Food Safety Assessment of GM Crops

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Debate on Genetically Modified Food Crops

- Species barriers are crossed, unknown effects
- Impact on the environment, biodiversity
- Long term effects on human health
- Adequate test systems
- Traceability, labelling and GM-free foods
- Contribution to a sustainable agriculture
- Stakeholders and interests

First Generation of Modified Food Plants with Agronomical Traits

- Improved disease resistance (viruses, fungi)
- Improved pest resistance (lepidoptera, beetles)
- Tolerance for herbicide (glyphosate, glufosinate)
- Slow ripening

Future Transgenic Crops

- Golden rice provitamin A
- Iron-fortified rice transgenic for ferritin
- Tomato β-carotene / lycopene enriched
- Lupin higher methionine levels
- Maize detoxification of mycotoxins
- Insect resistant maize transgenic for avidin
- Cassava detoxification of cyanogens
- Fructan-beet non caloric sweetener
- Alfalfa transgenic phytase, P-availability
- Canola vitamin E enriched
- Coffee-beans caffeine-free

Future Transgenic Crops

<table>
<thead>
<tr>
<th>Crop</th>
<th>trait</th>
<th>transgene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rice</td>
<td>+ provit. A</td>
<td>phytoene synthase (daffodil)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>phytoene desaturase (Erwinia)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>lycopene cyclase (daffodil)</td>
</tr>
<tr>
<td></td>
<td>iron↑</td>
<td>ferritin (Phaseolus)</td>
</tr>
<tr>
<td></td>
<td>cyanogen↓</td>
<td>metallothionein (rice)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>phytase (mutant, Aspergillus)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>hydroxynitril lyase</td>
</tr>
</tbody>
</table>

Global Status of Biotech Crops in 2004

11 countries have adopted biotech crops
- USA 61.2 million
- Brazil 3.6 million
- Canada 2.2 million
- China 1.1 million
- Argentina 0.9 million
- Spain 0.6 million
- Philippines 0.5 million
- France 0.4 million
- Germany 0.3 million
- Taiwan 0.3 million
- Colombia 0.1 million
- Others 0.3 million

20% of the worlds population depends on GM crops
### Future Transgenic Crops

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<thead>
<tr>
<th>Crop</th>
<th>Trait</th>
<th>Transgene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tomato</td>
<td>provit.A↑&amp; lycopene↑</td>
<td>lycopene cyclase (Arabidopsis)</td>
</tr>
<tr>
<td>Tomato</td>
<td>provit.A↑</td>
<td>phytoene desaturase (Erwinia)</td>
</tr>
<tr>
<td>Tomato</td>
<td>flavonoids↑</td>
<td>chalcone isomerase (Petunia)</td>
</tr>
<tr>
<td>Lupin</td>
<td>methionine↑</td>
<td>seed albumin (sunflower)</td>
</tr>
<tr>
<td>Maize</td>
<td>fumonisin↓</td>
<td>de-esterase+de-aminase (µbial)</td>
</tr>
<tr>
<td>Maize</td>
<td>insect res.</td>
<td>avidin (chicken)</td>
</tr>
</tbody>
</table>

### Future Transgenic Crops

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<th>Transgene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beet</td>
<td>+fructans</td>
<td>1-sucrose:sucrose fructosyl transferase</td>
</tr>
<tr>
<td>Alfalfa</td>
<td>+phytase</td>
<td>phytase (Aspergillus)</td>
</tr>
<tr>
<td>Canola</td>
<td>vit.E↑</td>
<td>γ-tocopherol methyl transferase (Arabidopsis)</td>
</tr>
<tr>
<td>Coffee</td>
<td>caffein↓</td>
<td>antisense xanthosine-N-7-methyl transferase (coffee)</td>
</tr>
</tbody>
</table>

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**Nutritional and Safety Assessments of Foods and Feeds Nutritionally Improved through Biotechnology**

Prepared by a Task Force of the ILSI International Food Biotechnology Committee

IFT’s Comprehensive Reviews in Food Science and Food Safety, Volume 3, 2004

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**New Healthy Diets and Major Uncertainties**

- Which compounds/fruits/vegetables
- Bioavailability of compounds
- Interaction between components
- Matrix effects on availability of nutrients
- Current (non)-nutrient levels and variability
- Losses of compounds through food processing
- Scientific evidence of risk/benefits ???

