Friends of the Earth

GM 2.0
AUSTRALIAN REGULATORS ENGINEERING THE TRUTH

CONTENTS

EXECUTIVE SUMMARY

In recent years large agrochemical companies such as Dow, Syngenta, Bayer, Monsanto and other players have been investing in a suite of risky new genetic modification (GM) techniques, which industry refers to collectively as 'New Plant Breeding Techniques'. Industry is arguing that these techniques are much more precise than older genetic engineering techniques - or even that they are not really genetic engineering at all – in order to attempt to circumvent regulation and public resistance to GMOs.

Now the GM giants are making a concerted push to have these emergent techniques escape GM laws in the United States, Europe and Australia. Industry is arguing that these techniques – which include oligo-directed mutagenesis (ODM) and site-directed nucleases (SDNs) such as zinc-finger nucleases (ZFN) and CRISPR[1] - only result in small predictable changes to the genome and are therefore much more precise that earlier genetic engineering techniques. Interestingly, this is exactly the same argument they used when GM crops were originally introduced – and is equally untrue for these techniques.

Unfortunately, our regulators - the Office of the Gene Technology Regulator (OGTR) and Food Standards Australia New Zealand (FSANZ) - seem all too ready to allow products derived from these risky new techniques to go untested and unlabelled into our food chain.

New genetic engineering techniques such as ODM and SDNs both rely on the natural DNA repair systems of the plant, which we still do not fully understand. Consequently, even the way these techniques work is still hotly contested among scientists. 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.*"[2]

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 of the biosafety risks, is that there is insufficient knowledge regarding the risks posed by these techniques. 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. [3]

The Norwegian Environment and Development Agencies also recently commissioned a review of these techniques. This concluded that further biosafety research needs to be performed before these techniques are commercialised.[4]

The Australian Gene Technology Act[5] defines gene technology as "any technique for the modification of genes or other genetic material". This would clearly include new GM techniques unless they were specifically exempted in the regulations. Unfortunately, our regulators - the Office of the Gene Technology Regulator (OGTR) and Food Standards Australia New Zealand (FSANZ) - are already working closely with industry to deregulate these techniques.

On its website the OGTR professes a commitment to "accountability: through open and transparent processes".[6] However, documents obtained by Friends of the Earth under Freedom of Information laws reveal that the assistant Health Minister Fiona Nash gave policy approval for drafting amendments to the Gene Technology Regulations on 8th July 2015 and that the agency has already issued drafting instructions to deregulate a number of these new GM techniques.[7] This has occurred without any public input or consultation. Furthermore, it appears the agency has misled the Senate – claiming in Senate Estimates that drafting instructions have not yet been issued.[8] Questions asked by Senator Rachel Siewert reveal that the OGTR plans to conduct public consultation on these proposed changes in early 2016.[9]

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 GM techniques should be considered genetic engineering. Furthermore, FSANZ also appears to have deliberately misled the Senate, in response to Senate questions, by stating "*FSANZ is not aware that any members of the expert panel have potential conflicts of interest.*" FSANZ would have been aware of these patents and other potential conflicts at the time, as this information is well documented and publicised.

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[10] - conclusions strongly disputed by overseas regulators.[11]

It's time our regulators stopped letting industry write the rules for them and put public health and our environment before private profit.

Friends of the Earth is calling for:

- These new GM techniques and the products derived from them to be subject to a comprehensive case-by-case risk assessment, including full molecular characterisation and independent safety testing to minimise any potential risks to human health and the environment;
- All products derived from new GM techniques to be labelled to protect choice for farmers, producers and consumers;
- The precautionary principle to be enshrined in both the Gene Technology Act and the Food Standards Australia New Zealand Act, given the experimental nature of these technologies and the risks associated with them;
- The Government to impose strict liability on all dealings with GMOs licensed by the OGTR, so that liability for GM contamination and the resultant losses and costs rests fully on the licensees and the owners of GM patents;
- A moratorium on the commercialisation of these new GM techniques until our regulatory system for GMOs is adapted to deal with the potential risks posed by them.

1. These techniques pose unknown risks and need to be regulated

Some of these techniques are being referred to by industry as 'gene editing' - implying a level of precision that simply does not exist. These techniques include oligo-directed mutagenesis (ODM) and site-directed nucleases - such as zinc finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), meganucleases (MN) and the clustered regularly interspaced short palindromic repeat (CRISPR/Cas) system. Some of the other techniques such as agroinfiltration, reverse breeding and transgrafting use GMOs developed by standard methods in new ways. Cisgenesis can use both standard and new techniques – it is genetic engineering but uses genes from the same or closely related species.

