Food from Genome Edited Plants: How and Whether to Regulate?

Dr Janet Gorst
Symposium & Workshop on Risk Assessment & Regulation of Genome Edited Plants
Manila, The Philippines
8 - 10 October 2019
• How we assess food from GMOs

• The regulatory problems with genome editing

• What Food Standards Australia New Zealand (FSANZ) is doing to address the issue
Food Standards Australia New Zealand (FSANZ)

http://www.foodstandards.gov.au

Food Standards Australia New Zealand

Food Standards Australia New Zealand (FSANZ) is a statutory authority in the Australian Government Health portfolio. FSANZ develops food standards for Australia and New Zealand.

The Code is enforced by state and territory departments, agencies and local councils in Australia; the Ministry for Primary Industries in New Zealand and the Australian Department of Agriculture and Water Resources for food imported into Australia. Read the list of agencies and departments responsible for enforcement.

25th Australian Total Diet Study

NOW AVAILABLE

25th Australian Total Diet Study
FSANZ offices in Canberra & Wellington
approximately 100 staff in Canberra & 15 staff in Wellington
The Food Standards Code

FSANZ develops standards that regulate the use of ingredients, processing aids, colourings, additives, vitamins and minerals. The Food Standards Code also covers the composition of some foods, e.g. dairy, meat and beverages as well as foods developed by new technologies such as genetically modified foods.
GM food regulation by FSANZ

Two separate legislative instruments came into effect in 1999

Standard 1.5.2 – Food produced using gene technology
Provides definitions, conditions for the sale of food produced using gene technology, labelling requirements

Schedule 26 – Food produced using gene technology
Provides a list of permitted foods produced using gene technology, additional definitions
Schedule 26 – Food produced using gene technology

• First approvals in 2000

• Schedule 26 currently contains 79 approvals covering 102 lines from 9 crop species – canola, corn, cotton, lucerne, potato, rice, soybean, sugarbeet, safflower

<table>
<thead>
<tr>
<th>Commodity</th>
<th>Food derived from:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Canola</td>
<td>(a) herbicide-tolerant canola line GT73</td>
</tr>
<tr>
<td></td>
<td>(b) herbicide-tolerant canola lines Topas 19/2 and T45 and herbicide-tolerant and pollination-controlled lines Ms1, Ms8, Rf1, Rf2, Rf3</td>
</tr>
<tr>
<td></td>
<td>(c) herbicide-tolerant canola line Westar-Oxy-235</td>
</tr>
<tr>
<td></td>
<td>(d) herbicide-tolerant canola line MON88302</td>
</tr>
<tr>
<td></td>
<td>(e) herbicide-tolerant canola line DP-073496-4</td>
</tr>
<tr>
<td></td>
<td>(f) herbicide-tolerant canola line MS11</td>
</tr>
<tr>
<td></td>
<td>(g) DHA canola line NS-B50027-4, subject to the condition that oil derived from DHA canola line NS-B50027-4 must not be used as an ingredient in infant formula products</td>
</tr>
<tr>
<td>2 Corn</td>
<td>(a) herbicide-tolerant corn line GA21</td>
</tr>
<tr>
<td></td>
<td>(b) insect-protected corn line MON810</td>
</tr>
<tr>
<td></td>
<td>(c) herbicide-tolerant and insect-protected corn line Bt11</td>
</tr>
<tr>
<td></td>
<td>(d) insect-protected corn line Bt176</td>
</tr>
<tr>
<td></td>
<td>(e) herbicide-tolerant corn line T25</td>
</tr>
<tr>
<td></td>
<td>(f) herbicide-tolerant corn line NK603</td>
</tr>
</tbody>
</table>
Standard 1.5.2 – Food produced using gene technology

Key definitions:

**food produced using gene technology** means a food which has been derived or developed from an organism which has been modified by gene technology.

**gene technology** means recombinant DNA techniques that alter the heritable genetic material of living cells or organisms.

**PROBLEM #1** – do these definitions apply to genome editing?
GM food safety assessment

Based on concepts, principles and guidelines developed at an international level

- FAO/WHO
- OECD
- Codex

Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants
Data Requirements For GM Safety Assessment

3.5.1 Foods produced using gene technology

Applications to vary the Code are required to approve the use of new foods produced using gene technology. Approved genetically modified (GM) foods are specified in Schedule 20 – Food produced using gene technology.