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**International Food Safety Strategies for Foods Derived from Modern Biotechnology**

- International Food Biotechnology Council (1990)
- OECD Task Force on the Safety of Novel Foods and Feed, 1998-present
- CODEX Task Force on Foods Derived from Biotechnology, 1999-2004
- EU, 1996-present
- ILSI, Task Forces, 1996 - present

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**Safety aspects of genetically modified foods of plant origin**

Report of a Joint FAO/WHO Expert Consultation on Foods Derived from Biotechnology

World Health Organization, Headquarters
Geneva, Switzerland
29 May - 2 June 2000
Safety Evaluation of Foods

- Foods are complex mixtures of nutrients, vitamins, minerals and other health-beneficial substances.
- Foods contain also anti-nutrients, and natural toxins.
- Safety evaluation of whole foods as performed with single chemicals or food additives is not possible.

Concept of Substantial Equivalence

- OECD, 1993

- Traditional foods are considered to be safe, through their history of use (empirical evidence)
- Traditional foods serve as comparator for GM foods
- Concept of Substantial Equivalence (SE) or Comparative Safety Assessment (CSA)

Substantial Equivalence or Comparative Safety Assessment

- Is not a safety assessment in itself
- It identifies but does not characterise the hazard
- Is the starting point of the assessment, rather than the endpoint
- Structures the safety assessment of a GM food relative to its conventional counterpart

Substantial Equivalence or Comparative Safety Assessment

A Systematic Comparison of:

- Agronomic properties
- Morphological characteristics
- Compositional parameters of the GM organism and its closest traditional counterpart

Risk-Analysis Strategies for Transgenic Foods

Phase 1

- Tracing of differences between the GM food and the conventional product (Concept of Substantial Equivalence)
- Introduced genes
- (New) proteins
- (New) metabolites and toxins
- Toxicity / nutritional investigations

Phase 2

- Gene transfer
- Degradation
- Toxicity

Allergenicity

Whole foods
Risk-Analysis Strategies for Transgenic Foods II

**Phase 3**

- **Intake studies**
  - Role of the product in the diet
  - Intake of the product by the consumer

**Phase 4**

- Risk assessment of transgenic foods

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**Long-Term Effects**

- Very little known about long-term effects of any foods
- Wide genetic variability, dietary changes over time
- Pre-market safety assessment should provide already assurance that the GM food is as safe as its conventional counterpart
- Epidemiological studies are unlikely to identify adverse effects
- Randomised Controlled Trials could be used to investigate long-term effects, but are difficult to conduct

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**Long-Term Effects**

- A 90-days study is the minimum requirement to test the safety of repeated consumption of a food
- Additional studies may be considered on a case-by-case basis (proliferative changes observed in a 90-days study)
- Highest dose levels should not cause nutritional imbalance and lowest levels should be comparable to anticipated human intake

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**OECD Task Force on the Safety of Novel Foods and Feed**

**OECD Consensus documents:**

- Crop components to be compared: key food and feed nutrients, antinutrients, and toxicants
- **Completed:** soybean and low-erucic acid rapeseed, potato, sugar beet, maize, rice
- **In progress:** wheat, sunflower, and cotton

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**ILSI Crop Composition Database: Establishing Natural Variability in Crop Composition**

Contact
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Washington, DC 20005
Phone: (202) 659-0074
Fax: (202) 659-3859
E-mail: lkurtyka@ilsi.org
www.cropcomposition.org

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**Importance of High Quality Crop Composition Data**

- Composition studies are a key factor in the substantial equivalence evaluation process
- Assesses important nutritional and anti-nutritional endpoints
- Provides for an assessment of "unexpected" or "pleiotropic" effects
- Composition analyses form the baseline for studies of nutritionally enhanced crops

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**Scope of Maize, Soybean and Cottonseed Data**

- **Years:** 1995, 1997 - 2002
- **Geographic Regions**
  - U.S. and Canada (IL, IN, IA, NE, CO, OH, MO, KS, NC, WI, PA, AR, MN, other)
  - South America (Brazil, Argentina)
  - Europe (France, Germany, Hungary, Italy, Spain)
- **Number of Analytes:** 114
- **Number of Datasets:** 1,820
- **Number of Datapoints:** 70,658

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**Most Common Food Allergens**

- More than 170 foods cause food allergies
- Most common foods “The Big Eight”:
  - cow’s milk
  - peanuts
  - eggs
  - soybeans
  - fish
  - tree nuts
  - crustaceans
  - wheat

