

# Animal Use in Food Safety Assessment

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**In the EU concern is mostly on food safety, less on access to food.**

**Food safety aspects are addressed in a forest of regulations, many of which involve animal testing**

# Current EU Regulations and Guidance

- 20+ EU Directives and Regulations dealing with food and feed safety, contaminants, and plant health and protection;
- Guidance documents, guidelines and working documents developed or in use:
  - 37 subject-specific Guidance Documents;
  - 10 general Guidance Documents.

# Current EU Regulations

- Council Dir. 89/107/EEC: food additives for use in foodstuffs;
- Dir. 95/2/EC: food additives other than colours and sweeteners;
- Dir. 94/35/EC: sweeteners for use in foodstuffs;
- Dir. 94/36/EC: colours for use in foodstuffs;
- Dir. 88/388/EEC: flavourings for use in foodstuffs;
- Reg. 2232/96: basic rules for the use of flavouring substances in or on foodstuffs;
- Reg. (EC) 2065/2003: smoke flavourings in or on foods;

# Current EU Regulations (2)

- Framework Reg. 1935/2006: food contact materials;
- Reg. (EC) 1831/2003: scientific assessment of feed additives;
- Council Dir. 87/153/EEC: guidelines for the assessment of additives in animal nutrition
- Dir. 201/79/EEC: safety of feed additives for the environment;
- Dir. 2001/18/EC: deliberate release into the environment of GMO's;
- Reg. (EC) 1829/2003: genetically modified food and feed;
- Reg. (EC) 258/97: on novel foods and novel food ingredients;

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# Current EU Regulations (3)

- Com. Rec. 97/618/EC: the scientific aspects and the presentation of information on novel foods;
- Reg. (EC) 1924/2006: on nutrition and health claims made on food;
- Council Dir. 91/414/EEC: on placing of plant protection products on the market;
- Com. Reg. (EC) 2074/2005: measures for certain products under Reg. (EC) 853/2004 on food of animal origin (marine biotoxins);
- Reg. (EC) 1907/2007: regulatory framework for chemicals, REACH.

# Current EU Guidance Documents

- Guidance on submissions for food additives evaluations by the SCF;
- Guidance from the AFC (now CEF) Panel on submission of a dossier on a Smoke Flavouring Primary Product for evaluation by EFSA;
- Guidance from the AFC (now CEF) Panel on submission of a dossier on a substance to be used in Food Contact Materials for evaluation by EFSA;
- Joint AFC/BIOHAZ guidance document on the submission of data for the evaluation of the safety and efficacy of substances for the removal of microbial surface contamination of foods of animal origin;

# Current EU Guidance Documents (2)

- Guidance from the AFC Panel on submission for safety evaluation of sources of nutrients or of other ingredients proposed for use in the manufacture of food;
- Guidelines for the assessment of additives in feedingstuff.  
Part I: additives other than micro-organisms and enzymes;  
Part II: enzymes and micro-organisms
- Opinion on the development of an approach for the environmental risk assessment of additives, products and substances in animal feed;
- Guidance for applicants on the presentation of applications for the request of authorisation of additives for use in animal nutrition;



# Current EU Guidance Documents (3)

- Com. Reg. 49/2008: Detailed rules for the implementation of 1831/2003;
- Guidance document of the GMO Panel for the risk assessment of genetically modified plants and derived food and feed;
- Guidance document of the GMO Panel for the risk assessment of genetically modified micro-organisms and their derived products intended for food and feed use;
- Guidance document of the GMO Panel for renewal of authorisations of existing GMO products;

# Current EU Guidance Documents (4)

- Guidance on the Safety and nutritional assessment of GM Plant derived Foods / Feeds – role of animal feeding trials;
- SCF opinion on the assessment of novel foods. Recommendations concerning the scientific aspects of information necessary to support applications for placing on the market of novel foods and novel food ingredients;
- Technical Guidance for applications for preparation and presentation of the application for authorisation of a health claim;
- Guidance Document on risk assessment for birds and mammals under Council Dir. 91/414/EEC.

# Example of an average EU Pesticide Dossier



# **Discrepancies in data requirements: a few examples:**

- Level of detail for active ingredient testing (food, feed, pesticides, enzymes, flavourings);
- Extensive testing of preparations (feed) or limited (food supplements);
- Efficacy testing required (feed) or not (food);
- Mandatory data requirements mentioned (chemicals) or not (food, feed additives);

## **Discrepancies in data requirements: a few examples (2):**

- Assessment of individual substances (additives) or groups of related substances (flavours);
- Data requirements based on exposure assessments (chemicals) or unrelated to exposure (additives);
- Botanical preparations when considered a 'medicine' or a 'food supplement' (with a claim) require different data;
- Botanical products in general are not regulated at all.



