Submission regarding NBT consultation paper

Introduction

Many thanks for the opportunity to comment on the Food Standards Australia New Zealand's discussion paper on 'New Breeding Techniques'. Whilst we appreciate the chance for input, we are deeply concerned that this process is just a retrospective attempt to validate an unaccountable and highly conflicted decision that Food Standards Australia New Zealand (FSANZ) has already made. Documents revealed under Freedom of Information laws show that FSANZ has been consulting with the biotechnology industry on this issue for years.

In 2012 and 2013 FSANZ convened an expert panel – comprised almost entirely of genetic engineers with gene technology patents – to look at whether these new genetic modification (GM) techniques should be considered genetic engineering. Furthermore, FSANZ appears to have deliberately misled the Senate, in response to Senate Estimate questions, by stating "FSANZ is not aware that any members of the expert panel have potential conflicts of interest."[1] FSANZ would have been aware of these patents and other potential conflicts at the time, as this information is well documented and publicised. The chair of the expert panel Peter Langridge even alerted FSANZ to his potential conflicts of interest in an email.[2]

Not surprisingly, the panel concluded that the majority of these techniques do not pose significant food safety concerns and that they either be deregulated or undergo a simplified form of food safety assessment[3] - conclusions strongly disputed by overseas regulators.[4]

Disturbingly FSANZ appears to have adopted the advice it received from this expert panel in full. Correspondence between FSANZ and the Minister obtained by FoE under Freedom of Information laws stated that:

> *"We have considered the key findings of the expert panel and concur with their conclusions regarding which foods should be regarded as GM food, and which should not."*
>
> "*Foods derived using oligo-directed mutagenesis, zinc-finger nuclease technology used to introduce small, site-specific mutations involving one or a few nucleotides, and seed production technology are not captured by the standard and therefore do not require pre-market approval."* [5]

In other words FSANZ has made a *de facto* decision not to regulate these techniques in food that is completely unaccountable, unchallengeable and hasn't been subject to any Parliamentary scrutiny. Now FSANZ appears to be attempting to validate this decision through this formal process.

A flawed process

FSANZ's pro-industry bias is again reflected in the composition of the Expert Advisory Group on New Breeding Techniques (EAG NBT) it has convened to provide "expert advice on issues

relevant to the review, such as the current science relating to NBTs and potential food safety issues associated with the use of NBTs." This includes a number of scientists with personal patents and commercial interests in these new GM techniques.[6]

It is also reflected in the language used in the consultation document. For example, in its use of the industry PR term 'new breeding techniques' rather than using the more accurate term 'new genetic engineering techniques'.

Definitional issues

In 2016, the Food Standards Australia New Zealand Amendment (Forum on Food Regulation and Other Measures) Act passed through Federal Parliament. This deleted the definition of GMO and GM product from the Food Standards Act.

The definition of GMO in the Food Standards Australia New Zealand Act 1991 was then the same as that in the Gene Technology Act 2000 and referred to an organism (or progeny of an organism) that has been modified by gene technology. The Act defined gene technology as "any technique for the modification of genes or other genetic material". [7] This definition would clearly include new GM techniques unless they were specifically exempted.

Friends of the Earth warned at the time that by deleting this definition from the Act, FSANZ was attempting to deregulate these techniques by stealth, since the definition in the Food Standards Code is much weaker. This defines gene technology as "recombinant DNA techniques that alter the heritable genetic material of living cells or organisms". Predictably, FSANZ is now claiming that "A degree of uncertainty exists about whether foods produced using NBTs are '*food produced using gene technology*' because some of the new techniques can be used to make defined changes to the genome of an organism without permanently introducing any new DNA, although it may be present in the genome initially."[8]

This inconsistency in the national scheme regulating GM plants and foods should not now be used as a loophole by which these techniques are deregulated.

Answers to FSANZ's specific questions

3.1.1 Do you agree, as a general principle, that food derived from organisms containing new pieces of DNA should be captured for pre-market safety assessment and approval?

Yes. All new genetic modification techniques should be assessed for safety before being allowed in our food. They should also be labelled for consumer choice. This includes gene editing, GM rootstock grafting, cisgenesis, intragenesis RNA interference and null segregants.

One of the key findings of the Preliminary Report of the Third Review of the Gene Technology Review was that there are **"**strong arguments to support the maintenance of a process-based trigger" for the regulation of GMOs.[9]

Should there be any exceptions to this general principle?

