Submission to the Technical Review of the Gene Technology Regulations 2001

Introduction

Many thanks for the opportunity to comment on the Office of the Gene Technology Regulator (OGTR)'s proposed changes to the Gene Technology Regulations 2001. Whilst we appreciate the chance for input, we are deeply concerned about the opaqueness of the process so far. Documents revealed under Freedom of Information laws show that the OGTR has been consulting with the biotechnology industry for at least two years now – urging them to "make the case" for deregulation and to make submissions prior to the start of the public consultation period.[1] Other stakeholders were denied the same opportunity. This has resulted in a biased discussion paper that does not adequately characterise the potential risks associated with the new genetic modification (GM) techniques.

The Australian Gene Technology Act[2] defines gene technology as "any technique for the modification of genes or other genetic material". This would clearly include all new GM techniques unless they were specifically exempted in the Gene Technology Regulations. As the OGTR's discussion paper states:

> *The Explanatory Statement to the 2001 GT Regulations (the 2001 Explanatory Statement) states that "The definition of 'genetically modified organism' in the GT Act was intentionally cast very broadly to ensure that the definition did not become outdated and ineffectual in response to rapidly changing technology."*

That is to say, as gene technologies are developed, the intended default setting of the scheme is to regulate all new gene modification technologies and their products.

It is evident that this review process is designed to narrow the scope of the Gene Technology Act so it no longer has the broad scope necessary to ensure that all new GM techniques and their uses are assessed and licensed. This is contrary to the purpose of the Act.

We strongly recommend that new GM techniques as well as null segregants are regulated as GMOs. The OGTR should dedicate effort to improving the current inadequate system of GMO regulation rather than attempting to limit its scope.

If the OGTR allows these new GM techniques to be deregulated, anyone from amateur biohackers - to industry - to terror groups would be free to use them to genetically modify plants, animals and microbes. Entirely new diseases and poisons could be made. And they could enter our food chain and our environment with no safety testing and no labelling. The results could be catastrophic.

The biotechnology industry argues that these techniques just make small changes to the genome, like mutagenesis. However, unlike mutagenesis - which results in random mutations – these techniques can be used sequentially to make profound, targeted changes to the genome. For example, using SDN1 or ODM a

bacterial genome could theoretically be re-engineered sequentially to create an organism able to produce the anthrax toxin.

Gene editing techniques such as CRISPR/Cas9 have been deemed "weapons of mass destruction and proliferation" in the US Government's annual worldwide threat assessment report this year.[3] All of the options outlined in the OGTR's discussion paper apart from Option 2 would leave certain applications of these techniques unregulated - despite the present paucity of scientific evidence of their safety.

We are concerned that none of the OGTR's Gene Technology Technical Advisory Committee (GTTAC) abstained from offering advice on the regulation of these new GM techniques even though some of them have clear conflicts of interest. GTTAC's advice has affected the way the OGTR's various options are presented in the paper. We strongly disagree with the GTTAC's assertion that "organisms altered by some site-directed nuclease techniques and oligo-directed mutagenesis are unlikely to pose risks that are different to natural mutations, conventional breeding or mutagenesis."[4] This conclusion is at odds with those drawn by overseas government agencies.[5]

Austrian government agencies are among the few globally to consider the biosafety risks posed by new GM techniques. Their conclusion, over three separate, high-level reviews, is that there is insufficient knowledge of the biosafety risks posed by these techniques to be confident of their safety. On this basis, they argue that products derived from new GM techniques should be regulated in the same way as those created using older GM techniques and require a comprehensive case-by-case risk assessment. [6]

Contrary to the OGTR's assertion, not all of these techniques are new. Restriction endonucleases - of which zinc finger nucleases are an example[7] – were already in existence when the Gene Technology Act 2000 was enacted. These techniques are referred to in the 1980 Australian Academy of Science publication *Recombinant DNA: An Australian Perspective.* These techniques are quite clearly GM and need to be regulated in the same way as older GM techniques.

We therefore oppose the OGTR's proposed deregulation of the new GM techniques.

Genetic engineering techniques such as oligo-directed mutagenesis (ODM) and site-directed nucleases (SDNs) both rely on the natural DNA repair systems of living organisms, which are far from fully understood. Consequently, the way these techniques work is still hotly contested, even among scientists with relevant expertise and experience. According to a recent review commissioned by the Norwegian Environment and Development Agencies this "poses many uncertainties connected to mode of action as well as potential unintentional effects."[8]

Nowhere in the OGTR's discussion paper is there any reference to the potential ecological impacts of the products of the new GM techniques, particularly if gene drives are used to extinguish whole species of organism such as mosquitoes. For instance, the role of mosquitoes as pollinators and as food for migratory birds is much debated.

