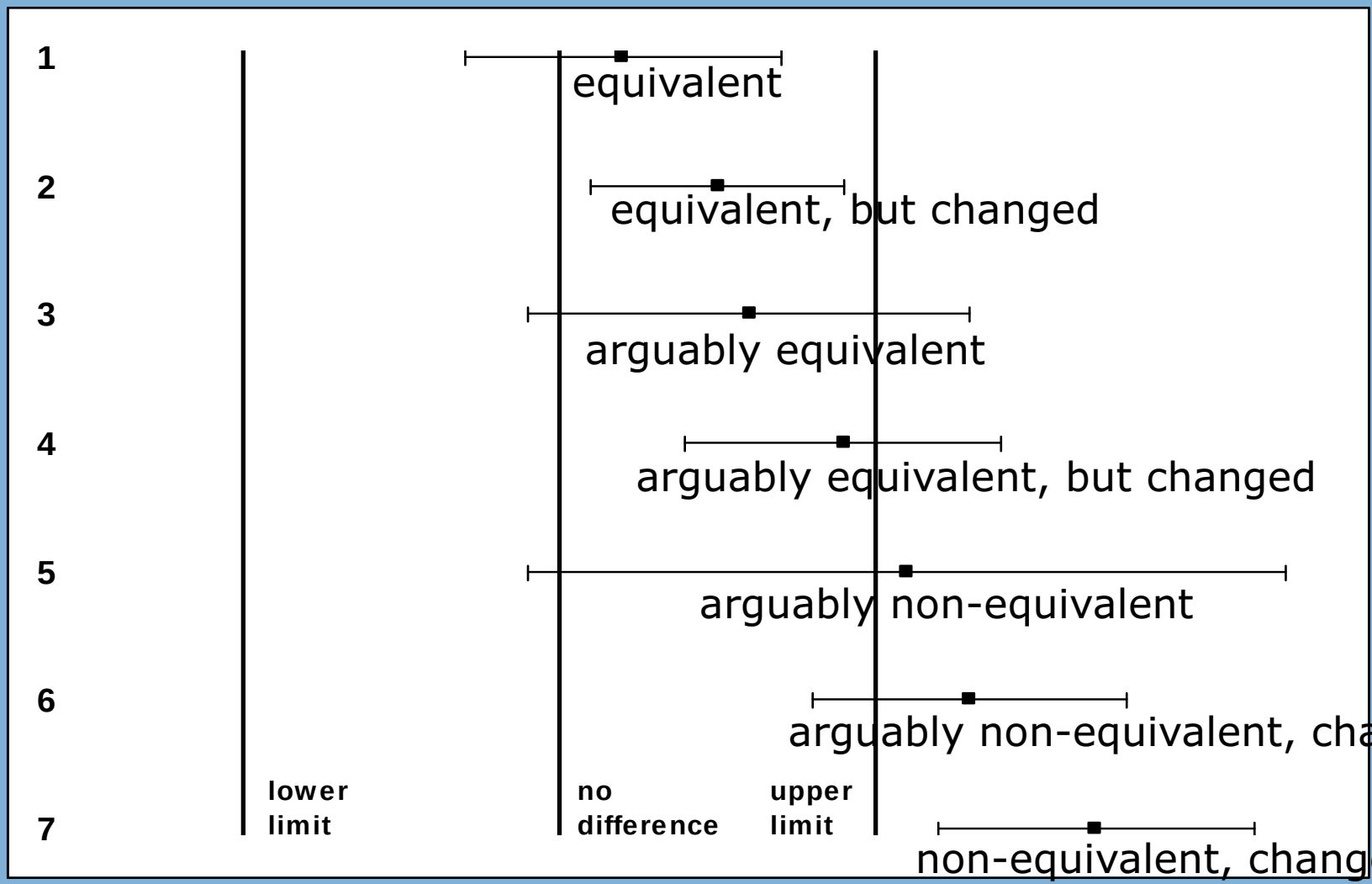

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Outcomes with fixed limits of concern