# **EU legislation and animal testing:**

- Animal welfare considerations are hardly mentioned;
- There is no guidance or reference on how to reduce the need for experimental animal use;
- There is no guidance on alternative approaches (refinement, replacement);
- This phenomenon is likely not limited to food and feed safety testing.

# Challenges and opportunities:

- With so many different requirements and approaches, it is timely to make proposals for harmonisation and for new methodologies;
- Not necessarily the most conservative approach is the better one;
- An all-inclusive overview of EU data requirements for chemicals, cosmetics/household products, food and feed additives, pharmaceuticals, veterinary medicines and pesticides would be a good starting point.

# EFSA initiatives

## **Self-Task of the Scientific Committee (2005) to:**

- Develop the comprehensive overview and share this with all Scientific Panels;
- Determine which GDs are currently used with an impact on animal welfare;
- Make an inventory of current activities in Panels that relate to animal welfare (e.g. QPS, data sharing).





*The EFSA Journal (2007) 1-76*

**Draft report of the Scientific Committee  
Working Group on the  
Welfare of Experimental Animal  
“Overview of the test requirements in the  
area of food and feed safety”  
(Question No EFSA-Q-2005-231)**



*The EFSA Journal (2009) 279, 1-13*

## **TECHNICAL REPORT OF EFSA**

**List of guidance, guidelines and working documents  
developed or in use by**

**EFSA1**

**Prepared by the Secretariat of the Scientific Committee  
(Question No EFSA-Q-2005-00299)**

**Issued on 24 April 2009**



*The EFSA Journal (2009) 1052, 1-77*

**Scientific Opinion of the Scientific Committee**  
**“Existing approaches incorporating replacement, reduction**  
**and refinement of animal**  
**testing: applicability in food and feed risk assessment”**  
**(Question No EFSA-Q-2005-0231)**  
**Adopted on 8 April 2009**

# EFSA initiatives (2)

## Self-Task of the Scientific Committee (2005) was also to:

- propose a process to harmonise the application of guidance and the use of animal welfare approaches;
- Propose an action plan to improve sharing of information with organisations active in the area of animal welfare (e.g., validation centers);
- Inform the Panels frequently of new developments of alternative approaches and **stimulate the inclusion in scientific opinions of improper use of animal testing in dossiers presented.**

# **Regulatory risk assessors' statements on unjustified experimental animal use**

## Why such statements?

- Unjustified animal tests may still provide useful data and cannot be rejected;
- Publicly exposing malpractices is negative publicity to the industry which submitted the dossier;
- Publication has an educational purpose with respect to available alternative methods.

## **EFSA initiatives (3)**

**Unfortunately, the activity was given low priority after 2008 and is at a very low level today.**

**Highest priority: safe food and feed**

# Food Safety is everybody's concern



**In order to ensure food safety, risk assessment of all foods, food additives, food contaminants and food ingredients is considered necessary.**



# Too many substances, too many tests:

- In certain areas, indeed practical and pragmatic approaches are considered and applied to cope with the work;
- In other areas, however, there is a tendency to require more testing;
- New areas, such as nanotechnology applications tend to result in additional animal testing.

# Risk assessment of additives, contact materials, drug residues, pesticides and contaminants

- Animal testing requirements vary from (minimum):
  - 3 *in vitro* mutagenicity tests (for food contact materials at migration levels of  $< 0.05 \mu\text{m/kg food}$ );  
to:
- Acute, subchronic, chronic, carcinogenicity, topical studies (skin, eye) and special studies (sensitisation, allergenicity, reproductive toxicity, developmental toxicity and neurotoxicity studies).

# Numbers of food and feed additives, food contact materials, pesticides and drug residues that need evaluation

- Food additives (total): **33**; supplements: **>1000**; flavours: **+/- 3000**; preservatives etc.;
- Feed additives/ingredients;
- Food contact materials and food processing aids: **+/- 100/year**;
- (veterinary) drug additives and other feed additives: **+/- 50/year**;
- Pesticides: (existing): **+/- 400**; (new): **2/year**
- GMOs: **10-15/year**.