The paper also ignores consumer choice. People have a wide range of reasons for opposing the use of genetically modified organisms (GMOs). These include environmental, health and ethical reasons. Everyone has a legitimate right to know if products contain GMOs so that they can avoid them if they want to. While markets are a state issue under the national scheme, deregulation would undermine the capacity of the states to be GM free. This contradicts the notion that this is simply a technical review – it's much bigger – and requires a far better analysis of all the impacts of deregulation.

It is apparent from the Discussion Paper that the OGTR is under pressure from the GM industry to adopt a product-based approach to regulation as is used in the USA and Canada, rather than the process-based

approach used in the rest of the world and in Australia's Gene Technology Acts. A product-based approach is unscientific because it ignores the means of production and does not assess the unique risks posed by GMOs.

We recommend that:

- Option 2 be adopted as it is the only one of the 4 options presented that may adequately address the potential risks posed by all the ODM and SDN techniques, and the products derived from them;
- Null segregants produced using Techniques to Support Breeding (TSBs) such as Seed Production Technology (SPT) be regulated as GMOs;
- The Precautionary Principle in the Gene Technology Act 2000, be applied rigorously to all assessments, licensing and monitoring of new GM techniques and their products, since there is insufficient scientific evidence available on which to justify a decision not to regulate any of these techniques and their products;
- All new GM techniques and the products derived from them be subject to a comprehensive case-by-case, scientific risk assessment, including full molecular characterisation and independent safety testing to minimise any potential risks to human health and the environment;
- All new GM techniques be placed in the highest risk category initially, including ODM, SDN, RNA Inference, Seed Production Technology (SPT), Reverse Breeding and Accelerated Breeding;
- All products derived from new GM techniques be labelled to protect the right to know and choice for farmers, processors and consumers;
- The Government impose the Polluter Pays Principle and strict liability on all dealings with GMOs that the OGTR licenses - so that liability for GM contamination and any resultant harm, losses and costs rests fully on the licensees and patent holders;
- A moratorium on the commercialisation of all these new GM techniques –especially gene drives - be introduced until our regulatory system for GMOs is fully adapted to deal with the potential risks they pose;
- Since this Regulatory Review is much broader in scope than merely a Technical Review of the regulations, all final decisions of the review should be subject to parliamentary review processes and approval, concurrent with the scheduled review of the Gene Technology Act 2000.

Our responses to the OGTR's specific consultation questions follow.

1.Which option/s do you support, and why?

We support Option 2 since it is the only one of the options presented that near adequately addresses the potential risks posed by ODM and SDN. However, we only support this option if its scope is extended to all new GM techniques and null segregants.

It is our well-founded judgement that all new GM techniques and their products should be regulated as GMOs. This was clearly the intent of the Gene Technology Act 2000 and the mirror legislation in other jurisdictions, so we are deeply concerned that the OGTR has excluded from consideration null segregants produced using what have been termed 'Techniques to Support Breeding' (TSBs). These include Seed Production Technology (SPT), Reverse Breeding and Accelerated Breeding. The OGTR's decision to exclude these techniques from the discussion paper and from regulation amounts to a *de facto* regulatory decision - which is clearly outside the OGTR's remit.

The concept behind all TSBs is that the genetic modifications introduced to aid breeding are segregated out to create non-GM crops. However an Austrian Government review warns of the possibility of unintended effects. These 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. [9]

The authors of this government review conclude that:

> *"a thorough characterisation of the final products of RB and AB is needed to exclude the unexpected presence of GM modifications."*[10]

They also recommend that the final breeding plants produced be assessed for traits expected for the initial modifications, such as early flowering and unintentional changes to the regulation of other genes. They argue that this requires a thorough assessment of the resulting plants, in case molecular evidence cannot exclude off-target effects.

In the case of SPT they argue that:

> *"Maintainer lines for SPT need to be grown in containment, or risk assessed according to GM regulation… The absence of transgenic traits contained in the maintainer lines needs to be confirmed by appropriate monitoring."*[11]

The OGTR's proposal to exclude from the definition of GMO the offspring of GMOs that appear not to have inherited the GM trait, is misleading and unscientific. These organisms need to be assessed for safety in case any unforeseen genetic modifications have occurred and been passed on. Their products should also be labelled for consumer information and choice.

The OGTR's assertion that organisms produced using ODM and SDN "do not pose different risks to conventionally bred organisms," are strongly refuted by overseas government agencies. Reviews commissioned by the Austrian and Norwegian governments concluded that there is insufficient knowledge regarding the risks posed by these new GM techniques and that products derived from them should require a comprehensive case-by-case risk assessment.[12]

2.Are there other risks and benefits of each option that are not identified in this document?

The OGTR's discussion paper does not adequately characterise the risks associated with all new GM techniques and their products. The use of these techniques would create risks, hazards and costs that may be even greater than those raised by older cut-and-paste GM techniques. These include food safety concerns;[13] GM contamination of non-GM crop plants or wild relatives; [14] biosecurity concerns; environmental impacts - including impacts on biodiversity;[15] and the potential extinction of species – with unforeseeable ecological consequences - if gene drives run out of control.