No. In its discussion paper FSANZ refers to GM rootstock grafting. A review commissioned by the Austrian Government concluded that the risks associated with GM rootstock grafting are the same as transgenesis and include:

- Novel gene products (such as RNA and proteins moving from the GM rootstock into the rest of the plant and potentially also into food products such as fruit.[10]
- Stably inherited alterations to affect gene expression;
- horizontal gene transfer between the rootstock and the rest of the plant. [11]
- Suckers developing on the GM rootstock, producing leaves and fruits that are GM.
- Impacts on soil organisms such as nematodes, which are capable of directly taking up RNA from the environment.[12]

FSANZ's 2012 report on 'New Plant Breeding Techniques' also concluded that plants with GM rootstock "may contain novel RNA and/or protein as a result of the genetic modification to the rootstock. Depending on the genetic modification, the food may also have altered composition or other characteristics."[13] The report further states that it was the view of the panel that foods produced using this technique "should be regarded as GM food and undergo premarket safety assessment".

3.1.2 ***Should food from null segregant organisms be excluded from pre-assessment and approval?***

No. We strongly oppose the deregulation of 'null segregants' – the offspring of GMOs which supposedly no longer contain any GM DNA. This is an assumption that needs to be tested via regulation involving full molecular characterisation. The definition of a GMO in Australia should include organisms derived from GMOs, or those that include temporal GMOs, as is the case in the EU.

If no, what are your specific safety concerns for food derived from null segregants?

A review commissioned by the Austrian Government concluded that the risks associated with using GM techniques in the plant breeding process to produce null segregants are same as transgenesis and include:

- Undetected secondary insertions of GM materials that may be retained during segregation;
- Changes to the expression of the target genes which may be preserved in subsequent generations;
- Unintentional changes to the regulation of other genes. [14]

The assumption that there have been no unintended genetic changes therefore needs to be tested before products derived from these techniques are allowed in our food. Hence the need for a full safety assessment.

3.1.3 ***Are foods from genome edited organisms likely to be the same in terms of risk to foods derived using chemical or radiation mutagenesis? If no, how are they different?***

No. While chemical and radiation mutagenesis can increase the rate of random DNA point mutations, gene editing techniques cause DNA double strand breaks and can be used sequentially to make dramatic differences to DNA. They are also prone to additional unexpected mutations. They therefore carry both different and greater risks and warrant pre-market safety assessment and approval.

We oppose the proposed deregulation of GM techniques such CRISPR (SDN-1) when used to make naturally repaired DNA breaks.

SDNs - also referred to as site-specific nucleases (SSN)[15] - use enzymes to cut DNA at specific sites so that genes can be deleted or new genes inserted. The cut DNA is repaired by the natural DNA repair systems of the plant. There are currently four major classes of SDNs: meganucleases, zinc finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and clustered regularly interspersed short palindromic repeats (CRISPR)/Cas9 reagents.[16]

- **Zinc-finger nucleases (ZFN)**
    - This technique involves the use of an engineered enzyme to introduce site-specific mutations into the plant genome. Depending on the type of ZFN technology deployed, mutations can either be restricted to one or a few nucleotides or involve the insertion of a new piece of DNA;
- **Transcription activator-like nucleases (TALEN)**
    - These enzymes are similar in structure in ZFNs but have longer DNA binding sites;[17]
- **Meganucleases/homing endonucleases**
    - These are naturally occurring DNA cutting enzymes that have been isolated from a range of organisms including yeast and green algae;[18]
- **CRISPR/Cas9-Nucleases**
    - These are synthetic enzymes developed from a bacterial enzyme that is part of the bacteria's immune system that is used to recognise and destroy foreign DNA;[19]
    - This technique has only been developed in the last couple of years. Scientists have been excited by its versatility leading many to inaccurately characterise it as a 'precise gene editing tool'.[20]

SDN-1 cuts the DNA without the presence of a donor DNA repair template. This can result in site-specific random mutations or deletions but can also result in the deletion of whole genes and even parts of chromosomes. It can also cause genomic inversions or translocations.[21]

The ways in which DNA double stand breaks are repaired and the potential consequences of misrepair are still not fully understood.[22] A review commissioned by the Norwegian Government observed that our understanding of these mechanisms is still in its infancy and that the majority of the studies have been done on mammalian cells not plant, microbial or other animal cells.[23]

The Austrian Environment Agency's recent review found that SDNs can result in a number of possible unexpected effects. However, because of the current lack of knowledge regarding the mechanisms involved in these techniques, significant uncertainties are associated with an assessment of unintended effects.[24]

And the review commissioned by the Norwegian Government found that:

> *"There are several factors that influence both DNA binding and DNA repair, unfortunately they are to a large extent not fully understood. The lack of mechanistic understanding is a severe limitation for identifying potential hazards from SDNs and more research in this field is greatly recommended. Identifying unintentional effects in a system which is not fully understood becomes very difficult."*[25]

According to the Austrian Environmental Agency[26] unexpected effects caused by SDNs can result from:

- Unexpected mutations in genes sharing similar DNA sequences to the target gene;
- Knock-out mutations that result in fusion genes which could create potentially toxic fusion proteins;
- Unintended mutations as a result of the methods used to introduce SDNs into the target cells. This usually involves older GM techniques such as *Agrobacterium*-mediated transformation or bombardment using a gene gun;
- Changes in gene expression;
- Genes introduced using SDN-3 techniques behaving differently when inserted into different parts of the genome.