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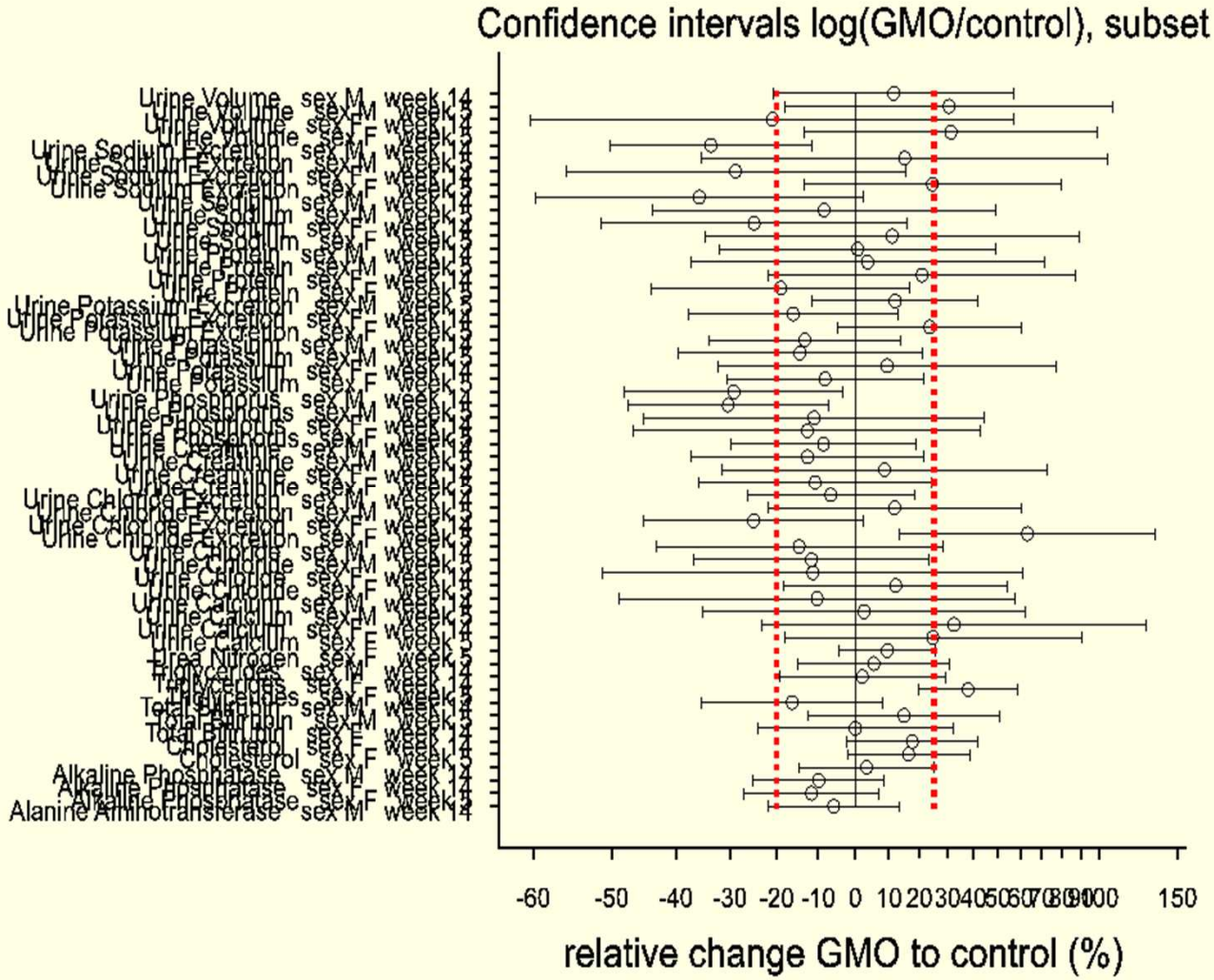
124 endpoints total

68 x Type 1 or 2 (equivalent) (not shown)

43 x Type 3 (arguably equivalent)

8 x Type 5 (arguably non-equivalent)

5 x Type 6 (arguably non-equivalent, changed)



Background variation represents crops and conditions with a history of safe use

Statistical approaches require availability of data

- concurrent data (reference varieties in the same experiment)
- historical data (literature, databases)

Background variation can be used to set empirical limits of concern

- several statistical approaches possible, work in progress

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Example use of concurrent data

