Australian Regulatory Requirements for GM crops

Andrew Bartholomaeus
Professor (Adj)
Therapeutic Research Unit, School of Medicine, University of Queensland
&
School of Pharmacy, University of Canberra

General Principles

Why do risk assessment

- Minimalist approach would be to simply make producer/supplier liable for product safety and quality
  - This is generally the case for consumer goods and for new non GM crop varieties
- **Public Safety**;
  - Long, and ongoing, history of large scale public injury and death from food contamination.
  - Risk Assessment guides risk Management
- **Public confidence**;
  - in the food supply is essential for acceptance of food innovation
  - Highly motivated anti-technology, anti industry protagonists are highly active and vocal but working from a general ignorance of relevant science
  - Independent, transparent, consultative review of the safety of new technologies provides a counterbalance
- **Socio – Political Considerations**

Principles of "Good" Regulation

- Ethical regulation is proportionate to risk
  - Regulatory requirements are ideally evidence based and founded on good science.
  - Regulatory burden (& cost) should be commensurate with the risk to be managed
  - Data requirements should address & inform viable risk management options
- Value of information (VOI)
    - Data is necessary only where the information has a material influence on outcome (risk management strategies)
      - eg why assess endogenous allergens
        - Risk management is constant regardless of any increase or decrease in the levels
        - Natural variability is not regulated
        - > 3 fold increase needed to have any clinical significance (on an individual basis)
        - De novo generation of allergens & exclusion of introduced allergens would change RM & therefore has value **if the postulated outcome is plausible**
        - **What is the evidence? (none)**
- A "Precautionary approach" is **NOT** necessarily precautionary and may be risk generating
  - The broader consequences of regulatory imposts need to be considered
- Objective is Balance, proportionality, pragmatism, cost effectiveness, impartiality, & most importantly - **scientific integrity**

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  - proportionality,
  - pragmatism,
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  - impartiality, &
  - most importantly - **scientific integrity**

Building public confidence

- Requires more than just getting it right and conveying the facts
- A complex area involving
  - Communication
  - Credibility
  - Transparency
  - Competence
  - Confidence
  - Science
  - Political and authoritative support
- An understanding of psychology and sociology is useful if not essential

Importance Of Consensus

nature climate change

ARTICLES

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The pivotal role of perceived scientific consensus in acceptance of science

Stephan Lewandowsky*, Gilles E. Gignac and Samuel Vaughan

Although most experts agree that CO_2 emissions are causing anthropogenic global warming (AGW), public concern has been declining. One reason for this decline is the 'manufacture of doubt' by political and vested interests, which often challenge the existence of the scientific consensus. The role of perceived consensus in shaping public opinion is therefore of considerable interest: in particular, it is unknown whether consensus determines people's beliefs causally. It is also unclear whether perception of consensus can override people's 'worldviews', which are known to foster rejection of AGW. Study 1 shows that acceptance of several scientific propositions—from HIV/AIDS to AGW—is captured by a common factor that is correlated with another factor that captures perceived scientific consensus. Study 2 reveals a causal role of perceived consensus by showing that acceptance of AGW increases when consensus is highlighted. Consensus information also neutralizes the effect of worldview.

"..vital role of highlighting a scientific consensus when communicating scientific facts. Appealing to a consensus is particularly valuable where social norms are ambiguous. ..people may be particularly susceptible to perceived consensus when forming their own beliefs about scientific issues that …are difficult to grasp, hotly debated or challenge people's world views

International Regulatory Environment

- Proportionality to risk
  - Current regulatory requirements in some jurisdictions are founded on discredited postulates & therefore:
    - Irrational
    - Discordant with the data
    - Excessive
- VOI - Some data requirements are irrelevant to viable risk management options
  - Eg why assess endogenous allergens
    - Risk management is constant regardless of any increase or decrease in the levels
    - Natural variability is not regulated
    - > 3 fold increase needed to have any clinical significance (on an individual basis)
  - De novo generation of allergens & exclusion of introduced allergens would change RM & therefore has value **if the postulated outcome is plausible**
    - **What is the evidence? (none)**
- Excessively "Precautionary approach" has generated economic and food security risks
- Balance, proportionality, pragmatism, cost effectiveness, impartiality, & **scientific integrity** are compromised