2.1 Unexpected effects

New GM techniques, like the older cut-and-paste genetic engineering techniques, can unintentionally interfere with the functioning of an organism's genome - namely its gene expression.

Despite a few GM crops being commercialised, the precise way in which plants' regulatory networks function is still poorly understood. This is illustrated by recent advances in epigenetics[16] and the current debate over whether all of the "junk" DNA in the human genome is actually "junk" - or if it performs regulatory functions[17]. Because of this lack of understanding of gene regulation, it is impossible to predict

all the consequences of genetic engineering processes. Unintended changes to plant chemistry arising from the use of new GM techniques may result from:

- unforeseen interactions between new or altered gene(s) and the plant's genes;
- gene irregularities arising from the genetic engineering process itself; and
- unintended alterations to plant biochemical pathways arising from the changed or new function(s) of the altered or new gene(s).[18]

Table 1 details the main types of new-GM techniques and the risks associated with them. Although unexpected effects have been seen for all the new GM techniques, they vary in the way that they operate.

Table 1: Unexpected effects associated with new GM techniques[19]

Technique	**Intended genetic modification**	**Potential unexpected effects**
Oligo-directed mutagenesis (ODM)	Targeted gene alterations	• Unexpected mutations in adjacent genes and genes sharing similar DNA sequences to the target gene; • Knock-out mutations resulting in fusion genes which could create potentially toxic fusion proteins; • Unintended mutations as a result of the methods used to introduce oligonucleotides into the target cells; • The integration of the oligonucleotides into the plant genome; • Changes in gene expression.
Site-directed nucleases (SDNs) 1 and 2	Targeted gene alterations/deletions	• Unexpected mutations in genes sharing similar DNA sequences to the target gene; • Knock-out mutations resulting 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; • Changes in gene expression.
SDNs 3	GM insertions/deletions	• Unexpected mutations in genes sharing similar DNA sequences to the target gene; • Knock-out mutations resulting 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; • Changes in gene expression; • Genes behaving differently when inserted into different parts of the

		genome.
Cisgenesis/Intragenesis	GM insertions from the same or closely related species	The same as transgenesis e.g.: • Multiple copies of the gene inserted; • Deletion or rearrangement of plant DNA around the intended genetic insert; • Genes behaving differently when inserted into different parts of the genome; • Bacterial DNA being incorporated into the plant genome resulting in the formation of potentially harmful fusion proteins.[20]
Transgrafting	GM insertions in rootstock	The same as transgenesis and specifically: • 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;[21] • Stably inherited alterations to affect gene expression; • horizontal gene transfer between the rootstock and the rest of the plant; [22] • 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.[23]
Techniques to support breeding: • Reverse breeding • Seed production technology • Accelerated breeding	Using GM techniques in the plant breeding process with the intention that no transgenes are present in the final plants	The same as transgenesis and specifically: • 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. [24]
Agroinfiltration	'Infiltrating' plant tissue with a liquid suspension of GM bacteria to express the transgenes in the tissues	The same as transgenesis and specifically: • Transgenes may become integrated into cells selected for further propagation; • Unexpected effects due to inheritable epigenetic effects on the regulation of both target and non-target genes.

2.2 Off-target effects

As well as the intended genetic modification of plant genes, unintended modifications have also been observed in GM crops that are currently grown commercially. To date, these modifications have arisen from the unintended insertion of multiple copies and fragments of the genetic cassette at different locations[25] and rearrangements of host DNA adjacent to the intended genetic insert.[26] Although gene-editing techniques such as CRISPR, ZFN and TALENs have been touted as much more precise than the older modes of genetic engineering, off-target effects have also been found to occur with all these techniques.[27]

2.3. Unexpected proteins

A primary function of genes is to produce proteins and there is concern that changes to the genome could result in the production of unintended novel proteins or changes to the chemical composition or structure of existing proteins. Although any intended novel protein resulting from the genetic modification may be characterised, altered proteins or unintended novel proteins are unlikely to be. The character of proteins produced by a plant is important for environmental, food and feed safety reasons, especially as some proteins are immunogenic, potentially even allergenic.[28]

2.4 Changes to the chemical composition of plants

There is also a danger that changes to plant genetic material, both intended and unintended, could unexpectedly alter the chemical composition of plants[29]. Plants produce chemicals for many important purposes such as defence against herbivores or to attract insect pollinators. Changes to chemical composition could also affect the nutritional quality or even the toxicity of the GM food/feed product. Unintended changes in plant secondary chemistry can also occur in conventional breeding. However, in GM plants there is potential for more radical unintended alterations to plant chemistry than there is with conventional breeding.[30]