The following information is required to support an application for a new genetically modified food. This information is in addition to that specified in Guideline 3.1.1 – General requirements.

Note:

Further explanatory information regarding some of the data requirements for this Guideline (3.5.1) is available in Part 2.3 of this Handbook (GM applications – additional information).

FSANZ is required by paragraph 18(2)(e) of the FSANZ Act to have regard to any written policy guidelines formulated by the Forum.

For the labelling of GM foods, the relevant Guideline is the Labelling of Foods produced or processed using New Technologies.

FSANZ will have regard to these policy principles during the assessment of applications involving foods produced or processed using new technologies. The Guideline is available at http://www.foodstandards.gov.au/code/chfs/downloads/FSANZ%20Labelling%20of%20New%20Technologies.pdf.

The information requirements outlined below take this Policy Guideline into consideration.

A Technical information on the food produced using gene technology

The application must contain the following information:

A.1 Nature and identity of the genetically modified food

This must include all of the following:

(a) a description of the GM organism from which the new GM food is derived. The description must include the nature and purpose of the genetic modification
(b) the name, line number and OECD Unique identifier of each of the new lines or strains of GM organism from which the food is derived
(c) the name the food will be marketed under (if known).

A.2 History of use of the host and donor organisms

The common and scientific names of host and donor organisms must be stated. Where information relating to an organism has been included in previous safety assessments prepared by FSANZ, it is not necessary to provide any further information. Where an organism has not been considered previously by FSANZ, the following information must be provided:

(a) For the donor organism(s) from which the genetic elements are derived:

(i) any known pathogenicity, toxicity or allergenicity of relevance to the food
(ii) history of use of the organism in the food supply or history of human exposure to the organism through other than intended food use (e.g. as a normal contaminant).

(b) For the host organism into which the genes were transferred:

(i) its history of safe use for food
(ii) the part of the organism typically used as food
(iii) the types of products likely to include the food or food ingredient
(iv) whether special processing is required to render food derived from the organism safe to eat.
GM food safety assessment - components

- An integrated, stepwise, case-by-case approach

**Laboratory/in silico**

- Molecular characterisation
  - Characterisation of inserted DNA and insertion site
  - Inheritance and genetic stability of inserted DNA
  - Northern analysis for RNAi

**Field trial**

- Assessment of newly expressed proteins or other novel substances
  - Potential toxicity and allergenicity of new proteins
  - Protein levels in the plant
  - Toxicity of novel metabolites (e.g. from herbicide)

**Dietary exposure**

- Assessment of the whole food
  - Compositional analysis (key constituents relevant for human health)
  - Assessment of nutritional impact (if significant compositional changes introduced)

**PROBLEM #2 – would this approach be applicable to food from genome edited plants?**
“We shouldn't forget that there are also other promising novel... breeding technologies, post-GM, and we shouldn't make the mistake of regulating them to death as we have done with GM.” – Prof. Anne Glover (2013): [then] Chief Scientific Adviser to the President of the European Commission

PROBLEM #3 – how much do we actually need to regulate food from genome edited plants?

PROBLEM #3a – and while we’re at it, do we still need to regulate transgenesis so stringently?

https://www.flickr.com/photos/dusting/501791705/

From a regulatory perspective, is there a single definition for genome editing?

**PROBLEM #4 – genome editing encompasses a broad range of changes that span transgenesis and conventional breeding – so how do we regulate it?**

<table>
<thead>
<tr>
<th>transgenic stage involved</th>
<th>SDN-1</th>
<th>SDN-2</th>
<th>SDN-3</th>
<th>ODM</th>
<th>Trans</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td>double-stranded DNA break</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td>targeted site of DNA change</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✗</td>
</tr>
<tr>
<td>heritable change</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>introduction of a DNA ‘template’</td>
<td>✗</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>relatively small bp changes</td>
<td>✓</td>
<td>✓</td>
<td>✗</td>
<td>✓</td>
<td>✗</td>
</tr>
</tbody>
</table>
Modifying a genome: conventional breeding

Traditional cross-breeding

Induced mutagenesis

http://www.knowledgebank.irri.org/ricebreedingcourse/The_IRRI_irrigated_breeding_program.htm

A genome is not static and changes occur spontaneously and from conventional breeding