The concerns associated with the use of these new GM techniques are the same as those raised by older genetic engineering techniques. These include food safety concerns,[12] environmental impacts - including those on biodiversity[13]- and GM contamination of neighbouring non-GM crops or wild relatives.[14]

1.1 Unexpected effects

The main concern regarding new GM techniques, as well as older genetic engineering techniques, is that they can unintentionally interfere with the functioning of an organism's genome - namely gene expression.

Despite GM crops being commercialised, the precise way in which the plant's regulatory network functions is still poorly understood. This is illustrated by recent advances in epigenetics[15] and the current debate over whether all of the "junk" DNA in the human genome is actually "junk" - or if it performs regulatory functions[16]. Because of this lack of understanding of gene regulation, it is not possible to predict all the effects of the genetic engineering process. Unintended changes to plant chemistry arising from the use of new GM techniques may result from:

- unforeseen interactions between the 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).[17]

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 discussed, they vary in the way that they operate. For a more detailed explanation of each of these techniques and the risks posed by them see Appendix 1.

Table 1: Unexpected effects associated with new GM techniques[18]

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.[19]
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.[20] » Stably inherited alterations to affect gene expression; » Horizontal gene transfer between the rootstock and the rest of the plant; [21] » 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.[22]
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. [23]
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.

1.2 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[24] and rearrangements of host DNA adjacent to the intended genetic insert.[25] Although gene-editing techniques such as CRISPR, ZFN and TALENs have been touted as much more precise than genetic engineering, off-target effects have also been found to occur with all these techniques.[26]

1.3. 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 is likely to be characterised, altered proteins or unintended novel proteins may not 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.[27]

1.4 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[28]. Plants produce chemicals for many purposes such as defence against herbivory or to attract insect pollinators. Changes to chemical composition could 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.[29]

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.[30]. Changes in secondary metabolites could also affect how weedy and vigorous a GM crop is - an important environmental concern should outcrossing to wild or weedy relatives be possible.[31]

As a recent 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."*[32]

1.5 Land use changes

The use of these crops 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.[33] This is also true for the vast majority of commercialised GM crops and has led to a massive increase in herbicide use.[34]

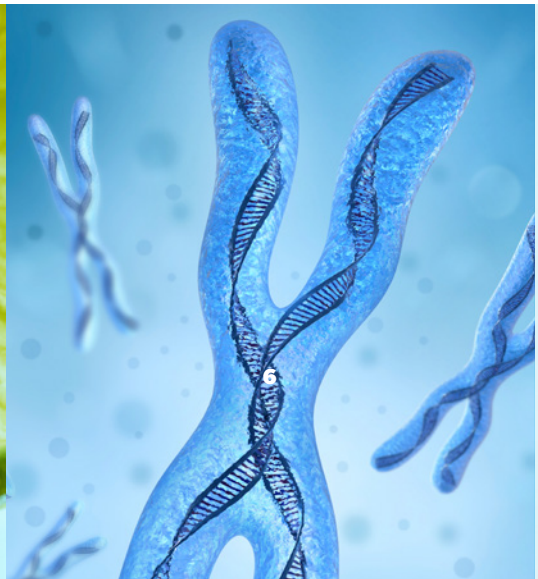
1.6 Socio-economic impacts

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; making the real costs of GM crops expensive for tax-payers, farmers and companies involved in producing our food.

Conventional and organic farmers, beekeepers, seed developers, as well as the whole food production chain, are constantly threatened by contamination from GM crops. In the food sector, contamination is not covered by any regulations. Instead, Australian Government policy requires mostly non-GM stakeholders in the food industry to pay for 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 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 unsustainable farming practices. Biotech companies, traders and other GMO users must take responsibility to prevent contamination to ensure that the conventional and organic market can flourish without unjust financial burdens.

Biotech companies are also slowly taking control of the food chain, obtaining patents on genetic traits used in conventional and GM crops. These powers enable them to exert tremendous power over the market to maintain repeated sales year on year, shifting the balance of economic power towards the biotechnology companies. As a result, farm-saved seeds are under threat – as well as local varieties of crop plants and agricultural biodiversity.[35]



2. How should these techniques be regulated?

Industry has argued that certain techniques such as ODM, SDN-1 and SDN-2 only result in small, intentional changes to the plant genome, similar to traditional mutagenesis, and therefore do not need to be regulated. It is true that they may typically involve intentional changes to a small number of DNA bases but the techniques used are considerably different from traditional mutagenesis.

