



What do you mean, “It won’t do you any harm to eat it?”

Assessment of food safety

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Safety assessment of genetically engineered (GE) foods

- Regulatory environment
- Relevant concepts
- The use of mammalian toxicity studies: ILSI-IFBiC TF10 deliberations
 - on assessing the safety of transgenic proteins
 - on assessing the safety of whole foods



Regulatory environments for genetically engineered (GE) foods

Canada

- regulates plants with novel traits (PNTs)
- GE crops or non-GE crops with no history of production or safe consumption
- a conventionally bred crop could trigger assessment as a PNT

US, EU and others

- new rDNA insertions in a plant trigger regulatory scrutiny

Smyth and McHughen (2008) Plant Biotech. J. 6, 213-225



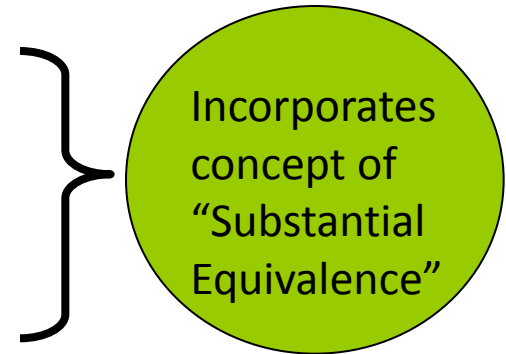
The Novelty Approach:

- The regulatory focus in Canada is on the product, not the process used to create the product
- ‘Novelty’ is used as a regulatory trigger
- Generally speaking, a product is considered novel if it has a heritable characteristic that is different from its conventional counterpart
 - Heritable characteristics may be introduced by conventional breeding, mutagenesis, genetic engineering, etc.



Information requirements for GE food safety assessment:

- Characterization of derived line
- Genetic modification considerations
- History of host and donor organisms
- Dietary exposure
- Nutritional considerations
- Toxicology considerations
- Allergenicity considerations
- Chemical considerations



From: Food Directorate, Guidelines for the Safety Assessment of Novel Foods



“*Substantial equivalence* is a concept used to identify similarities and differences between the genetically modified food and a comparator with a history of safe food use which subsequently guides the safety assessment process”.

World Health Organization, 2000. Report of a Joint FAO/WHO Expert Consultation on Foods Derived from Biotechnology.

“The concept of *substantial equivalence*is not a safety assessment in itself....it aids in the identification of potential safety and nutritional issues...”

CODEX, 2009. Foods derived from modern biotechnology.



Intended and unintended changes

- Must be considered when assessing GE foods for potential adverse health effects.
- Intended changes
 - direct and indirect effects of primary and secondary gene products
- Unintended changes
 - predictable
 - beyond the expected change but still explicable based on current knowledge
 - unpredictable
 - beyond our current understanding of gene regulation and interaction
 - “unknown unknowns”

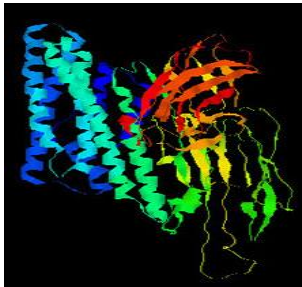
Chao and Krewski, 2008. Reg. Tox. Pharm. 52: 208-222



Intended and unintended changes: Safety assessment

Intended changes

- assess the safety of the primary gene product
- ie. toxicity, allergenicity of an introduced protein



Unintended changes

- is there a compositional change in the plant in relation to a conventional comparator?
- assess the safety of the whole food?
- unintended changes are not assessed in non-GE plants

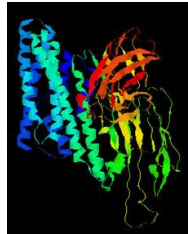
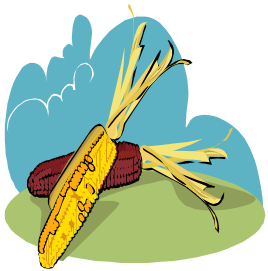
Kok et al., 2008. Reg. Tox. Pharm. 50, 98-113



ILSI-IFBiC Task Force 10 Background

Early in 2008 IFBiC established TF10 to develop consensus recommendations on:

- when it is scientifically appropriate to conduct mammalian toxicity studies with GE foods and/or proteins, and
- when appropriate, how best to design and use such studies in the safety assessment of GE foods



CODEX Alimentarius Guideline regarding the safety of an introduced protein

The assessment of potential toxicity should focus on:

- amino acid sequence similarity between the protein and known protein toxins and anti-nutrients
- stability to heat and processing and to degradation in appropriate gastric and intestinal model systems
- oral toxicity studies may need to be carried out if the protein present in food is not similar to proteins that have previously been consumed safely in food.