**Conventional breeding**
- Traditional cross breeding & selection
- Mutation breeding (plants)
- Cell culture techniques

**Spontaneous changes**
- Insertions (transposons)
- Deletions
- Small nucleotide changes

**Conventional breeding**
- Whole genes (traditional breeding)
- Massive nucleotide changes (mutagenesis)
- Somaclonal variation

Products of conventional breeding are presumed safe and in most countries do not require pre-market approval.
Domestication and conventional breeding can result in many different varieties

http://4.bp.blogspot.com/-CLGRUZY0A7w/T14bkt86MBI/AAAAAAAAA28/F2iDH2lwLk0/s1600/heirloom-tomatoes-6.jpg

PROBLEM #5 – because genome editing has less time and cost associated with it than transgenesis, it is likely many more crops and varieties within those crops will be edited. If pre-market safety assessment is required, will regulators be able to cope with the avalanche?
No matter how a food is produced or what the food is, there are generic regulations that must ensure it is safe........is this all we need?
Process vs product regulation

The end product is what we eat and the safety of that product must be the prime consideration - but there are other factors that favour product regulation:

• The same products from different processes
• It is unlikely that a single process is used – inevitably traditional breeding will be involved
• Innovation and reducing costs are becoming paramount
• Future proofing
• Detection and enforcement

PROBLEM #6 – is there/should there be a difference in approach between regulating for cultivation and regulating for consumption?

PROBLEM #7 – even if there is no requirement for a pre-market safety assessment, are we going to require some minimum data?
PROBLEM #8 – current regulation (with associated definitions) of transgenesis is inadvertently influencing regulation of genome editing

FIGURE 1. The international regulatory landscape regarding genetically modified organisms

Tetsuya Ishii & Motoko Araki (2017) A future scenario of the global regulatory landscape regarding genome-edited crops, GM Crops & Food, 8:1, 44-56
Global perspective on genome editing

### PROBLEM #9 – there are already different definitions of what constitutes a ‘product’

<table>
<thead>
<tr>
<th>Country</th>
<th>SDN-1 null segregant</th>
<th>SDN-2 null segregant</th>
<th>SDN-3</th>
<th>ODM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Env</td>
<td>Food</td>
<td>Env</td>
<td>Food</td>
</tr>
<tr>
<td>Argentina/Chile/Brazil/Colombia</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Australia</td>
<td>x</td>
<td>?</td>
<td>✓</td>
<td>?</td>
</tr>
<tr>
<td>Canada</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EU</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Japan</td>
<td>x</td>
<td>x</td>
<td>Depends</td>
<td>Depends</td>
</tr>
<tr>
<td>United States</td>
<td>Plant x</td>
<td>Animal ✓</td>
<td>Plant x</td>
<td>Animal ✓</td>
</tr>
</tbody>
</table>

X = no pre-market safety assessment  
★ = product trigger
FSANZ - Addressing the issue

- In May 2012 and August 2013, FSANZ hosted two technical workshops to discuss various new breeding techniques with a panel of invited experts in the fields of plant breeding and plant biotechnology.

- The aims of the workshops were to:
  - Improve FSANZ’s understanding and knowledge of certain new plant breeding techniques.
  - Provide advice to FSANZ on whether there are safety concerns with food derived using certain new plant breeding techniques.
  - Provide a scientific opinion on whether derived food products should be regarded as GM food.

What are these new techniques?

- **Reverse Breeding**
- **Hybrid Seed Production Technology (SPT)**
- **Accelerated breeding following early flowering**

**Transient transgenics – null segregants**

- **Site-directed nucleases – SDN** e.g. ZFN, TALENs, CRISPR/Cas9

**‘Precision biotechnology’**

- **Oligonucleotide-directed mutagenesis (ODM)**

Encompasses genome editing

**GM Rootstock Grafting**

**Cisgenesis/Intragenesis**

**Agro-infiltration (including non-germline and germline tissue)**
FSANZ - Addressing the issue

- In February 2018, FSANZ released a consultation paper seeking feedback from the community on whether food derived from NBTs should be captured for pre-market safety assessment and whether definitions relating to the GM standard should be changed to improve clarity about which foods require pre-market approval.

- A preliminary report summarising the views of submitters in response to the consultation paper, along with submissions was released in August 2018.