New GM techniques may be more precise in their positioning of the intended alteration to genetic material than older genetic engineering techniques but studies show these techniques can still result in unexpected and unpredictable effects. These effects can arise from unforeseen genomic interactions associated with the novel genetic material, genomic irregularities and changes to the secondary chemistry of the plant.[36]

As mentioned in section 1, unexpected effects have been observed for all of these techniques. And as Agapito-Tenfen and Wikmark (2015) point out that "*these techniques are too new to make strong claims that all outcomes are predictable and known*".[37] Many of these GM techniques are new so it is not yet possible to fully evaluate the potential for unintended changes. However, it is evident that unintended changes to genetic material cannot be excluded, and indeed, might even be expected. Although more targeted than the random insertion of genes into plant genomes seen with older genetic engineering techniques, the potential for unforeseen genomic interactions, genomic irregularities and unintended biochemical alterations still remain with new GM techniques.[38]

The review by the Austrian Environment Agency concluded that "*partly such unintended effects would be similar as for crops developed by GM technology, due to the fact that comparable methodological steps are involved... Respective risk issues thus need to be addressed by a comprehensive molecular characterisation, taking into account the experiences with risk assessment of GMOs.*"[39]

It has also been suggested that cisgenic GM plants do not carry the same risks as transgenic GM plants because the components are derived from the same or closely related species.[40] However, the genetic engineering process is identical for cisgenesis, intragenesis and transgenesis (where the genes are from an unrelated species), regardless of the origin of the inserted genes. Therefore, the concerns regarding unintended genetic changes and unforeseen genomic interactions - that could have an adverse effect on human health or the environment - remain the same.[41]

As noted in section 1, all the new GM techniques discussed have the potential to cause unintended effects. These could have serious consequences for the environment, food and feed safety. A process-based safety assessment approach for crops derived from new GM techniques is therefore important - because it requires any detected unintended changes to be assessed for their implications to the environment, human and animal health. This is in addition to assessing the consequences of the new characteristics of the plant.[42]

It also should be taken into account that all of these techniques can be used to change longer sequences of DNA if applied repeatedly - as in the case of "multiplex automated genome engineering".[43] This method can be compared to an assembly line that goes round in circles with many workers introducing small changes every time the cell passes around.[44] As the Netherlands Commission on Genetic Modification (COGEM) states, in its consideration of ODM "a successive cycle of directed mutagenesis could introduce an entirely new sequence"[45].

There is strong evidence that the current regulatory regime does not adequately assess the safety of GMOs, particularly their long-term health impacts[46]. However, the current regulatory approach to GMOs should be the minimum requirement for these new GM techniques (despite its shortcomings) because it at least provides a basis for assessing any potential risks that result from the genetic engineering process. Unintended changes could impact food, feed and environmental safety but there would be no requirement for these to be detected and assessed if such plants are exempt from GMO regulations.[47]

If any of the plants resulting from new GM techniques were exempted from the GMO regulations, they would also be exempt from GMO labelling regulations for GMO seeds, crops and food/feed products. This would mean that farmers, producers and consumers who wish not to grow, use, or eat foods derived from genetic engineering technologies could be restricted in the choices available to them.[48]

2.1 Current regulatory regimes need to be improved

Although existing GM crop regulations are a good starting point for the regulation of these new techniques, other criteria need to be incorporated into risk assessments to help address potential hazards. According to a recent review commissioned by the Norwegian Environment and Development Agencies it is impossible to predict what mutations may occur due to the use of SDNs, therefore:

> *"comprehensive untargeted profiling methods (such as omics) should be applied in order to detect and identify unintentional mutations in the entire host genome."*[49]

Companies are not currently required to submit this information to either Food Standards Australia New Zealand (FSANZ) or the Office of the Gene Technology Regulator (OGTR) as part of the approval process for GM crops.

2.2 The trade implications of regulation

The UN Cartagena Protocol on Biosafety deals with the import and export of living GMOs. A key element of its definition of living modified organism (LMO) is that the genetic material has been altered by direct intervention through "modern biotechnological techniques". The Protocol defines modern biotechnological techniques as "*in vitro* nucleic acid techniques, including the use of recombinant DNA and direct injection of nucleic acid into cells or organelles" and cell fusion "that overcome natural physiological reproductive or recombinative barriers and are not techniques used in traditional breeding and selection".[50] These new GM techniques would clearly fall under this definition.