Such changes could affect the toxicity or palatability of these plants to wildlife. For example, an increased susceptibility to aphid infestation in certain GM maize varieties appears to have been due to differences in both amino acid composition and secondary metabolites between the GM lines and non-GM counterparts.[31] Changes in secondary metabolites could also affect how weedy and vigorous a GM crop is - an important environmental impact if outcrossing to wild or weedy relatives were to occur.[32]

As a 2014 paper in *Trends in Biotechnology* observes:

> "*If organisms modified with genome editing in which a gain of function unintentionally arises are released without rigorous risk assessments, they may rapidly affect the local ecosystem by seriously threatening native species. Even if they do not pose a serious threat to native species, the released organisms may negatively affect the environment owing to cross breeding.*"[33]

2.5 Land use changes

The use of crops created using new GM techniques may also result in detrimental changes in agricultural practices. For example, in a 2012 review of the use of new GM techniques in plant breeding, all of the crops developed by ODM and SDNs were herbicide tolerant.[34] This is also true for the vast majority of commercialised GM crops and has led to a massive increase in herbicide use.[35] In South America, extensive areas of rainforest have been cleared to grow GM soybean and corn varieties. This has resulted in regional and global environmental impacts.[36]

2.6 Socio-economic impacts

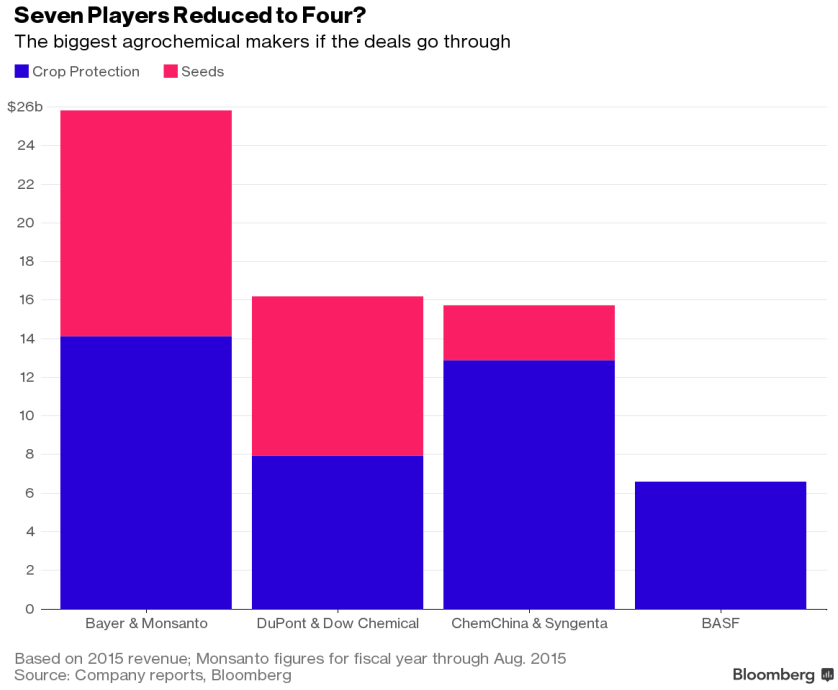
Evidence from the food industry and farming experiences worldwide shows that the cultivation and trade of GM crops has far-reaching social and economic impacts that make the real costs of GM crops and foods more expensive for tax-payers, farmers and companies involved in food production.

Conventional and organic farmers, beekeepers, seed developers, and the whole food production chain, are constantly threatened by contamination from GM crops. GM contamination jeopardises access to markets and increases the need for testing and Quality Assurance. In the food sector, GM contamination is not covered by any regulations. Instead, Australian Government policy requires non-GM stakeholders in the food industry to bear the additional costs of measures to secure their GM-free status. In effect, those that suffer from contamination are forced to clean up at their own expense, while the GM polluter profits.

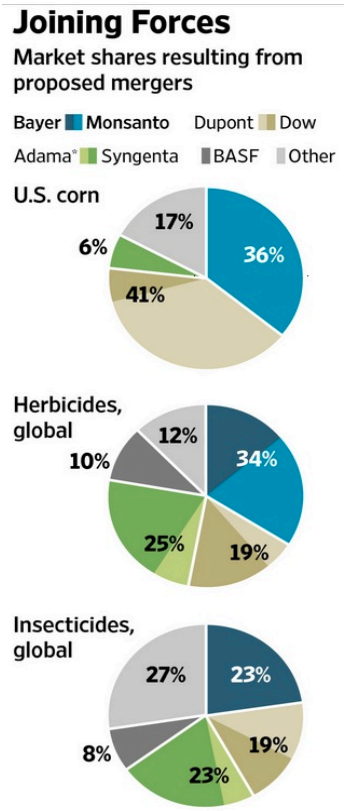
The costs of segregating GM and conventional crops, as well as for testing, currently falls on the conventional and organic sectors, distorting the market in favour of big agribusiness and less sustainable farming practices. Biotech companies, traders and other GMO users must take full responsibility for preventing contamination and ensuring that the conventional and organic markets can flourish without unjust financial burdens.