CODEX, 2009. Foods derived from modern biotechnology. WHO/FAO.



Conclusions of ILSI TF6 on Protein Safety

- Reasoning based on CODEX

- Tier I. Basic Hazard Assessment

- history of safe use
 - bioinformatics
 - expression level and dietary intake
 - mode of action
 - *in vitro* digestibility and lability

- Tier II. Supplementary Hazard Assessment

- triggered when concerns raised in Tier I
 - toxicology studies

Delaney et al., 2008. Food Chem. Tox. 46, S71-S97



Task Force 10 views on transgenic protein safety assessment

- Toxicology testing of proteins introduced into GE crops has shown no evidence to date of adverse effects
 - acute toxicity studies, 28-day repeated dose studies
- Introduced proteins are often variants of those found in nature
- Where toxicological evaluation is necessary it should be hypothesis-driven and employ an appropriate study design and endpoints to address the hypothesis



EFSA 2009 position on protein safety testing

“Unless reliable information is provided demonstrating the safety of the newly expressed protein, the safety assessment of proteins with no history of safe use (for consumption as food) should normally include a repeated-dose toxicity test (normally 28 days) and not rely on acute toxicity testing. Depending on the results of his test, further testing may be necessary.”



TF10 views on what constitutes reliable information about protein safety

- If an introduced protein has no HOSU but is structurally similar to those that do, its mode of action is likely to be similar
- Modifications in the primary structure of a non-toxic protein are not likely to make it toxic
- Proteins denature and lose functionality during food/feed processing. Human dietary exposure to functionally active introduced proteins in processed food fractions is likely to be low and pose negligible risk.



TF10 views on the use of toxicology studies to assess transgenic protein safety

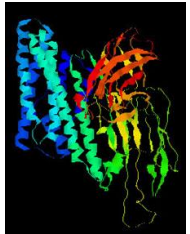
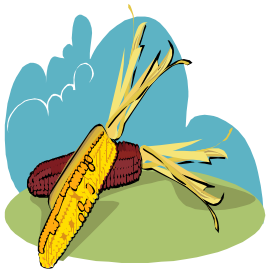
- Toxicology studies may be needed on a functionally active introduced protein if it is
 - structurally or functionally related to known mammalian toxins
 - stable in simulated gastric fluids
 - stable to food processing conditions
 - not sufficiently characterized regarding its mode of action and where there is a toxicologic basis of concern
- Toxicological evaluation should be hypothesis-based



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Mammalian “toxicity” studies have been conducted to assess the safety of whole GE foods

- primarily rodents (mice, rats)
- 14d, 28d, 90d, multi-generation
- general health, clinical chemistry, hematology, histopathology, reproductive parameters, immune parameters, others.
- EFSA recommends 90-day rodent feeding study for detecting unintended adverse effects of GM foods

EFSA, 2008. Safety and nutritional assessment of GM plants and derived food and feed: The role of animal feeding trials. Food Chem.Tox. 46, S2-S70



TF10 discussions on whole food safety evaluation

- No unintended compositional changes have been observed in GE crops that have been associated with adverse consequences in rodent studies
- TF10 concurs with EFSA that 90-day studies add little to the safety assessment of a GE food when differences are not observed in the composition of a GE crop relative to its conventional comparator



TF10 discussions on whole food safety evaluation

- Modifications in plant metabolic pathways may result in the production of new metabolites or significant changes in existing metabolites
- If this raises safety concerns, focus the toxicologic assessment on
 - individual metabolites/constituents or
 - relevant fractions of the food based on changes in metabolites/constituents



Whole food studies – challenges and considerations

- The 90-day study has a relatively large capacity to detect adverse effects of chemicals
 - measures the effects of repeated exposure from post-weaning to sexual maturity
- Single chemical toxicity studies use a dose range with at least one dose many-fold higher than human exposure levels
 - purpose is to identify major toxic effects, indicate target organs
- For whole foods, it is unlikely that substances present in small amounts and/or with low toxic potential will result in any observable effects.



Will an animal study be sensitive enough if the test material is a whole food?

- There are practical limits to how much whole food can be incorporated into rodent diet
- Rodent diets must be nutritionally balanced and palatable
- Rodents can only be fed low multiples of the amounts that might be present in human diets
- Generating a dose-response is difficult



TF10 discussions on whole food safety evaluation

- Due to the limitations of whole food studies, general health screen uninformative
- Animal testing should be hypothesis-driven and testable using appropriate and relevant design considerations and endpoints
 - enriched fractions or individual metabolites
 - must know what you're looking for (target organ, tissue, receptor)
 - study design will depend on the question to be answered



In safety assessment (and in everything else that matters) -
it's important to use the right tools for the job!

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Thank you!

Questions?

