

ILSI-IFBiC Task Force 10:
Mammalian Toxicology Studies for the Safety
Evaluation of GM Crops

TF Update and Preliminary Views on Protein
Safety and Whole Foods Testing

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Task Force 10 Background

Early in 2008, IFBiC established a new task force focused on assembling an international panel of scientific experts from government, academia and industry to develop consensus recommendations on when it is scientifically appropriate to conduct mammalian toxicity studies with genetically modified (GM) proteins and/or foods and, when appropriate, how to best design and use such studies in the safety evaluation of GM food/feed crops.

Task Force 10 Membership

- Sue Barlow - Consultant
- Andrew Bartholomaeus – Food Standards Australia New Zealand
- Genevieve Bondy – Health Canada
- Amechi Chukwudebe – BASF
- Bryan Delaney – Pioneer, a Dupont Company
- Bruce Hammond – Monsanto Company
- Corinne Herouet-Guicheney – Bayer CropScience
- Joseph Jez – Washington University
- Daland Juberg – Dow AgroSciences
- Hideaki Karaki – Retired (Univeristy of Tokyo)
- John Kough – U.S. Environmental Protection Agency
- Sue MacIntosh – MacIntosh and Associates
- Li Ning – Institute of Nutrition and Food Safety, Chinese Center for Disease Prevention and Control
- Wayne Parrott – Center for Applied Genetic Technologies, University of Georgia
- Alaina Sauve – Syngenta Biotechnology, Inc.
- Kate Walker, ILSI IFBiC
- Flavio Zambrone – Planitox, ILSI Brazil

Task Force Progress

- Formation of TF and recruitment of international representatives
- Initial 2-day meeting of entire TF (2008)
- Assignment to protein, whole foods, and shared elements subcommittees
- Initial draft of manuscripts
- Full TF meeting – July 2010 to develop consensus and finalize manuscripts

Future Work

- Finalize views on protein safety and whole food testing – invited presentation to EFSA, October 2010
- Publication
- Outreach activities across geographies and venues (technical meetings, scientific meetings, ILSI workshops)

Safety Assessment through Substantial Equivalence

- Characterization of the new gene product, most often a protein
- Comparison of the agronomic and phenotypic characteristics of the new plant to conventionally bred plants
- Comparison of the new food to conventional food with regard to the nutritional and biochemical composition, including possible presence of anti-nutrients and toxins

Proteins

Views on Protein Safety

- Primary safety assessment of any protein before introduction into a food/feed crop by genetic engineering includes bioinformatics screening and testing potential digestibility through in-vitro incubation with proteases
- When possible, protein mode of action is assessed to confirm it does not pose identifiable or anticipated safety concerns
- Proteins that are not structurally or functionally related to known mammalian toxins and are digestible or altered significantly after processing are unlikely to pose a toxicological risk from exposure or consumption (ILSI TF 6)

Views on Protein Safety

- Acute and repeated-dose toxicology testing of proteins (including homologous proteins with variant structures, e.g., amino acid sequence or content) introduced into commercial food/feed GM crops to date has found no evidence of adverse effects
- Where toxicological evaluation of proteins is considered necessary or prudent, it should be driven by specific endpoint-related hypotheses and employ relevant and appropriate techniques to address the hypotheses

Views on Protein Safety

- When the following types of information are available, a 28-day repeat-dose study should not be required:
- Where an introduced protein does not have a history of safe use, but is structurally and functionally similar to those that do, the mode of action is likely to be demonstrably similar.
- Modifications in the primary structure of a protein are highly unlikely to increase its toxicity potential where stability is not significantly changed. This is based on our understanding of the evolutionary divergence in protein families across species and learnings from the engineering of proteins to improve biological function (e.g., enzymes).
- Most proteins denature and lose biological function when heated, digested, or exposed to food/feed processing. Thus, human dietary exposure to functionally active introduced proteins in such foods is likely to be very low.

Whole Foods (WF)

WF Testing

- We are not aware of any precedence where a *de novo* toxin has resulted from conventional crop breeding
 - This would require introduction of multiple genes for toxin expression
 - Extremely unlikely that transformation of crops using biotechnology will result in the production of a *de novo* toxin when the introduced genes do not code for toxin production

Views on WF Safety Evaluation

- Baseline testing strategy for whole foods obtained from GM crops is composition evaluation (comparison of substances including nutrients, antinutrients to those in WF from non-GM crops)
- Other components in the evaluation include agronomic evaluation, molecular characterization of the gene insert and safety assessment of the inserted proteins

Views on WF Safety Evaluation

- Rodent models are used to detect the presence of unintended adverse changes in WF that may have occurred as a consequence of transformation
- Subchronic (90-day) rodent toxicology studies have been conducted with WF obtained from many different GM crops

90-Day Studies on GM Crops: Results

- No adverse effects have been observed in more than 40 toxicology studies (some for registration purposes) conducted on WF obtained from GM crops.
- 90-day rodent studies performed with GM plants modified for agronomic input traits have not contributed significantly to the weight of evidence evaluation of GM crop safety when no unintended changes have occurred
- For 1st generation GM crops, the absence of toxicity findings, coupled with knowledge of how these crops were modified and the nature of the intended changes, makes it highly unlikely that unintended changes would be manifested.

Considerations in WF Testing

- EFSA has concluded that 90-day studies add little to the safety assessment of a GM crop when differences are not observed in composition or agronomic studies
- TF10 concurs and further concludes that any testing should be hypothesis-driven and be testable using an appropriate design
 - Must know what you're looking for (target organ, tissue, receptor)
 - Is an animal model/study going to be an accurate and sensitive marker?