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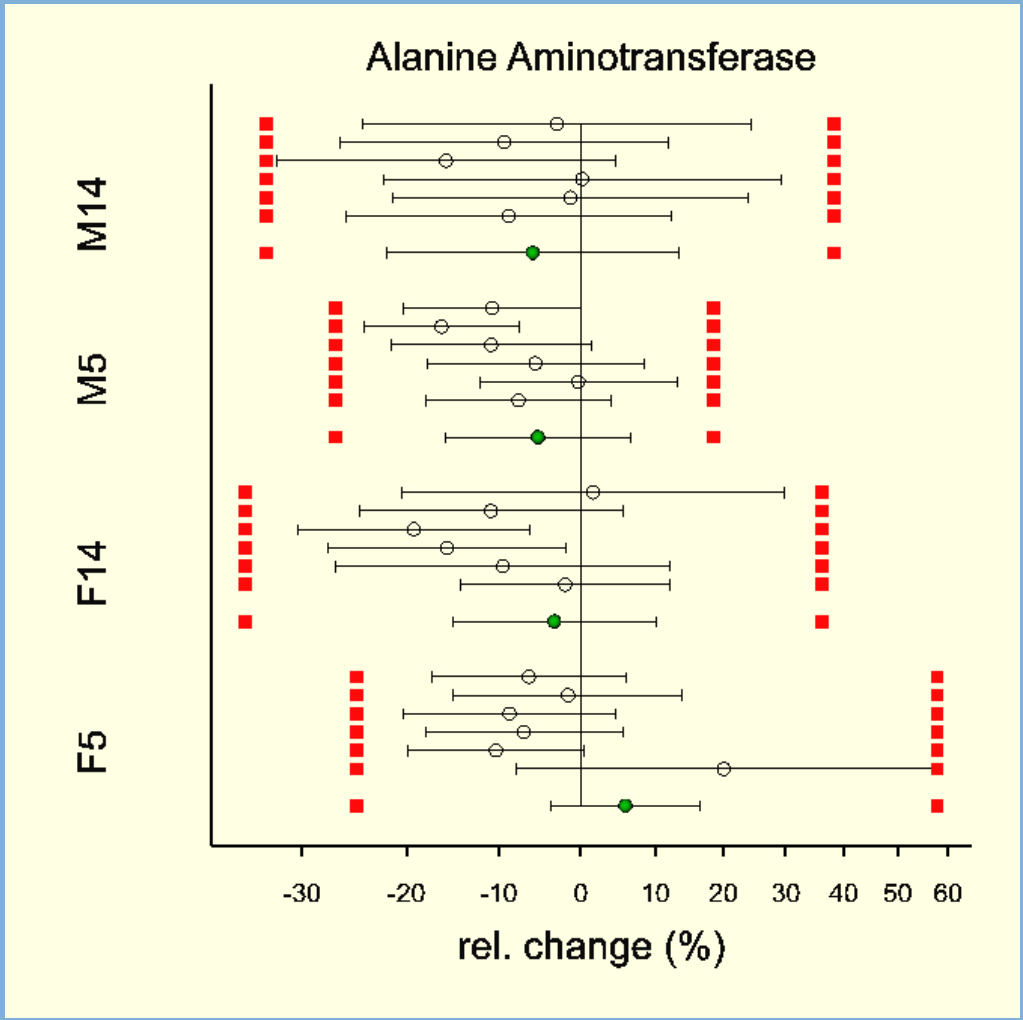
- MON863 study
- F5 = females at 5 weeks, etc.
- lower bar in each group is GMO vs. control comparison
- other bars are ref vs. control comparison
- red: limits of concern based on ref-control comparisons
- Could also be done for all groups together, or even for multiple endpoints



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Example, estimated limits of concern