Biotech companies are also slowly taking control of the food chain, from seed to spoon. As well as owning GM patents, they are obtaining patents and plant breeders rights on genetic traits used in conventional crops. These monopoly powers enable them to exert tremendous power over the market to maintain repeated seed and chemical sales year on year, shifting the balance of economic power towards the biotechnology, seed and agrichemical conglomerates. As a result, farm-saved seeds are under threat – as well as local varieties of crop plants and agricultural biodiversity.[37]

Mergers of agrichemical and GM corporations now in progress would lead to just four mega entities dominating most of the global seed and agricultural chemical supplies and markets.[38]



Source: ETC Group (2016) *The Industrial Food Chain's Recipe for a Box Lunch: Briefing Note*, 31/5/16[39]



Source: *Wall Street Journal*[40]

2.7 Specific concerns associated with ODM and SDN

All forms of ODM and SDN can result in unexpected mutations – termed 'off-target effects'. These can result in the production of toxins. Unlike radiation and chemical mutagenesis techniques - which produce essentially random mutations - ODM and SDN can be used to make targeted changes to the genome, resulting in pronounced and often unintended effects. They can also be used sequentially, to make even more dramatic changes to the genome. Genomes are complex systems in which a single change can cascade into changes in the form and functioning of other parts of the system.

A discussion of these two techniques and the specific risks associated with them follows.

Oligo-directed mutagenesis (ODM)

This involves introducing short DNA fragments (oligonucleotides) into cells which trigger the cell to modify its own DNA by matching the introduced DNA fragments - allowing targeted changes to be introduced.[41] This technique can change, insert or delete one or a few base pairs of DNA.[42]

There are four types of ODM approaches:

- Single-stranded oligo-deoxynucleotides (SSOs or ssODMs);
- Chimeric RNA-DNA oligonucleotide molecules (RDOs);
- Small Fragment Homologous Replacement (SFHR);
- Triple helix-forming oligonucleotides (TFOs).[43]

According to a recent review commissioned by the Norwegian Environment and Development Agencies, there is still scientific dispute over how these techniques even work and there is evidence that the different types of oligonucleotide molecules may trigger distinct cell responses.[44]

It asserts that most of the published ODM studies use animal cells and there is a:

> *"lack of published scientific literature for ODM techniques applied to plant species. This poses extra challenges for the identification of potential unintended effects and thus raises knowledge gaps."*[45]

The review also notes that there have been no studies looking at the unintended impacts of ODM in plants.[46] Unintended effects associated with ODM in animal cells include cell death and unpredicted mutations.[47] The authors argue that until more studies determine exactly how oligonucleotides function, it will be difficult to conduct any research into possible unintended effects.[48]

Another review by the Austrian Environmental Agency also concluded that:

> *"neither the efficiency nor the specificity of the ODM technology can be sufficiently controlled" and it observes that ODM may lead to off-target mutations.*[49]

And that such effects:

> *"may also not be easy to anticipate, as single mutations can have relevant effects, e.g. lead to an increase in expressed plant toxins."*[50]

The Agency warns of the possibility of the following unintended effects with ODM:[51]

- Unexpected mutations adjacent to the target site;
- 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 ODM- oligonucleotides into the target cells. These can involve chemicals or bombardment using a gene gun;
- The integration of the ODM oligonucleotides into the plant genome similar to the integration of transgenic DNA;
- Changes in gene expression.

Site-directed nucleases (SDNs)

These gene-editing techniques - also referred to as site-specific nucleases (SSN)[52] - 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. 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.[53]

These techniques can be subdivided into three different subcategories[54]:

- 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;[55]
- SDN-2 cuts the DNA and provides a DNA template (donor DNA) containing the desired mutations i.e. nucleotide substitutions or short insertions/deletions. It can be used to repair undesirable spontaneous mutations or to introduce new genes;
- SDN-3 uses a large stretch of donor DNA and can result in the integration of large DNA fragments (transgenes).

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.[56]

- **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;[57]
- **Meganucleases/homing endonucleases**
    - These are naturally occurring DNA cutting enzymes that have been isolated from a range of organisms including yeast and green algae;[58]
- **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;[59]
    - 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'.[60]

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.[61]

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."*[62]

According to the Austrian Environmental Agency[63] 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.[64] 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.[65]

The Austrian Environment Agency's review also found that ZFNs result in significant unexpected mutations.[66] This is also an important problem for the TALEN technique and, according to another recent review, can result in severe side effects.[67] Fine *et al.* (2014) highlighted that indentifying 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.[68]

Studies suggest that CRISPR results in even more off-target mutations than ZFN and TALENs.[69] For example, a recent study found that CRISPR/Cas9 can result in hundreds of unexpected mutations.[70]

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,[71] therefore:

> *"comprehensive untargeted profiling methods (such as omics) should be applied in order to detect and identify unintentional mutations in the entire host genome."*[72]

Risks common to both techniques

Biosecurity risks

If the OGTR allows these new GM techniques to be deregulated, anyone from amateur biohackers - to industry - to terror groups would be free to use them to genetically modify plants, animals and microbes. Entirely new diseases and poisons could be made. And they could enter our food chain and our environment with no safety testing and no labelling. The results could be catastrophic.

