Annex 10

Issues Raised by Member States on Animal Feeding Trials with Whole GM Foods/Feed

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Special meeting of the EFSA Advisory Forum on GMO risk assessment in Europe
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EFSA Report Animal Feeding Trials

“Safety and Nutritional Assessment of GM Plants and derived food and feed:

The role of animal feeding trials”

EFSA GMO Panel, November 2007

Issues Addressed

- Experience with the safety and nutritional assessment of (GM) food and feed
- Methodologies for toxicological testing of chemicals, pesticides, food additives, contaminants
- Methodologies for safety and nutritional testing of whole foods/feed
- Potentialities and limitations of animal feeding trials with whole foods/feed
  - Capacity
  - Sensitivity
  - Predictivity
  - Margins of exposure
- Standards for diet formulation
- Data collection, analysis and interpretation
- Strategies for the safety and nutritional assessment of gm plant derived food and feed

Long-Term Adverse Effects of GM Food/Feed

- Fundamental pillar of the risk assessment
- Very little is known about potential long term effects of ***any foods*** on human health
- Many confounding factors:
  - the wide genetic variability in the human population,
  - variations in dietary habits,
  - changes in food compositions over time.

Difficulties with Animal Feeding Trials with 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

Basic Elements of the Safety Assessment

- Molecular Characterization of the Modification Process and rec.DNA Organism
- Agronomical and Phenotypical Characterization
- Food/Feed Safety Assessment
- Environmental Risk Assessment

- Comprehensive Risk Assessment
  - *All available evidence should be considered*
  - *Iterative process*

Toxicity and Allergenicity Testing of Single Substances

- *In vivo* tests in laboratory animals (OECD guidelines (EFSA GM Plant Guidance Document, 2006)
  - *Single dose toxicity testing*
  - *Repeated-dose toxicity testing*
  - *Reproductive and developmental toxicity testing*
  - *Immunotoxicity testing*

- Specific tests may be carried out:
  - *In silico search for sequence homology*
  - *Digestibility tests*
  - *Genotoxicity tests*
  - *Immunochemical cross-reactivity tests*

Purpose of 90-day rodent feeding trials for the safety assessment of GM food and feed

efsa
European Food Safety Authority

When indicated by molecular, compositional, phenotypic, agronomic or other analysis, there may be cause to check in a *sentinel* study whether the GM plant or derived food or feed is as safe and nutritious as the traditional near isogenic non-GM parental line.

Capacity of a Whole Food Animal Feeding Trial to Detect Adverse Effects

- Relatively large capacity to detect compounds which exert adverse effects

- Toxic substances with a LOEL of 100 mg/kg bw/day (median value from databases) would need to be present in a GM plant at 0.4%= 4000 ppm in a rat feeding study

Capacity of a Whole Food Animal Feeding Trial to Detect Adverse Effects

It is unlikely that substances present in small amounts and/or with a low toxic potential will result in any observable unintended effects in the 90-day rat feeding study

90-Days Study in Rodents Predictive for Long Term Effects?

- US NTP study of 40 industrial and agro chemicals (British Toxicology Society, 1994):
  - For majority of compounds studied toxicological findings in the 2 year rodent test were also seen in 3 month subchronic tests
- Monographs of JECFA and other data indicated that the lowest NOEL for a substance in many cases came from a subchronic study" (Munro et al.,1996)
- Similar observations in dog studies (Box and Spielman, 2005)

Animal Testing of Whole GM Food/Feed

- Subchronic, 90-day toxicity study is not designed to detect effects on r*eproduction or development*, other than on adult reproductive organ weights and histopathology.