# **Too many substances, too many tests:**

**Practical and pragmatic approaches are considered and applied to cope with the work.**

# **Examples of pragmatic approaches providing adequate safety, based on existing data:**

- Margin of exposure concept (MoE):
- Threshold of toxicological concern (TTC) concept;
- Qualified presumption of safety (QPS) concept;
- Proven history of safe use (botanical preparations)

# Examples of pragmatic approaches (1): Margin of Exposure (MoE)

- Predominantly for carcinogens;
- Benchmark dose level is driving the approach;
- based on observed effect data, not on extrapolation;
- The 'margin' to be considered safe is a risk management decision.

## **Examples of pragmatic approaches (2): Threshold of Toxicological Concern (TTC)**

**“Safety assessment in the absence of  
substance-specific hazard data,  
based on very low level of exposure  
to that substance”**

# What is the TTC Concept Based On?

- “The threshold of toxicological concern (TTC) is a principle, which refers to the establishment of a human exposure threshold value for all chemicals, below which there would be no appreciable risk to human health.”
- The TTC concept proposes that a minimum value can be identified for many chemicals, including those of unknown toxicity, based on consideration of their chemical structures.



# Threshold of toxicological concern (TTC)

- Reliable exposure estimation;
- Adequate low exposure toxicity data available;
- Conservative estimate of expected no-effect level.

## **But:**

- Lack of reliable exposure data;
- Chemical classes in database are limited;
- Chemicals in database (730) are limited.

# **Examples of pragmatic approaches (3): Qualified Presumption of Safety (QPS)**

- Currently applied for micro-organisms intentionally added to food and feed;
- Based on adequate safety data of similar strains of micro-organisms;
- Database of effects of 'known' micro-organisms should be updated annually and, as appropriate, QPS status should be reconsidered;
- Botanicals?

# Examples of pragmatic approaches (4): Proven history of safe use

- Predominantly for medicinal products and defined botanicals;
- ‘Proven history’ is not well defined: EMEA (medicines) is more liberal than EFSA (food);
- No guidance available yet on level of detail and quality required for historical proof;
- For health claims human data are required (not animal data).

**But not only pragmatic safety  
assessment approaches, resulting  
in animal use reduction:**

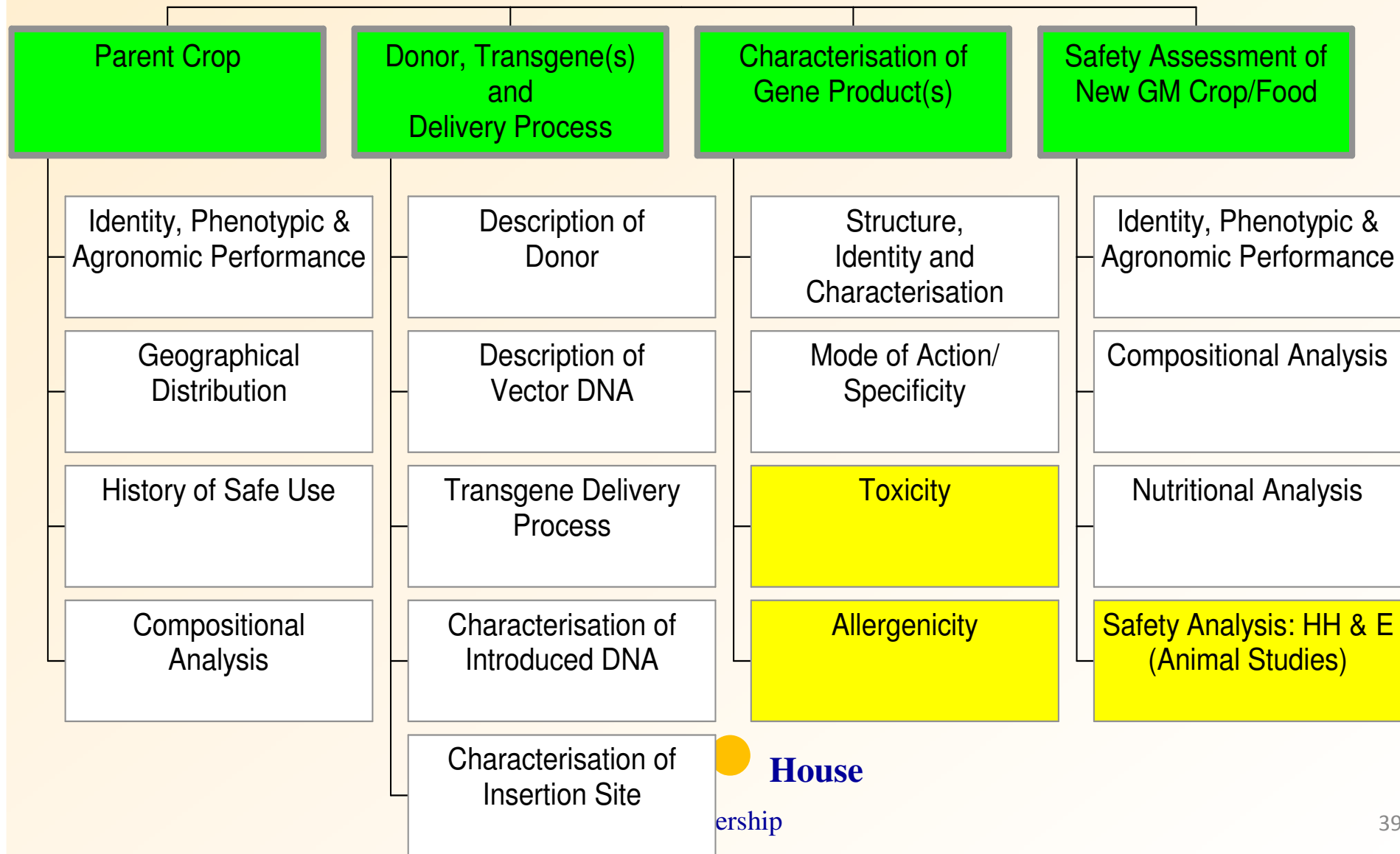
**In another area we see the  
contrary....**