Gene editing techniques such as CRISPR/Cas9 have been deemed "weapons of mass destruction and proliferation" in the US Government's annual worldwide threat assessment report this year.[73] Yet all of the options outlined in the OGTR's discussion paper, apart from Option 2, would leave applications of these techniques and their products unregulated.

Market impacts

If these techniques were deregulated in Australia, before being approved in key export markets, the impacts on Australia's commodity exports could be disastrous.

The European Union has yet to make a decision on whether it will regulate these new GM techniques and their products as GM. The decisive view on the matter will be made in the European Court of Justice. It will rule in the next 18 months on whether or not new GM techniques, including ODM, ZFN1, TALENs, and CRISPR/Cas9, fall under EU GMO law.[74]

Australia's key trading partners have zero tolerance policies for unapproved GMOs in commodity trade, as illustrated by this statement from the EU Commissioner for Health and Consumer Protection:

> *"There is no flexibility for unauthorised GMOs - these cannot enter the EU food and feed chain under any circumstances."*
>
> Markos Kyprianou, EU Commissioner for Health and Consumer Protection[75]

A survey of country governments conducted by the Food and Agriculture Organisation (FAO) found that 73% of them have zero tolerance for unapproved GM varieties.[76] The FAO found that between 2002 and

2012 there were 200 cases of trade disruptions due to the presence of unapproved GMOs. The majority of the cases happened between 2009-2012, indicating increasing market sensitivity and trade problems.

Were Australia to deregulate the new GM techniques, it could have dramatic impacts on our access to overseas markets for all food exports.

If, for example - as appears likely - Europe declares all the new techniques are GM, traceability and zero tolerance for any GM contamination would be mandatory - as would testing protocols to detect the GMO. Without regulation, traceability cannot be assured, and without traceability Europe's zero tolerance policy could see a halt to EU food imports from Australia.

There are numerous examples of costly market rejection and disruption due to the presence of unapproved GMOs in export shipments. These include:

Triffid flax
When an unlicensed GM flax variety was found in a shipment to Japan, 35 countries closed their borders to Canadian flax exports, including 28 in the EU which accounts for 60 per cent of Canada's flax export market. A University of Saskatchewan study estimated the cost to the Canadian flax industry in the first year alone to be $29 million.[77]

Viptera corn
In 2015 the Swiss company Syngenta released a GM corn variety to market before it had been approved in key export markets, resulting in a Chinese import ban. The National Grain and Feed Association calculated the loss to farmers to be nearly US$3 billion.[78]

StarLink corn
This was a massive supply chain contamination incident involving a GM corn approved for animal feed but not for human foods. It resulted in the largest food product recall in history and is estimated to have cost US companies US$1 billion.[79]

LibertyLink rice
In 2006, an unauthorised variety of GM rice was detected in US exports. According to the US Rice Federation, "a robust long grain rice export market nearly vanished overnight".[80] The total cost to the US rice industry of the LibertyLink 601 contamination is estimated at around US$1 billion.

All the new GM techniques involve *in vitro* nucleic acid techniques and so fall under the Codex Alimentarius and Cartagena Biosafety Protocol definition of 'modern biotechnology'. Other countries could therefore reject shipments containing products derived from these new GM techniques that haven't been assessed for safety, without fear of World Trade Organisation reprisals. They are also subject to Liability and Redress under the Cartagena Protocol - which could prove very expensive.

Regulatory standards have proven to be the minimum standards that food exporters must meet. Market requirements are often far more stringent than regulatory requirements. For example, in Europe more than 40 GM foods are approved for human consumption, but barely any are actually present in the human food supply, because of the policy positions of food companies. Ultimately, food companies in overseas markets will determine whether new GM techniques are viewed as GM - not only governments or our regulators.

Food companies are a long way from coming to any final position on the products of these new GM techniques and it could be some time before they do. Therefore, the prudent position from a food

exporting perspective is to regulate all the new GM techniques and their products, then wait to see how the marketplace responds - not to commit supply chains to new GM products until there is more clarity.