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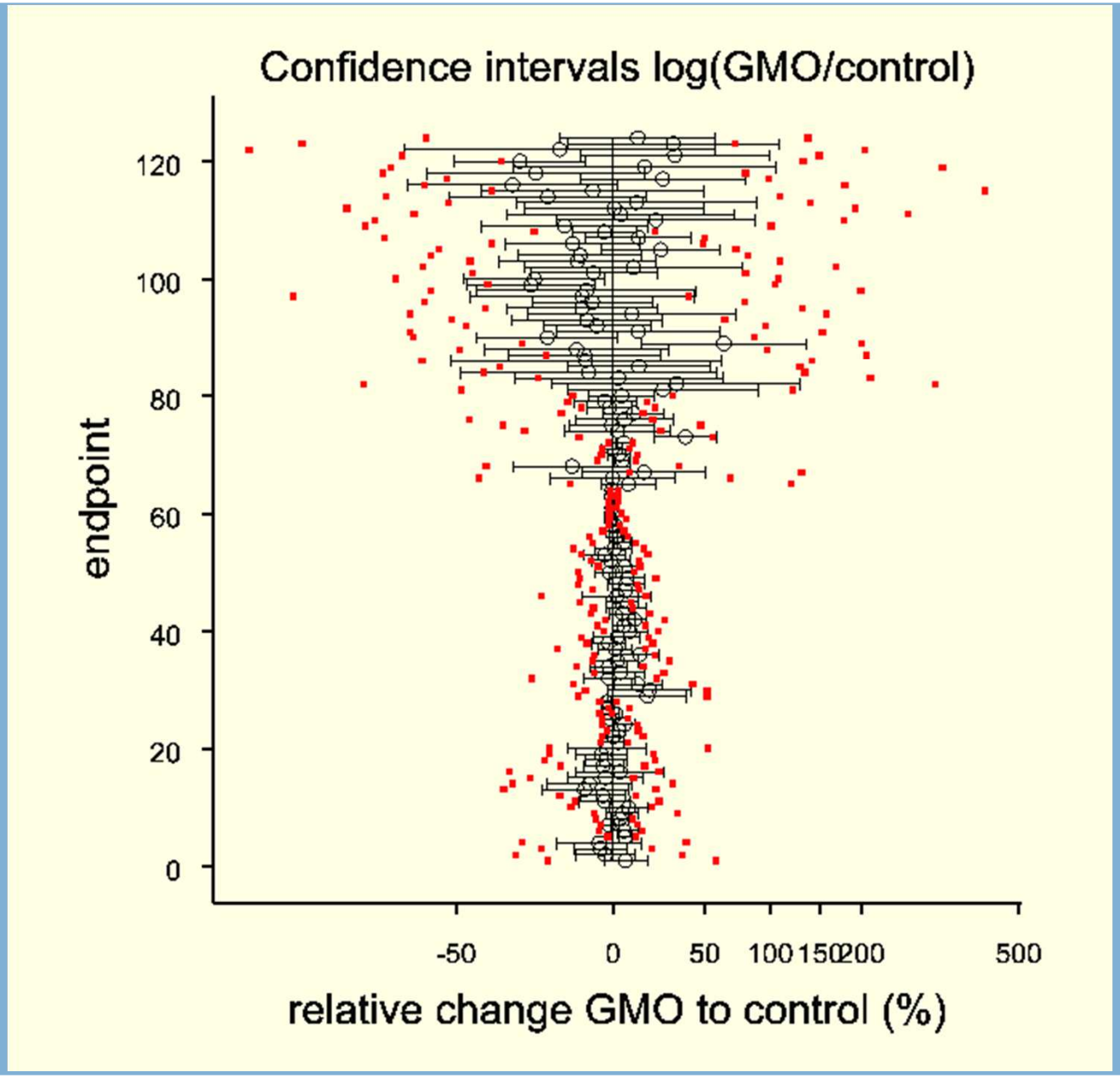

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Example: non-equivalent and arguably equivalent outcomes