FSANZ Consultation outcomes

**Outcome 1:** Views are divided on the risks or safety of food derived from NBTs and the need for pre-market safety assessment.

**Outcome 2:** Significant concerns remain for some submitters about the safety of genetically modified (GM) foods in general.

**Outcome 3:** A commonly held view is that changes to the definitions for ‘food produced using gene technology’ and ‘gene technology’ are required to improve clarity about what foods derived using NBTs are captured for pre-market assessment and approval.

**Outcome 4:** Many submitters desire more alignment between the Code and other regulatory schemes in Australia and New Zealand so there is consistency in outcomes between what is regulated as a genetically modified organism and what is regulated as a food produced using gene technology.
FSANZ Consultation outcomes

**Outcome 5:** Views are divided on whether the use of a process-based definition should continue or a more product-based approach should be adopted, with a variety of reasons being provided for or against either approach. Some submitters have suggested that a hybrid approach, incorporating both process and product-based elements, may be more appropriate.

**Outcome 6:** Labelling of GM foods continues to be an important issue for many submitters who wish to exercise purchasing choice. These submitters also want GM labelling applied to food derived using NBTs.

**Outcome 7:** A number of submitters consider that the harmonisation of regulatory approaches to NBTs, both domestically and internationally, is the best way to facilitate trade, deliver certainty, and provide the agricultural sector and consumers with access to innovative products.

…and that is as far as FSANZ has been able to get to date
A final thought....

PROBLEM #11 – there is no consistent answer about how (or whether) to regulate food derived from genome edited plants....and there is no forgetting that genome edited animals are waiting in the wings.

<table>
<thead>
<tr>
<th>Species</th>
<th>Target</th>
<th>Purpose of the edit/Trait targeted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cattle</td>
<td>Intraspecies POLLED allele substitution</td>
<td>No horns</td>
</tr>
<tr>
<td></td>
<td>Myostatin KO</td>
<td>Increased muscle yield</td>
</tr>
<tr>
<td></td>
<td>Beta-lactoglobulin KO</td>
<td>Elimination of milk allergen</td>
</tr>
<tr>
<td></td>
<td>Lysostaphin transgene</td>
<td>Disease resistance</td>
</tr>
<tr>
<td></td>
<td>Lysozyme transgene</td>
<td>Disease resistance</td>
</tr>
<tr>
<td></td>
<td>SP110 transgene</td>
<td>Resistance to tuberculosis</td>
</tr>
<tr>
<td>Chicken</td>
<td>Ovalbumin KO</td>
<td>Elimination of ovalbumin in egg</td>
</tr>
<tr>
<td></td>
<td>Immunoglobulin heavy chain locus</td>
<td>Germline gene editing</td>
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<tr>
<td>Goat</td>
<td>Beta-lactoglobulin KO</td>
<td>Elimination of milk allergen</td>
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<tr>
<td></td>
<td>FGF5</td>
<td>Hair length for cashmere production</td>
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<tr>
<td></td>
<td>Myostatin</td>
<td>Increased muscle growth</td>
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<tr>
<td></td>
<td>Prion protein KO</td>
<td>Elimination of prion protein</td>
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<tr>
<td>Pig</td>
<td>CD163 KO</td>
<td>PRRS Virus Resistance</td>
</tr>
<tr>
<td></td>
<td>RELA interspecies allele substitution</td>
<td>African Swine Fever Resistance</td>
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<tr>
<td></td>
<td>Myostatin KO</td>
<td>Increased muscle yield</td>
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<tr>
<td></td>
<td>vWF</td>
<td>Improved bleeding efficiency</td>
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<tr>
<td>Sheep</td>
<td>ASIP</td>
<td>Black/white coat color</td>
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<tr>
<td></td>
<td>BCO2</td>
<td>Disease resistance</td>
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<tr>
<td></td>
<td>Myostatin KO</td>
<td>Increased muscle yield</td>
</tr>
</tbody>
</table>

Examples of genome editing in livestock
https://www.agfront.com/2017/06/16/genome-editing-whats-big-deal/#.XbErL-gzY2w

Table reproduced and modified by Alison van Eenennaam from Van Eenennaam AL. 2017. Genetic modification of food animals. Curr Opin Biotechnol 44:27-34.
Thank you!

https://bigthink.com/1000-words/the-worlds-largest-human-dna-helix