Off-target effects

One of the main concerns with these techniques is unexpected mutations due to the SDNs cutting DNA outside the target site. This has been observed for the ZFN, TALEN and CRISPR techniques.[27] Agapito-Tenfen and Wikmark (2015) observe that small deletions can cause gene knockout and some mutations. While these may not lead to easily detectable changes they can still trigger safety concerns. Furthermore, it is unsafe to assume that these changes will not be heritable.[28]

The Austrian Environment Agency's review also found that ZFNs result in significant unexpected mutations.[29] This is also an important problem for the TALEN technique and, according to another recent review, can result in severe side effects.[30] Fine *et al.* (2014) highlighted that identifying off-target mutations for ZFN and TALEN is a daunting task because of the size of genomes and the large number of potential mutation sites to examine.[31]

Studies suggest that CRISPR results in even more off-target mutations than ZFN and TALENs.[32] For example, a recent study found that CRISPR/Cas9 can result in hundreds of unexpected mutations.[33]

Agapito-Tenfen and Wikmark (2015) conclude that off-target mutations occur with all SDN techniques and it is impossible to predict what these might be,[34] therefore:

> *"comprehensive untargeted profiling methods (such as omics) should be applied in order to detect and identify unintentional mutations in the entire host genome."*[35]

CRISPR has only been used for genetic engineering for the past 5 years. Reviews commissioned by the Austrian and Norwegian governments concluded that not enough is known about the risks posed by new GM techniques such as CRISPR. They recommended that products derived from these techniques require comprehensive case-by-case risk assessments.

Deregulating techniques such as CRISPR, given the knowledge gaps that exist around the risks they pose is completely at odds with the Precautionary Principle.

Mutations created using these techniques are fundamentally different to natural mutations

Industry claims that new genetic modification (GM techniques) such as CRISPR do not give

rise to any different risks to natural mutations are scientifically indefensible. Likewise, the argument that these mutations could occur naturally and therefore don't need to be regulated is disingenuous, since the natural mutation rate is extremely low. One plant study found that the probability of any letter of the genome changing in a single generation is about one in 140 million. In contrast these new GM techniques can cause hundreds of unwanted mutations in some organisms.[36]

Not all natural mutations are "safe" and most of them - if they would occur at all - are not used for straightforward and rapid commercial development and use.

Furthermore, no good criteria are available to distinguish risky mutations from less risky ones. As FSANZ's discussion paper notes, the size or specificity of the genetic change has relatively little relevance to the extent of change in the organism and consequently to the risk that it poses to the environment or food safety. [37]

Mutagenesis techniques do not have a 'history of safe use'

Industry arguments that new GM techniques such as CRISPR create similar results to chemical and radiation mutagenesis which have a history of safe use do not stand up to scrutiny. Neither of these techniques have been safely used in animals or microbes. Chemical and radiation mutagenesis also typically result in small point mutations – whereas SDN-1 results in DNA double strand breaks.

Unlike chemical and radiation mutagenesis which increase the rate of random mutation, all of these techniques can be used sequentially to make dramatic changes to the genome.

Chemical and radiation mutagenesis could also result in the production of allergens and toxins and should be regulated. Arguing that new techniques such as CRISPR should be deregulated because of the Government's failure to regulate other potentially risky techniques sets a dangerous precedent.

All of these techniques rely on older GM methods with the same associated risks

All of these new GM techniques rely on older GM methods such as protoplast creation, biolistics, electroporation, tissue culture, and *Agrobacterium*-mediated gene transfer. These can all cause unexpected mutations that would be extremely unlikely to occur in nature. This is why organisms produced using them need to be assessed for safety.[38]

All of the new GM techniques can also result in the accidental incorporation of bacterial or synthetic DNA into the chromosome. With no regulation, these unexpected effects won't be looked for.[39]

Detectability

Industry claims that organisms modified using these techniques would be indistinguishable from natural organisms and so regulation would be unenforceable are nonsensical. Existing SDN-1 products such non-browning mushrooms are patented – requiring full molecular characterisation and enabling traceability.