# **Regulatory risk assessment of GMOs in the EU: where science, lobbying and politics meet**

# International Risk Assessment Strategies for GMO's

- OECD Group of National Experts on Safety in Biotechnology, 1993, 1994, 1996
- OECD Task Force on the Safety of Novel Foods and Feed, 1998-present
- FAO/WHO Expert Consultations, 1991, 1996, 2000, 2001, 2003
- Codex Task Force on Foods Derived from Biotechnology, 1999-present
- EU Scientific Committees, 1996-2003; Joint Working Group on Novel Foods and GMOs
- ENTRANSFOOD, the EU Thematic Network on the Safety Assessment of Genetically Modified Food Crops, 2000-2003

# A fully integrated and iterative risk assessment approach of a new GM variety



# Risk Assessment of GMO's

- EU regulatory assessors have adopted a case-by-case approach, based on 'comparative assessment';
- Essential elements of the risk assessment are:
  - Compositional analysis;
  - Molecular characterisation (DNA sequence, genetic stability);
  - Substantial equivalence;
  - Toxicity, allergenicity, environmental assessment;

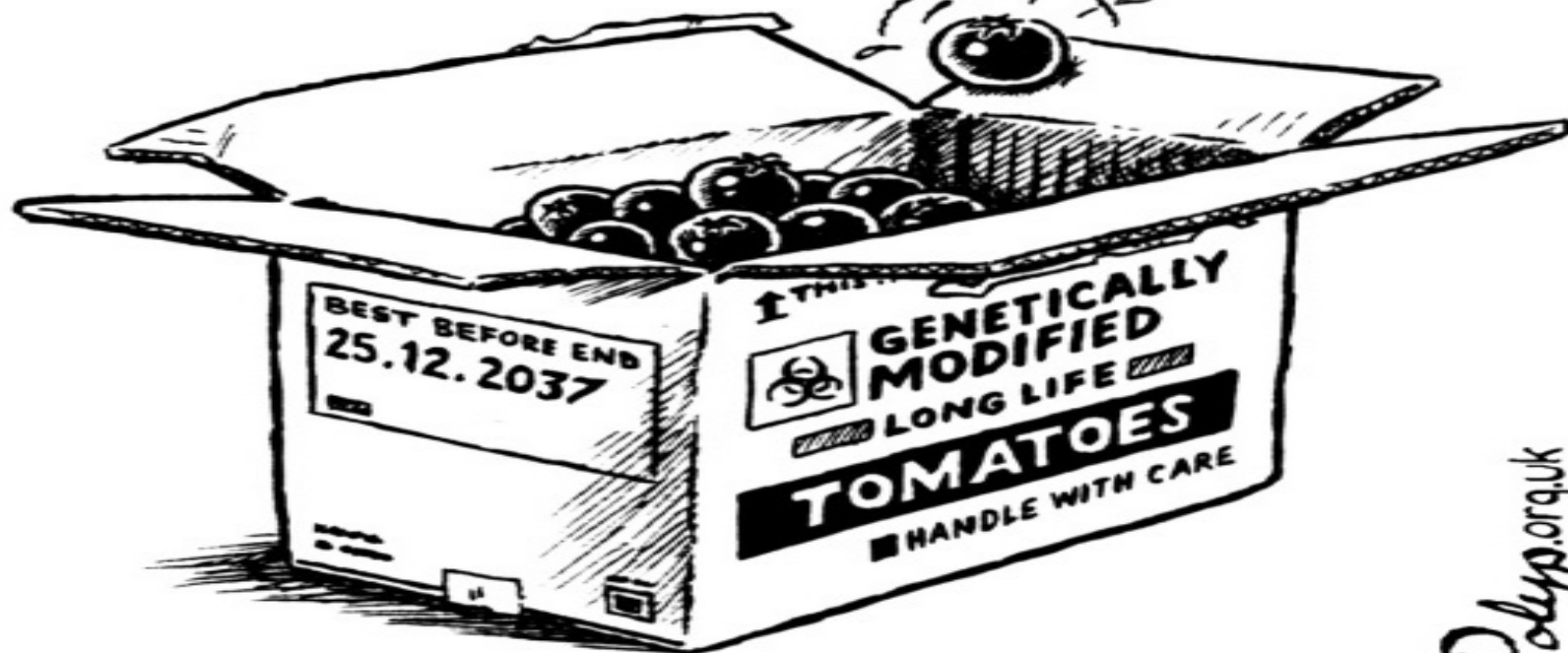


# Risk Assessment of GMO's

## (2)

- Risk managers increasingly require the 90-day toxicity study being under political pressure from NGO's;
- A 90-day study will only be sensible if the GMO can be fed at high concentrations;
- Testing the genetic insert (trait) is not appropriate;