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**Evaluation of Allergenicity of Genetically Modified Foods**

Report of a Joint FAO/WHO Expert Consultation on Allergenicity of Foods Derived from Biotechnology

22 - 25 January 2001, Rome, Italy

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**FAO/WHO 2001 Decision Tree**

- Source of Gene Allergenic
  - Sequence Homology
    - Yes
      - Specific Serum Screen
        - No
          - Likely Allergenic
            - High Probability of Allergenicity
        - Yes
          - Peptide Resistance & Animal Models
            - No
              - Likely Allergenic
                - High Probability of Allergenicity
            - Yes
              - No
                - Likely Allergenic
                  - High Probability of Allergenicity

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**ENTRANSFOOD CONSORTIUM**

- Consortium of Experts from Food industries, Plant breeding companies, Universities, Public/Private Research Institutes, Regulatory Agencies, and Consumers organisations
- 45 participants in RTD projects
- 62 participants in Working Groups
- Scientific disciplines: molecular biology, toxicology, biochemistry, plant breeding, analytical chemistry, and social science
- Total costs: € 12.302.449
- EU contribution: € 8.390.776
**Structure ENTRANSFOOD Activities**

- Integrated Discussion Platform
- Review and Position Papers
- Integrated Evaluation Documents
- Recommendations
- Research proposals
- Press releases, information on Web site

**Integrated Discussion Platform**

Contributors from: Academia, Food industry, Regulatory agencies, Consumer groups

**Societal Aspects**

- Review and Position Papers
- Integrated Evaluation Documents
- Recommendations
- Research proposals
- Press releases, information on Web site

**Gene Transfer**

- Detection of Unintended Effects
- Safety Testing of Transgenic Foods

**Unintended Effects in GMO’s,**

Random integration of transgenes

- Insertional mutagenesis
- Disruption of endogenous gene functions
  - Gene activation / inactivation
  - Production of new proteins
- Changes in
  - Phenotype
  - Enzymes
  - Metabolites
  - Toxins?

**Unintended Effects in Conventional Breeding**

Potato glycoalkaloids
- Pest resistance: glycoalkaloids up
- Cases of human poisoning

Celery
- Furanocoumarins
- Insect / Fusarium resistance
- Contact dermatitis in field workers

**ANALYSIS OF (UN)INTENDED EFFECTS**

- Plant
- Tissue
- DNA
- mRNA
- Proteins
- Metabolites

- Phenotypic alterations
- Phenotypic alterations
- DNA analysis
- Genomics
- Proteomics
- Metabolomics

**Safety Assessment of GM Food**

- Unintended effects
  - Specific analysis
    - Targeted approach
  - Profiling techniques
    - Non-targeted approach

www.entransfood.com
DNA Micro-Array Technology

Analysis of differential gene expression due to genetic modification

- Take GM crop plant/mutant/control
- Isolate mRNA
- Label RNA in RT-PCR reaction
- Combine equal amounts
- Hybridize to microarray
- Laser scanning of array
- Data analysis

• Identify (un)intended effects
• In vitro/vivo validation

Proteomics

1. Take GM crop plant/mutant/control
2. Isolate mRNA
3. Label RNA in RT-PCR reaction
4. Combine equal amounts
5. Hybridize to microarray
6. Laser scanning of array
7. Data analysis

• Identify (un)intended effects
• In vitro/vivo validation

Chemical Fingerprinting

Metabolomics

- Polar/water soluble compounds
- Apolar/membrane bound compounds

- GC-Chromatography
- NMR Acquisition
- Normalization of signals
- Differential Analysis
- Statistical interpretation
- Spectra subtraction
- 2D NMR analysis

Overlay spectra

Special Issue Food and Chemical Toxicology

Volume 42, issue 7, July 2004

Conclusions

1. The Comparative Safety Assessment strategy (Substantial Equivalence) is robust and adequate to identify hazards of GM foods, which are subsequently further investigated

2. Unexpected alterations in the composition of GM foods are thoroughly screened for by single compound analysis and profiling methods. The latter methods should be further developed and validated
Conclusions

3. GM foods with health-benefit properties are still under development and need thorough investigations of safety and health claims.

4. Transparency in the risk analysis process and interactive dialogue between all stakeholders about the risks and benefits of the GM technology is necessary in order to restore public trust in GM foods.

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- Gijs Kleter
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