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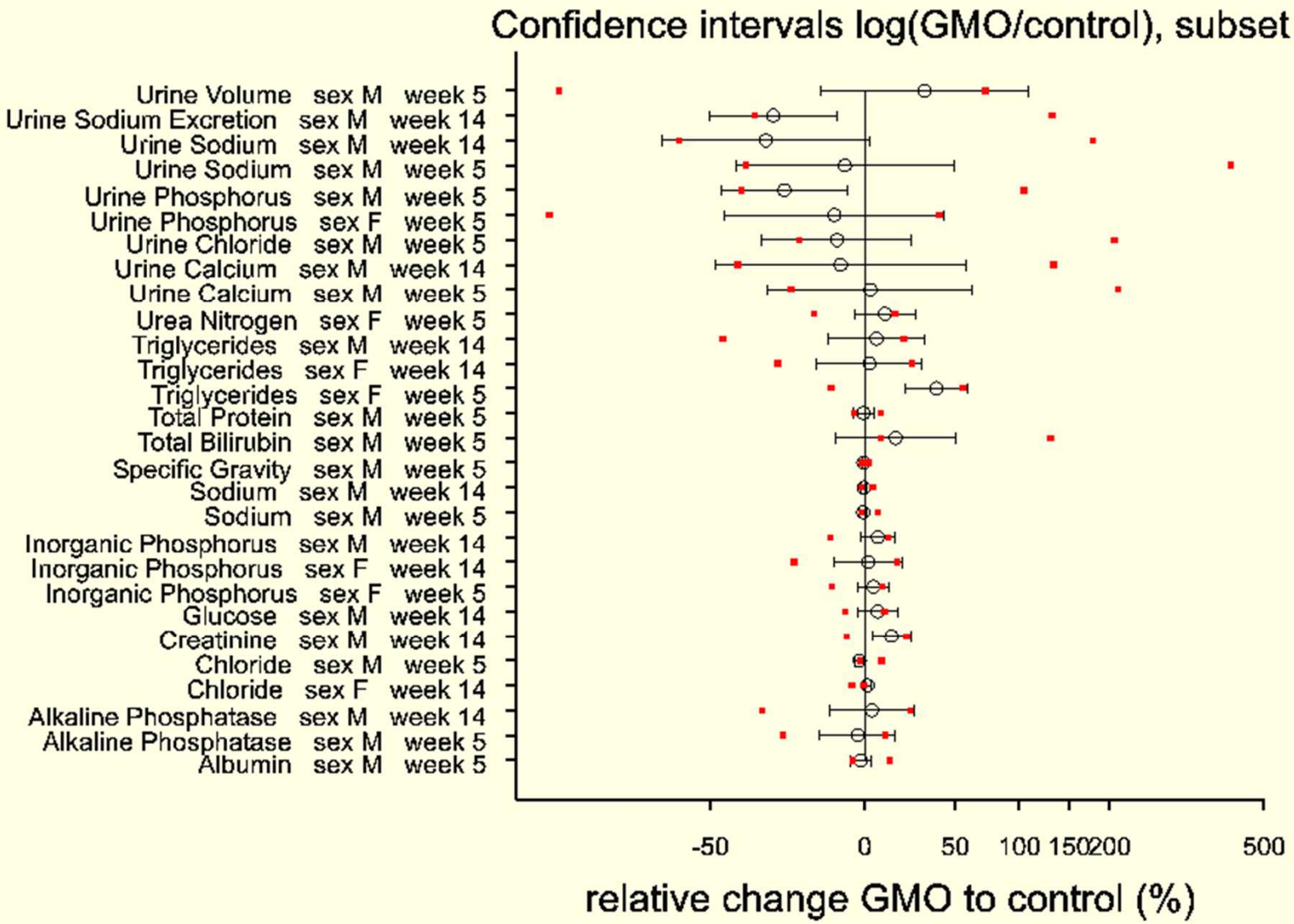

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Combining estimated and fixed limits

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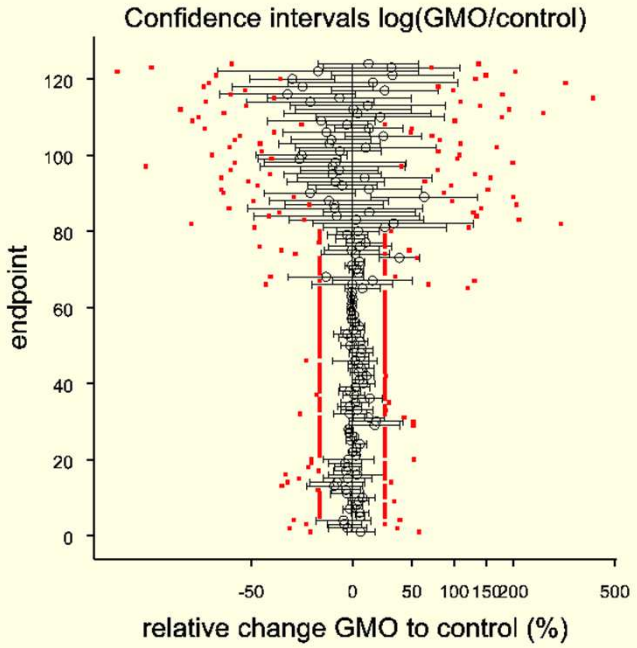