- 90-day study requires at least 80 animals;
- Requiring such a study means buying time and postpone the decision-making.

OK EVERYBODY~  
LISTEN CAREFULLY!  
HERE'S THE PLAN... WE ALL  
PRETEND TO BE HARMLESS  
FOR A FEW YEARS, AND THEN  
WHEN THEY RELEASE US  
INTO THE ENVIRONMENT~  
**WE GO WILD!**  
ANY QUESTIONS...?



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'HANDLE WITH CARE'

# Environmental Risk Assessment of GMO's (3)

- EU regulatory risk management authorities are not fully clear on what constitutes an environmental assessment;
- Essential elements of the environmental risk assessment currently include:
  - Toxicity to aquatic, terrestrial and sediment species including non-target species (e.g., sediment dwelling organisms, terrestrial insects);
  - Genetic stability of the trait/insert;
  - Long-term environmental effects;
  - Environmental impact assessment.

# In summary

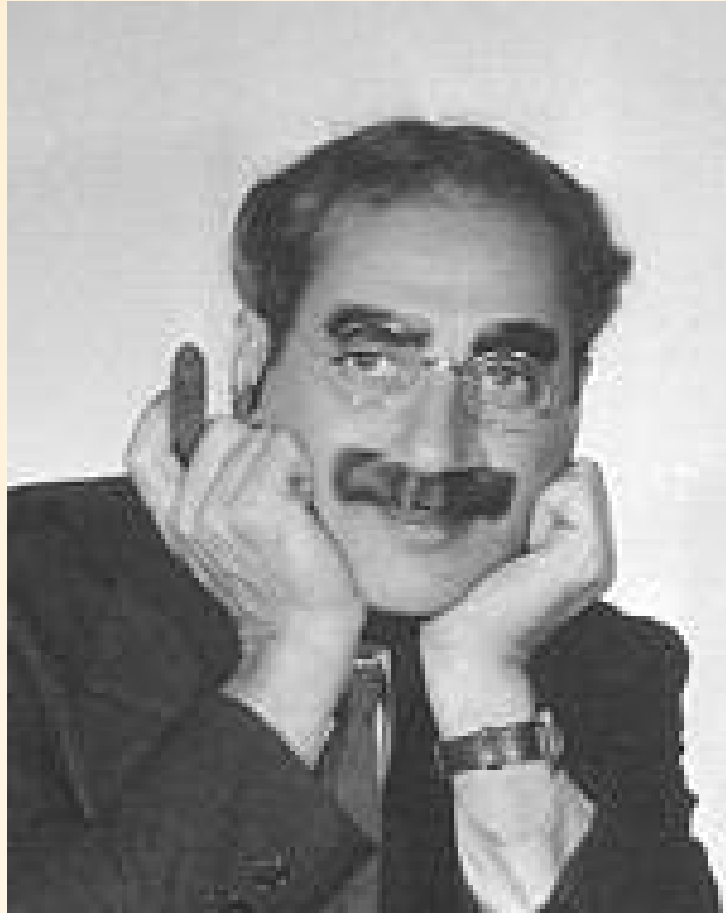
- Requirements for animal testing of food and feed additives, novel foods, food supplements and food contaminants should be harmonised and reconsidered;
- Testing data requirements should be set by the risk assessor, not the risk manager (blurred by politics);
- Animal welfare assessments should be routinely considered as part of regulatory risk assessment;
- Improper use of animal testing should be criticised in scientific opinions as an education tool.