Already a number of non-GM and organic certifiers have stated that they consider these new techniques GM. These include Verband Lebensmittel ohne Gentechnik (VLOG) - a German Industry Association representing over 350 companies with combined annual sales exceeding 170 billion euros.[81] The association recently released a statement arguing that plants and animals produced using these techniques should be regarded as GMOs. The association stated the products should be assessed for safety and labelled to ensure supply chain integrity.[82]

The European branch of the global peak organic industry body IFOAM (International Federation of Organic Agriculture Movements) has also released a position paper stating that it classifies these new techniques as GM.[83]

In the US, the Non-GMO Project has stated that it considers all the new techniques GM.[84] The US National Organic Standards Board (NOSB) has also recommended that the US Department Agriculture prohibit the use of these techniques in organic agriculture.[85]

It was in recognition of the potential market impacts of these new GM techniques that the New Zealand Government announced earlier this year that it will regulate them as genetically modified organisms (GMOs). On making the announcement New Zealand's Environment Minister Dr Nick Smith stated:

> *"The rationale for our cautious approach is that New Zealand is an exporter of billions of dollars of food products and we need to be mindful of market perceptions as well as the science. We will continue to monitor global rules around the regulation of GMOs and adapt our system over time in line with international developments."*[86]

3.Is there any scientific evidence that any of options 2-4 would result in a level of regulation not commensurate with risks posed by gene technology?

For the reasons already highlighted in our answer to question 2, we believe that all of the options presented would result in a level of regulation not commensurate with the risks posed by the new genetic modification techniques. We are led to this conclusion by the exclusion from consideration of null segregants produced using Techniques to Support Breeding such as Seed Production Technology (SPT).

We also assert that options 1, 3 and 4 are not commensurate with the risks posed by SDN and ODM. In its discussion paper the OGTR correctly states that:

> *"for pests or disease-causing organisms, for example pathogenic microorganisms, small sequence changes might give rise to significant risks. Blanket exclusions may not be commensurate with the level of risk posed by these techniques."*

We strongly agree with this statement and would add that small changes to the genomes of plants, animals and microbes can also result in significant changes to their phenotypes, with unforeseen wider consequences for ecological systems. Furthermore, unlike mutagenesis - which results in random mutations - ODM and SDN1 can be used sequentially to make dramatic, targeted changes to the genome. For example, using SDN1 or ODM a bacterial genome could theoretically be re-engineered sequentially to create an organism that produces the anthrax toxin.

All ODM and SDN techniques are also associated with off-target effects and the GMOs they produce need

to be rigorously assessed for safety before being released into the environment and the food chain.

Even the way that some ODM techniques work is still hotly contested among scientists. The idea of deregulating something that scientific experts still do not fully understand flies in the face of the precautionary principle which should be applied to all these decisions.

4. How might options 2-4 change the regulatory burden on you from the gene technology regulatory scheme?

This question is targeted at industry and institutions, reflecting the pro-industry bias of the consultation process. Since the present law already defines the new GM techniques and their products as subject to OGTR regulation and licensing, option 2 (augmented) should pose no additional regulatory burden on IBCs or industry.

5. How do you use item 1 of Schedule 1, and would it impact you if this item was changed?

This question again targets Institutional Biosafety Committees and industry, reflecting a pro-industry and institutional bias in the consultation processes. The interested public also has a legitimate interest in ensuring that regulatory settings are appropriate to the public interest.

Genetically modified organisms are allocated to various categories on the basis of perceived risk, for regulatory purposes. The lower risk categories such as Exempt or NLRD should not apply to the new GM techniques about which so little of their wider health and ecological impacts is yet known or understood. All projects that employ the new GM techniques for research or as a process of production, and the products made, should initially be regarded as potential biohazards and biosecurity risks. When much more is known about them and their potential for unforeseen consequences then perhaps their status as high-risk activities may be reviewed. Until then they should all be strictly regulated.

6. Might contained laboratory research on GM gene drive organisms pose different risks to other contained research with GMOs, and how could these risks be managed? Supporting information and science-based arguments should be provided where possible.

CRISPR gene drives carry even more biosafety and biosecurity hazards and risks than the older cut-and-paste GM techniques and genetically engineered organisms. When gene drives are engineered into fast-reproducing species they could theoretically alter their whole populations within short timeframes, from months to a few years, and may lead to species extinction. Unexpected mutations may also result. The potential implications for the environment, food security, peace, and even social stability are significant and unmanageable.

According to a recent report by the US National Academy of Sciences:

> *"There are considerable gaps in knowledge regarding a gene drive's effectiveness, both on the target organism and the environment, over time and across diverse genetic backgrounds. It is also essential to consider how gene drives will propagate throughout a population and affect not only the target species, but its entire ecological community.*

> *"Because gene-drive modified organisms are intended to spread in the environment, there is a widespread sense among researchers and commentators that they may have harmful effects for other species or ecosystems. For example, using a gene drive to suppress a non-native weed population may lead to unexpected consequences, such as the loss of habitat for native species or even the establishment of a second, more resilient invasive species."*[87]

Gene drives are intended to not only persist in nature but to also spread, and diminish or overwhelm wild species. A gene drive that spreads in the wild will also be subject to mutation and evolutionary pressures. The gene drive may fail to work, or the arising mutations may persist and spread through the whole population - with knock on effects to other species.