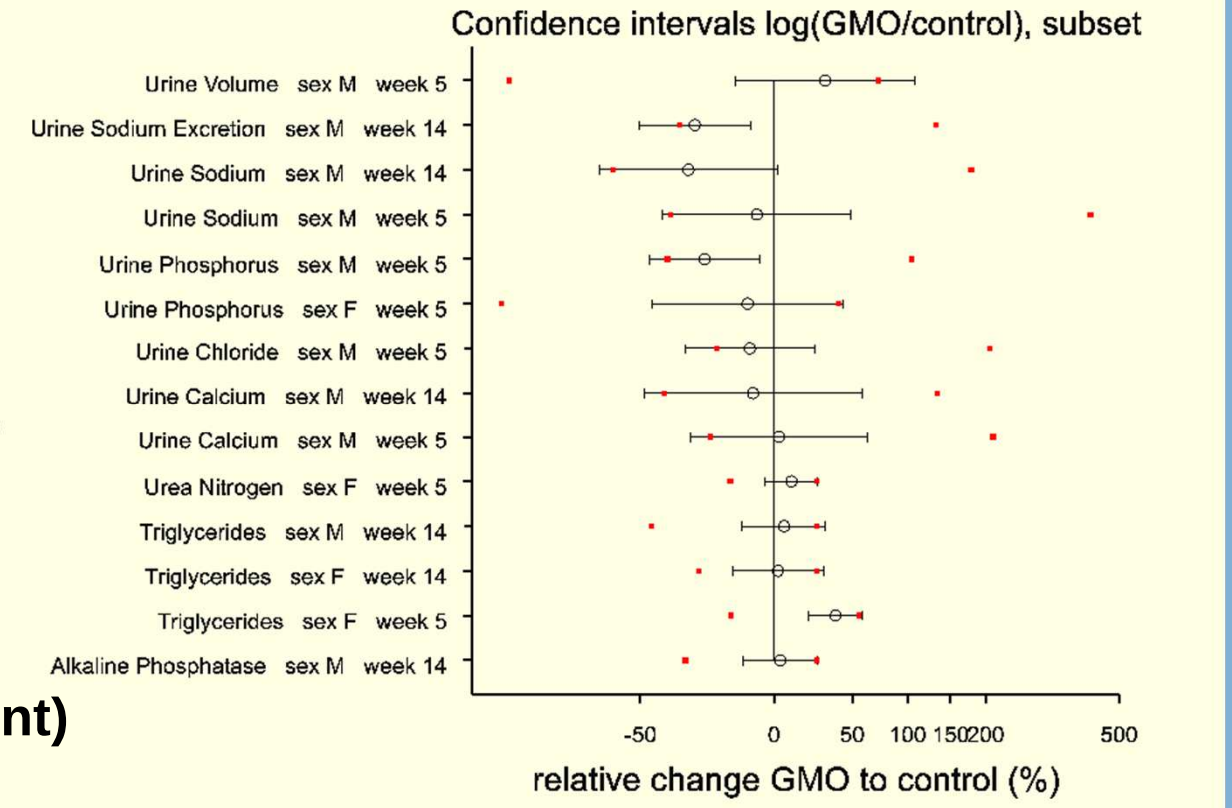

out of 124 endpoints:

11 x Type 3
(arguably equivalent)

3 x Type 4
(arguably equivalent, changed)

GUIDANCE DOCUMENTS

- **Environmental Risk Assessment (ERA) of GM Plants (2010)**
- **Guidance for risk assessment of food and feed from GM plants (2011)**
- **Guidance for Post-Market Environmental Monitoring (PMEM) (2011)**

All guidance documents available at

http://www.efsa.europa.eu/en/gmo/gmoguidance.htm