## In summary (2):

- Progress in the science of toxicology and risk assessment is very promising and preceding fast at a global scale;
- However, the current science management climate, at least in Europe, is at best tolerant, rather than strongly supportive:
  - budgets of national centers for alternatives are squeezed;
  - Visibility is often intentionally minimised;
  - Validation approaches are becoming increasingly complicated, bureaucratic and expensive;

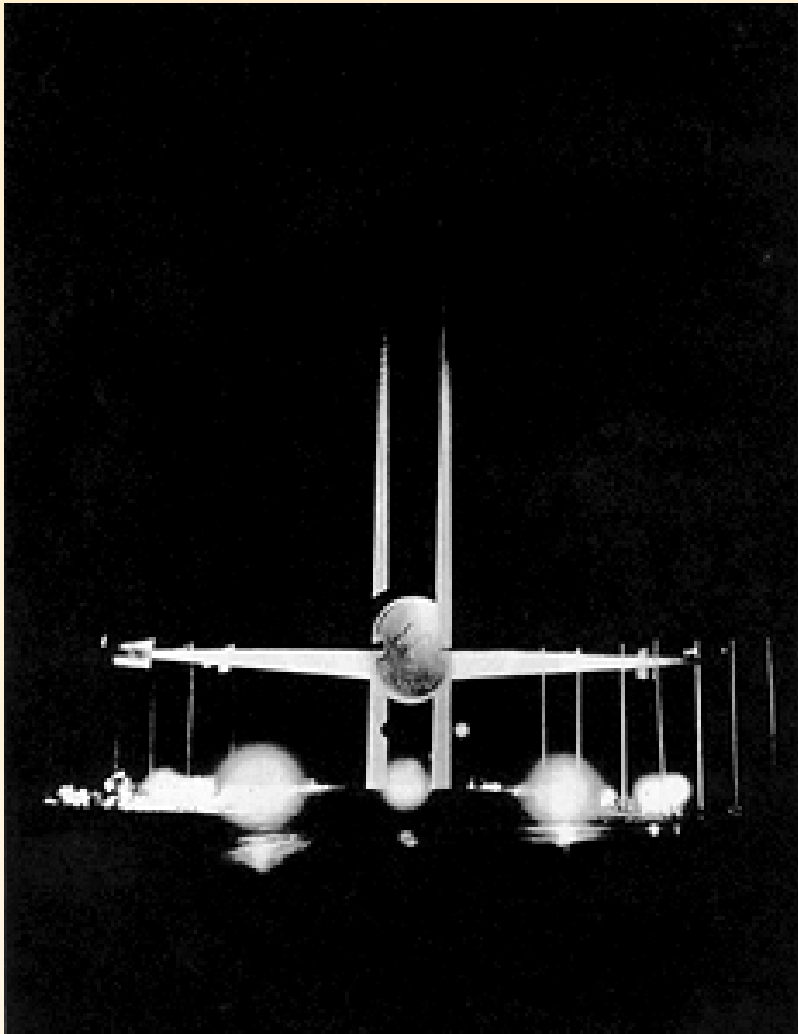
## In summary (3):

**Progress and achievements are not made by institutions or centers but by individuals with dedication, stamina and the guts to stand by their ideals.**



***"These are my opinions. And if you don't like them, I have others."***

Groucho Marx (1890-1977)



# “Aim higher and wider”

Motto of the 11th World  
Scouts Jamboree,  
Marathon, Greece, 1963