In addition, the underlying technology of CRISPR/Cas9 has been found to cause off-target effects (unintended breaks and insertions within the genome).[88]

These could cause unexpected phenotypes, and other genetic expressions and behaviours in the targeted species. By building the molecular 'scissors' of CRISPR/Cas9 into the genome and letting them repeat their actions over many generations, the risk of off-target cuts and unpredictable effects may be magnified. At this point in the development and understanding of gene drives, it is counter to the existing scientific evidence to present gene drives as a reliable mechanism with predictable future outcomes. They will be living, changing genetic elements, replicating beyond human control, prediction or recall.

Existing rules for containment of GMOs presume that escapees will have a manageable and limited persistence in the environment. Even so, rates of genetic contamination in agricultural crops and weed species by GMOs shows that even this assumption is tenuous. While gene drive developers claim there may in future be technical and geographical means to effectively contain gene drives, these hypothetical claims and assumptions need to be rigorously examined and tested before any releases are contemplated. Similar claims were made for the removal of antibiotic resistance marker genes from older GM organisms, because of their potential to be a health hazard, but these promises were never honoured.

Strict laboratory handling and containment rules for all gene drive research should be internationally agreed upon, and put into practice, before further research proceeds, even in the lab.

An immediate, international halt to gene drive releases and experimentation is necessary until such a framework is put in place globally under relevant, enforceable international instruments such as the Cartagena Biosafety Protocol.

OGTR advice in the document '*Regulatory requirements for contained research with GMOs containing engineered gene drives*' states that:

> *"Any GMO with a functional engineered gene drive is considered to have an advantage (as defined in regulation 3) due to its enhanced ability to contribute to the gene pool, and a minimum containment level of PC2 is required [Schedule 3 Part 2.1 (aa)]."* [89]

Public and independent scientists should have been invited to participate in the development of this guideline. Given the uncertainties now surrounding gene drives, we consider PC2 containment insufficient.

Research using gene drives has the deliberate intention that genes and genetic traits – especially those designed to drive disease carrying organisms to extinction – may be rapidly disseminated through entire populations of the host organism. But the ecological and other potentially negative consequences of such modifications and extinctions are as yet almost entirely unknown.

We therefore propose that a moratorium be placed on all gene drive research and commercial dealings while more scientific evidence is commissioned and accumulated on their potential negative impacts on public health, safety and the environment.

7. What RNA interference techniques are you using, and are there RNA interference techniques that you believe have unclear regulatory status? Please provide details of the techniques and science-based arguments for whether these techniques pose risks to human health or the environment.

Again this question is targeted at researchers and industry, reflecting the pro-industry bias of the consultation process.

Changing the nature, kind and quantity of particular regulatory-RNA molecules through genetic engineering can create biosafety risks. The potential hazards posed by RNA interference (RNAi)—based pesticides and genetically modified crops are well documented in the literature. These include off-target gene silencing, silencing the target gene in unintended organisms, immune stimulation, and saturation of the RNAi machinery.[90]

As Latham and Wilson (2015) observe

> *"The effects of long dsRNAs on mammalian cellular functions are typically profound and extend to complete inhibition of protein translation and cell death. Nevertheless, the implications of such molecules in the mammalian diet have hardly been tested."*[91]

To characterise, assess and mitigate any adverse effects arising from changes to RNA requires changing current approaches to the risk assessment of GMOs and we recommend the approach proposed by Heinemann *et al*.[92]

8. Do you have proposals for amendments to any other technical or scientific aspects of the GT Regulations? All proposals should be supported by a rationale and a science-based argument.

We recommend that all new GM techniques be regulated as GMOs and placed in the highest risk category initially, including ODM, SDN, RNA Inference, Seed Production Technology (SPT), Reverse Breeding and Accelerated Breeding. We have already outlined the rationale and science-based case for this in our responses to questions 1 and 2.

We support the findings of the reviews commissioned by the Austrian and Norwegian governments. These concluded that there is as yet insufficient understanding of the risks these new GM techniques pose and that products derived from them should all require a comprehensive case-by-case risk assessment - including full molecular characterisation.[93]

It is apparent from the Discussion Paper that the OGTR is under pressure from industry to use a product-based approach to regulation as used in the US and Canada, rather than the process-based approach used in the rest of the world. A product-based approach is unscientific as it does not assess the unique risks generated by genetic engineering techniques themselves.

We also disagree with the characterisation of this process as a technical review – it's not. The OGTR is looking at fundamentally altering the legislative approach to GM regulation, without reference to the

parliament or proper public participation processes. This raises much broader issues, which it is clear the OGTR has not discussed in this paper and are far beyond the scope of the OGTR's remit.

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