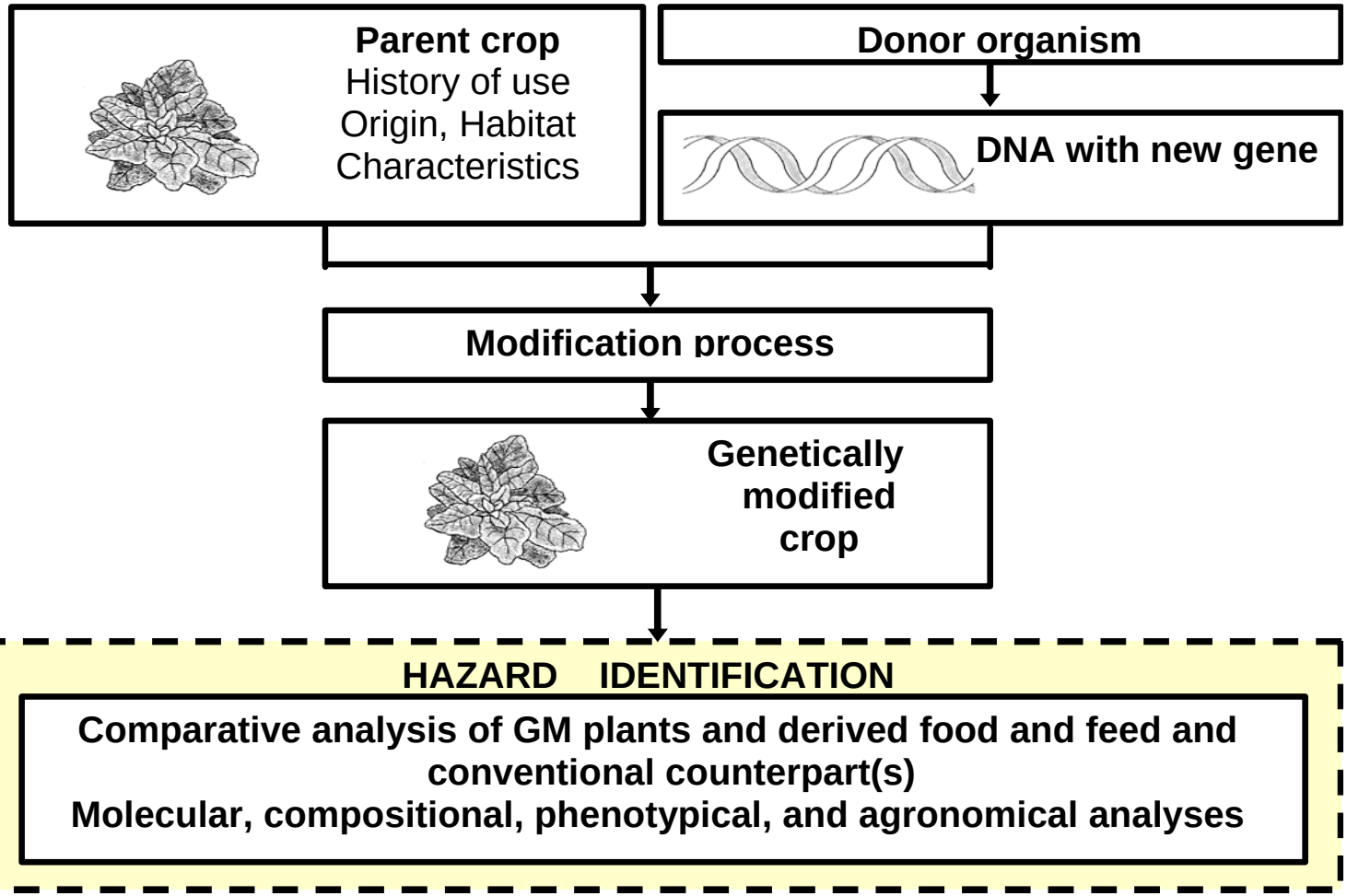
- In some cases, testing of the whole food and feed beyond a 90-day toxicity study may be needed.

Margins of Exposure (Safety Margins)