Claims that GMOs produced using SDN-1 are not detectable only consider the current unequivocal signatures of GMOs obtained through transgenesis. These signatures of course help using "cheap" and "rapid" detection methods but there are a number of techniques that can be used to identify organisms produced using SDN-1.[40]

The development of further protocols (including advances in the robustness of whole genome sequencing) and techniques may allow for better, cheaper and more reliable detection of small changes (e.g. one base pair changes) in genome edited organisms. These include 'BATCH-GE', a bioinformatics tool for batch analysis of DNA sequence data and spectroscopy methods for differentiating between genome-edited and conventionally bred plant varieties.[41]

It is evident that advances in detection technologies are needed, not only for genome-edited organisms, but for other techniques such as RNAi. Already networks of laboratories exist that coordinate and develop techniques to detect GMOs. In Europe, there is the European Network of GMO Laboratories (ENGL). ENGL could play a role in the discussion on detectability of new organisms generated with new techniques, if it were commissioned to do so. There just needs to be the political will to develop suitable detection technologies.

Even if claims that such changes could not be detected were true, not having an analytical control / enforcement method for tracing any product is not an acceptable legal argument, since numerous products in supply chains are only traced by documentary traceability tools. These include free range, organic, fair trade and products from specific countries of origin.

As the regulator of these techniques FSANZ should mandate that developers supply a detection test. Releasing untested GMOs into our food chain without a detection test is a recipe for disaster and we find it frankly astonishing that FSANZ is even considering this.

3.2 ***Are you aware of other techniques not currently addressed by this paper which have the potential to be used in the future for the development of food products?***

Yes – RNA interference and gene silencing.

Should food derived from other techniques, such as DNA methylation, be subject to pre-market safety assessment and approval?

Yes. RNA intereference which can result in DNA methylation and gene silencing is quite clearly a genetic modification technique and can result in heritable genetic changes. It therefore needs to be assessed for safety before being used in our food.

3.3 ***Do you think a process-based definition is appropriate as a trigger for pre-market approval in the case of NBTs****?*

Yes - genetically modified organisms pose unique risks and a process based trigger is appropriate for assessing these risks.

Finding 8 of the Preliminary Report of the third review of the Gene Technology Scheme was that there were "strong arguments to support the maintenance of a process-based trigger as the entry point for the Scheme (i.e. a broad range of technologies, including new technologies, are within the scope of the Scheme)."[42]

If yes, how could a process-based approach be applied to NBTs?

All genetic modification techniques should be assessed for safety and these new GM techniques are quite clearly genetic modification techniques under the Gene Technology Act - which until recently Standard 1.5.2 referred to.

The Gene Technology Act 2000 defines gene technology as "any technique for the modification of genes or other genetic material". This clearly includes all new GM techniques including RNA interference.

Are there any aspects of the current definitions that should be retained or remain applicable?

Standard 1.5.2 defines "food produced using gene technology" as "a food which has been derived or developed from an organism which has been modified by gene technology." It states that "gene technology means recombinant DNA techniques that alter the heritable genetic material of living cells or organisms." This definition clearly includes gene editing techniques. The intent of the Gene Technology Act and Standard 1.5.2 was to capture all new GM techniques. To ensure both consistency of definition and regulation the definition of gene technology in Standard 1.5.2 should be changed to that in the Gene Technology Act.

3.4 Are there other issues not mentioned in this paper, that FSANZ should also consider, either as part of this Review or any subsequent Proposal to amend the Code?

It is important that FSANZ consider the potential international trade impacts if it deregulates food produced using new GM techniques such as CRISPR. Key export markets such as the European Union have yet to make a decision on whether they will regulate these techniques as GM and have zero tolerance policies for unapproved GMOs. As Markos Kyprianou, EU Commissioner for Health and Consumer Protection puts it:

> *"There is no flexibility for unauthorised GMOs - these cannot enter the EU food and feed chain under any circumstances."*[43]

A survey of countries conducted by the Food and Agriculture Organisation (FAO) found that 73% of them have a zero tolerance for unapproved GM varieties.[44] The FAO found that between 2002 and 2012 there had been 200 cases of trade disruptions due to the presence of unapproved GMOs. The majority of the cases happened between 2009-2012, indicating increasing trade problems. Many of these cases cost GM countries millions or even billions of dollars in lost exports.

The OGTR has stated that some of these techniques are currently untraceable. If zero tolerance countries cannot test for these GM techniques, the result is likely to be much broader restrictions on food imports from Australia.