Current data requirements

- Jurisdiction dependent
- A mix of
  - Compositional analysis
  - Agronomic data
  - Biotechnology data (gene and insertion characterisation)
  - Toxicology
  - Allergenicity

FSANZ Application Hand Book

- Management by Exception is the norm
- Novel Protein Toxicity
  - "There is no requirement to conduct acute or short-term oral toxicity studies in animals on novel protein. "
  - "However, if the bioinformatic comparison and biochemical studies indicate either a relationship with known protein toxins/anti-nutrients or resistance to proteolysis, animal toxicity studies on the novel protein are required. Similarly, if novel substances are identified then animal toxicity studies are required."
- Allergenicity
  - The information provided in this part must enable FSANZ to consider whether:
    a) a newly expressed protein is one to which certain individuals may already be sensitive
    b) a protein new to the food supply is likely to induce allergic reactions in some individuals.
- Specifically
  a) source of the introduced protein
  b) any significant similarity between the amino acid sequence of the protein and that of known allergens
  c) the novel protein's structural properties, including, but not limited to, its susceptibility to enzymatic degradation (e.g. proteolysis), heat and/or acid stability
  d) specific serum screening where a newly expressed protein is derived from a source known to be allergenic or has sequence homology with a known allergen.

WF Toxicity Study Requirements by Jurisdiction

Country/Region	Regulatory requirement for whole food (WF) toxicity studies[a]
North America	
Canada	Not routinely required. In countries/regions where WF studies are not routinely required there is usually a regulatory option to request a WF or other toxicology study as appropriate, if a data gap is identified in the safety assessment.
United States	Not routinely required
Mexico	Not routinely required
South America	
Argentina	Not routinely required
Brazil	Required; WF study protocols are based on OECD Test No. 408 (OECD, 1998) and EFSA Scientific Opinion (EFSA, 2008a).
Asia/Pacific	
Australia/ New Zealand	Not routinely required
China	Requirement to conduct WF studies in country
India	Required; WF study protocols are based on international best practices, including guidance and peer reviewed publications available from the CODEX Alimentarius Commission, the Food and Agriculture Organization, the World Health Organization, the Organization for Economic Cooperation and Development, and the International Life Sciences Institute (http://moef.nic.in/divisions/cs/GEAC.htm).
Indonesia	Not routinely required
Japan	Not routinely required
Philippines	Not routinely required
South Korea	Not routinely required
Taiwan	Not routinely required
South Africa	Not routinely required
European Union	Recommendation to perform WF studies on a case-by-case basis according to OECD Test No. 408 (OECD, 1998) and EFSA Scientific Opinion (EFSA, 2008a); WF studies required for all single trait GM crops; not routinely required for multiple trait ("stacked") GM crops when single trait crops have already been tested.
Russia	Requirement to conduct WF studies in country

What Toxicology data should be required

- **Toxicology**
  - **None** ! (on Whole Food)
  - Not one credible study on WF in rats has called into question the adequacy, sufficiency or robustness of safety assessments based on agronomic and/or compositional data.
  - May be a need for truly novel substances produced such as new pesticide metabolites
  - Conduct studies on pure substance of interest
  - Insistence on animal studies not only does not promote public confidence but actively undermines it – if these are necessary then there must really be safety risks !
  - **No** role in:
    - intractable proteins
    - nutritional variation
    - Vague discredited postulates of "unintended unknowns"

Compositional analysis

- Scientific basis for even this requirement is now highly questionable
- Hugely expensive with no evidence that it adds anything to public health and safety
- Compositional Analysis
  - Not one instance exists of agronomic or compositional data revealing risks for commercial GM crops not predictable from a knowledge of the parent line and source of the transgene
- Clear evidence that considerable variation due to environment often exceeds genetic influence
- During GM commercialization backcrossing of elite hybrid with parent eliminates > 99.9 % of hybrid genetics (repetitive selection for introduced trait)
- Requirements for GM crops but not "conventionally" bred crops, which have greater genetic alteration, is irrational, logically inconsistent, discriminatory