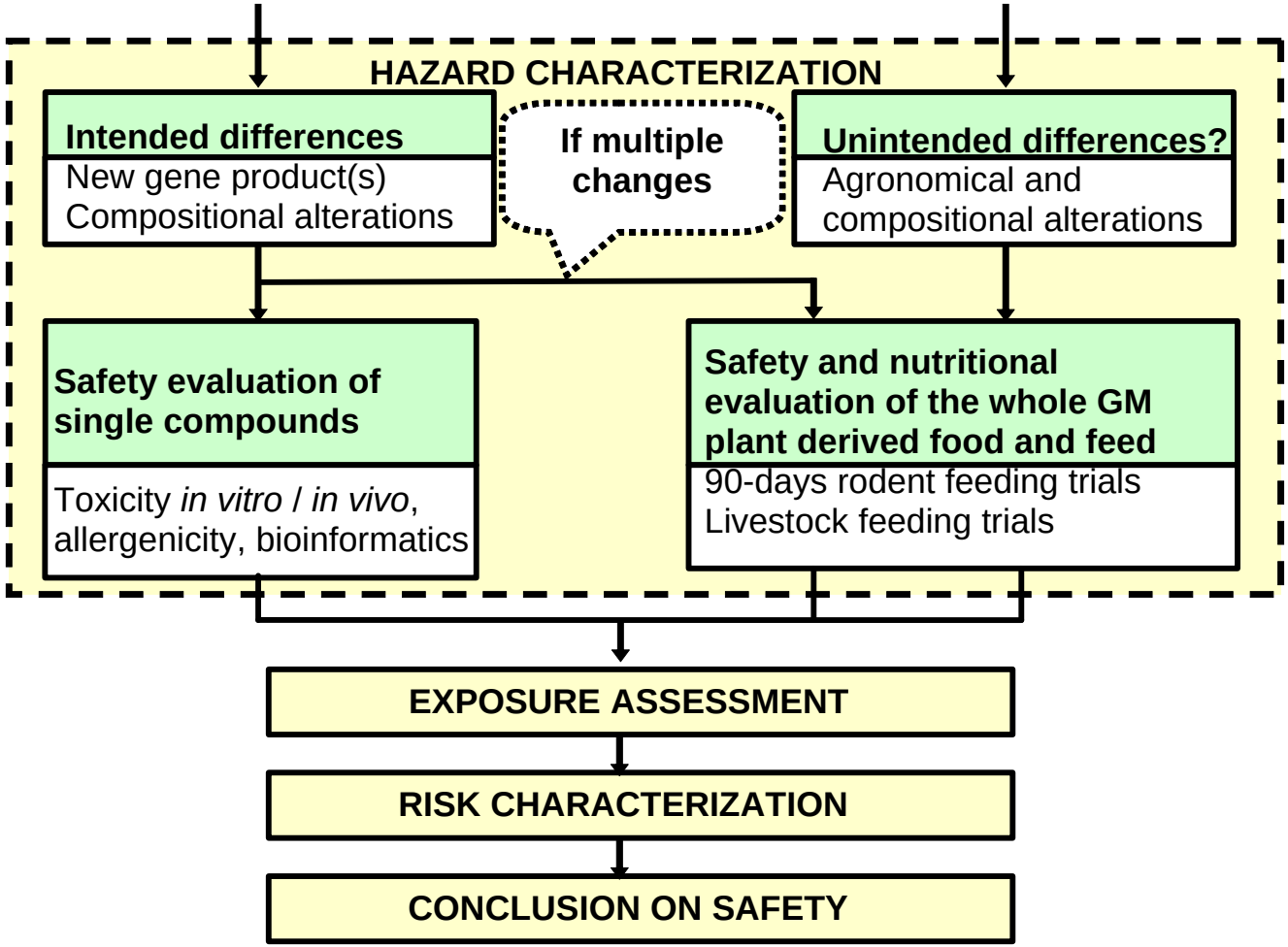
Maize

- 90 day rat subchronic studies with GM maize in the diet at 33 % (w/w) or more, may represent a NOAEL
- Averaged rat typically consumes 25 g maize/kg bw/day
- EU estimated intake for humans is 17g/person /day, corresponding to 0.24g maize/kg bodyweight /day
- This provides at least a margin of safety (MOS) of a 100 fold

Safety and Nutritional Assessment of GM Plant Derived Food and Feed -1



Safety and Nutritional Assessment of GM Plant Derived Food and Feed - 2



Conclusions/Recommendations Animal Feeding Trials Whole GM Foods/Feed

- A subchronic, 90-day rodent feeding study on whole GM plant derived foods/feed has sufficient specificity, sensitivity and predictivity to act as a *sentinel* study

- Testing of whole GM foods/feed in animal feeding studies is recommended in case of:
  - Differences identified by molecular, compositional, phenotypic, agronomic and other analyses
  - Any indications or remaining uncertainties for the potential occurrence of unintended effects

- Testing is hypothesis driven (no routine)

Conclusions/Recommendations Animal Feeding Trials Whole GM Foods/Feed

- In cases of structural alerts, indications from the subchronic study or other information on the whole GM plant derived food and feed suggesting the potential for reproductive, developmental or chronic toxicity, the performance of such testing should be considered.

- If foods are compositionally **equivalent**, animal feeding trials add little if anything to the safety assessment

- Animal feeding trial not to be done with first generation GM foods/feed

- Maybe with nutritionally enhanced GM foods?

Conclusions/Recommendations Animal Feeding Trials Whole GM Foods/Feed

It is recommended that OECD should develop supplementary guidelines for safety and nutritional testing of whole food and feeds:

- type of control and test diets,
- spiking regimes,
- type of test groups and number of animals per test group,
- dosage regimes,
- toxicological and nutritional endpoints to be measured.