We find it frankly inconceivable that FSANZ would consider deregulating foods produced using these techniques with no assessment of the potential trade impacts of doing so. Other countries have taken a more cautious approach to Australia's, with our key agricultural competitor New Zealand recently announcing that it will regulate organisms derived from these techniques as GMOs.[45]

Since FSANZ regulates food in both Australia and New Zealand it should seek regulatory consistency with New Zealand and regulate these foods produced using these techniques as GM.

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[1] Senate question 2358, asked 06 May 2015

[2] FOI document available at: http://emergingtech.foe.org.au/wp-content/uploads/2016/10/REDACTED-Document-65.pdf

[3] FSANZ (2012) *New Plant Breeding Techniques: Report of a Workshop hosted by Food Standards Australia New Zealand*, http://www.foodstandards.gov.au/publications/Documents/New%20Plant%20Breeding%20Techniques%20Workshop%20Report.pdf; FSANZ (2013) *New Plant Breeding Techniques: Report of a Workshop hosted by Food Standards Australia New Zealand*, August 2013, http://www.foodstandards.gov.au/publications/Documents/New%20Plant%20Breeding%20Techniques%202013%20Workshop%20Report.docx

[4] Eckerstorfer, M., Miklau, M. & Gaugitsch, H. (2014) *New plant breeding techniques: risks associated with their application*, Austrian Environment Agency, http://www.ekah.admin.ch/fileadmin/ekah-dateien/New_Plant_Breeding_Techniques_UBA_Vienna_2014_2.pdf

[5] FOI document available at: http://emergingtech.foe.org.au/wp-content/uploads/2016/02/Document-18-Min-Sub-N13000738-New-Plant-Breeding-Techniques-Workshop-Report-SIGNED_Redacted.pdf

[6] A list of expert advisory group members can be found here: http://www.foodstandards.gov.au/consumer/gmfood/Pages/Review-of-new-breeding-technologies-.aspx

[7] Gene Technology Act 2000, https://www.comlaw.gov.au/Details/C2011C00539

[8] FSANZ (2018) Consultation paper: Food derived using new breeding techniques, p. 4.

[9] Department of Health (2018) The Third Review of the Gene Technology Scheme: Preliminary Report, p. 2., http://health.gov.au/internet/main/publishing.nsf/Content/011C554B9847D6F0CA258169000FCBBE/$File/third-review-gene-technology-preliminary-report-2018.pdf

[10] Eckerstorfer, M.. *et al.* (2014) p. 38-42

[11] *Ibid.,* p. 38-39

[12] *Ibid.,* p. 42-43

[13] FSANZ (2012) *New Plant Breeding Techniques: Report of a Workshop hosted by Food Standards Australia New Zealand*, p. 3, http://www.foodstandards.gov.au/publications/Documents/New%20Plant%20Breeding%20Techniques%20Workshop%20Report.pdf

[14] Eckerstorfer, M. *et al.* (2014), p. 48-49

[15] *Ibid.,*p. 22

[16] For a fuller discussion of these techniques see Eckerstorfer, M. *et al.* (2014)

[17] *Ibid.,* p. 23

[18] *Ibid.,* p. 24

[19] *Ibid.*

[20] See e.g., 'Our superhuman future is just a few edits away', *New Scientist,* 26/9/15, p. 28-30

[21] Agapito-Tenfen, S.G. &Wikmark, O-G (2015) *Current status of emerging technologies for plant breeding: Biosafety and knowledge gaps of site directed nucleases and oligonucleotide-directed mutagenesis,* p. 16-17

[22] Vu, G. T. H., Cao, H. X., Fauser, F., Reiss, B., Puchta, H. and Schubert, I. (2017), Endogenous sequence patterns predispose the repair modes of CRISPR/Cas9-induced DNA double-stranded breaks in *Arabidopsis thaliana*. Plant J, 92: 57–67. doi:10.1111/tpj.13634

[23] Agapito-Tenfen, S.G. &Wikmark, O-G (2015), p. 22

[24] Eckerstorfer, M. *et al.* (2014) p. 25

[25] Agapito-Tenfen, S.G. &Wikmark, O-G (2015), p. 4

[26] Eckerstorfer, M. *et al.* (2014) pp. 25-29

[27] Agapito-Tenfen, S.G. &Wikmark, O-G (2015), pp. 18-21; Eckerstorfer, M. *et al.* (2014) pp. 25-29.

[28] *Ibid.,*p.22

[29] Eckerstorfer, M. *et al.* (2014) p. 26

[30] Agapito-Tenfen, S.G. &Wikmark, O-G (2015), p. 20

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[35]*Ibid.*, p. 8

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