Toxicity of novel herbicide metabolites

- ***Toxicity of novel herbicide metabolites in GM herbicide-tolerant plants***
- Data must be provided on the identity and levels of herbicide and any metabolites that may be present in the GM food.
- **Note:**
  - The information provided in this part will enable FSANZ to consider whether, as a result of the genetic modification, novel herbicide metabolites are present in the food. If novel metabolites (i.e. those not normally found in non-GM crops) are present then the application should include appropriate studies on:
    - (a) toxicokinetics and metabolism
    - (b) acute toxicity
    - (c) short-term toxicity
    - (d) long-term toxicity and carcinogenicity
    - (e) reproductive and developmental toxicity
    - (f) genotoxicity.
- Where data are not available or are not considered relevant to the safety assessment of the novel metabolite/s, a scientific rationale must be provided.

Assesing allergenicity Codex 2003

1. Is the source of the new gene a proven allergen?
2. Is the new protein nearly identical to a known allergen so cross-reactivity might occur?
3. If the protein is from wheat, barley or rye, is it a gluten?
4. Is there an increased risk the new protein will sensitize de novo (stability in pepsin, abundance)?
5. (Did insertion of the new gene significantly increase the endogenous allergens ??)
   - Value of Information & Relevance negligible
   - No practical application of information

Potential allergenicity of novel proteins

Prediction of allergenic potential of novel proteins is problematic

- no reliable animal models for the assessment of allergenicity

In practice, various criteria used in combination to assess potential allergenicity

- no single criterion is sufficiently predictive of either allergenicity or non-allergenicity

- 'weight of evidence' approach (international consensus)

- Large natural variation in allergen composition of non-GM soybean varieties as a function of germplasm and environmental factors (agricultural conditions, geographical location, etc)

Comparison of endogenous allergens in a GM and non-GM counterpart

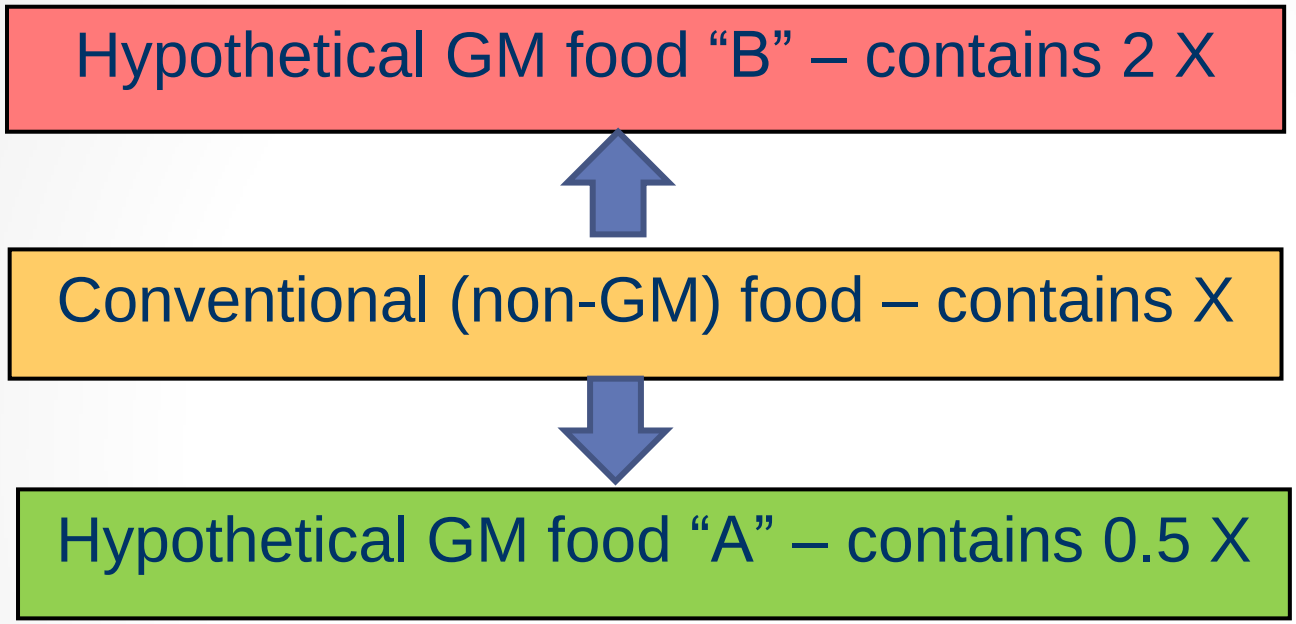
▲If a comparison is to be required in a formal safety assessment of a GM food:

- What is the assessment question this information can answer?
- How important is a change in the level of allergen(s) in a GM food if the conventional food is already known to be allergenic and is regulated as such (eg soy)?
- How will a change (difference between a GM and non-GM counterpart) be meaningfully interpreted in the context of GM food safety assessment?
- What degree of change would be relevant to the safety of (i) allergic individuals (ii) the general population?

There is nothing homogenous about "conventionally" developed crops

Bigger seeds: *Bunya® soybean seeds are larger than other varieties, which increases yield and makes them popular with soy manufacturers.*

Significance of Altered Endogenous Allergen Level



What evidence would support a determination of increased or decreased safety <u>for the general population</u> based on the levels of endogenous allergens in a GM food?

From a regulatory perspective:

All these foods would be treated equally in terms of allergenicity.

An individual who is allergic to the non-GM food would need to avoid all of these foods, irrespective of their mode of production.

GM food Allergenicity -regulatory questions

- Given that there is no pre-market assessment of conventional (non-GM) food, including for allergenicity, how is the allergen level in a GM food to be used in an assessment of general food safety?

Is higher level of allergen = higher exposure?

Are we saying that **higher levels of allergens** may lead to increase in sensitisation?

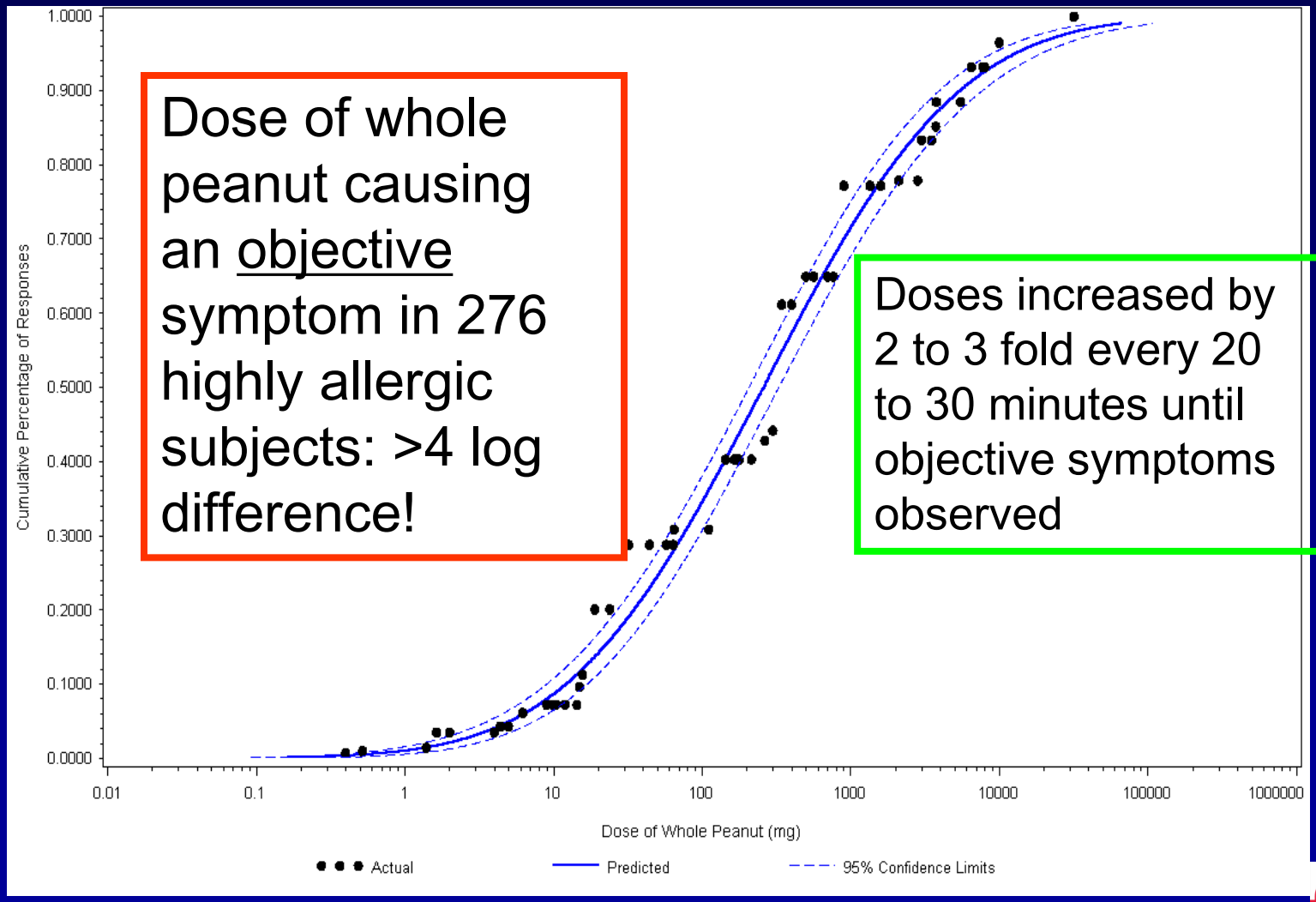
Could **increased consumption** of non-GM food also lead to increase in sensitisation?

Would knowledge about the natural levels of endogenous allergens in crop varieties, conventional or GM, assist in making the food supply safer for the general population?

In cases where a range of natural variation could potentially be determined for a plant, *e.g.* soybean, how could this knowledge be used in safety assessment of GM varieties?

• Richard E. Goodman, Ph.D., FAAAAI Food Allergy Research and Resource Program, Dept. of Food Science & Technology

Individual Peanut Allergic Subject's Thresholds from Food Challenges (expressed as whole peanut)



food allergy research & resource program farrp

Future Regulatory Rationalisation

- Management by exception
  - Corn has a long history of safe use despite millions of SNPs and random gene relocation occurring naturally
  - These mutations and gene translocations have never produced a toxic corn.
  - We now have multiple events in multiple strains of corn with multiple transgenes, some stacked
    - None have shown any potential for *de novo* production of unpredictable or unsafe components
    - As a first step should we reduce/remove data requirements for corn ? (composition & safety)
    - Could we approve a crop type and/or a variety of transgenes as a block and cease data requirements for those
      - Focus on what is actually new or unknown
    - Would a similar approach be reasonable for soy, canola, cotton
    - Is there scope for a similar approach for specific transgenes
      - Will insertion of BT gene in Brinjal be any more or less negligible risk than for corn or cotton
      - Why not approve it generically for insertion to food crops

Conclusions

- New technologies applied to food tend to raise concern and public confidence can be challenging to build.
- Initial response of policy makers tends to be to require increasing levels of toxicity testing despite strong evidence of a lack of value in this approach
- Animal studies are inherently less sensitive than compositional analysis and are better suited to determining what a substance does to an organism than determining whether a substance is present
- Regulatory focus should be on the characteristics of parent crop plant, the transgene itself and the process of GM crop development as these determine the potential for allergenicity or toxicity.