When announcing the New Zealand Government's recent decision[51] not to deregulate these new GM techniques the country's Environment Minister Dr Nick Smith said:

> *"New Zealand is an exporter of billions of dollars of food products and we receive a premium for our natural brand and high quality standards. These are minimalist changes because we do not want New Zealand getting ahead of market perceptions of these new biotechnologies."*[52]

There is zero tolerance for unapproved GM content in many of Australia's major export markets. That makes it essential to have prior assessment of not just the environmental and human health impacts, but also the economic impacts of any use of GMOs. Regulating these new techniques as GM is vital for the protection of food exporters.

As a major agricultural exporter, if Australia were to exempt any of these techniques from regulation it could result in serious trade implications.

2.3 Deregulating these new techniques would increase biosafety risk

The deregulation of these new techniques would lead companies to preference new, unregulated techniques over regulated approaches, at a time when we are only just beginning to understand the risks associated with them. It would also reduce the incentive to undertake biosafety research into these techniques, thus prolonging ignorance or uncertainty.

Independent safety testing standards and requirements are typically established by regulation. They are therefore unlikely to be developed if there is no legal requirement to conduct biosafety research according to independently agreed standards.

Detecting the products of some of the new techniques will also be difficult without regulatory requirements that ensure that the relevant information is in the public domain. This could make recall in the event that any adverse effects are detected extremely difficult.

Removing potentially harmful GM crops from the food chain has proven difficult enough as it is, without this additional problem - as illustrated by the example of StarLink. This unapproved GM maize variety was found to have contaminated the US food supply in 2000. Concerns were raised regarding its potential allergenicity and the product was recalled. Despite a costly recall, StarLink contamination was still being found in food as recently as 2013. [53] Agapito-Tenfen& Wikmark (2015) therefore call for further research into the practical and technical constraints of detecting products derived from these techniques.[54]

2.4 Further biosafety research is needed before these crops are commercialised

The recent review commissioned by the Norwegian Environment and Development Agencies stresses the limitations in our understanding regarding the potential adverse effects of these techniques. The authors argue that:

> *"according to the requirements of a scientifically based risk assessment and the application of the precautionary principle, further biosafety research needs to be performed a priori to commercial release."*[55]

3. The complicity of our regulators

3.1 The Office of the Gene Technology Regulator (OGTR)

The OGTR is the Australian regulator responsible for

> *"protecting the health and safety of people and the environment by identifying risks posed by or as a result of gene technology, and by managing those risks"*[56]

On it's website the OGTR professes a commitment to "accountability: through open and transparent processes".[57] However, documents obtained by Friends of the Earth under Freedom of Information laws reveal that the Assistant Health Minister Fiona Nash gave policy approval for drafting amendments to the Gene Technology Regulations on 8th July 2015 and that the agency has already issued drafting instructions to deregulate a number of these new GM techniques.[58] This has occurred without any public input or consultation. Furthermore, it appears the agency has misled the Senate – claiming in recent Senate Estimates hearings that drafting instructions have not yet been issued.[59] Questions asked by Senator Rachel Siewert in Senate Estimates reveal that the OGTR plans to conduct public consultation on these proposed changes in early 2016.[60]

The OGTR has also advised Dow AgroSciences that crops developed using its ZFN based EXZACT Delete technology, where the ZFN genes are purportedly no longer present, would not be considered a GMO and therefore would not be regulated under the Gene Tech Act.[61]

3.2 Food Standards Australia New Zealand (FSANZ)

FSANZ develops standards that regulate the use of ingredients, processing aids, colourings, additives, vitamins and minerals, including foods developed using new technologies such as genetically modified foods.[62]

According to the Food Standards Australia Act, two key goals of FSANZ are to achieve "a high degree of consumer confidence in the quality and safety of food produced, processed, sold or exported from Australia and New Zealand" and "the provision of adequate information relating to food to enable consumers to make informed choices."[63]

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 GM techniques should be considered genetic engineering. Two workshops were held which were chaired by Professor Peter Langridge, who was then Director and CEO of Australian Centre for Plant Functional Genomics.

According to the Centre's 2013 Annual Report the center has 73 gene technology related global patent applications either filed or granted.[64] Peter Langridge is named as an inventor on a number of these.[65]

The centre also has collaborations with DuPont Agricultural Biotechnology and Dow Agrosciences - one of the largest multinational seed companies.[66]

The new GM techniques that the Centre has conducted research in include:

- Cisgenesis in wheat[67]
- Genome editing in wheat using CRISPR/Cas9.[68]
- Seed Production Technology in wheat.[69]

Other panelists were:

Distinguished Professor James Dale

Professor Dale is the Director of Centre for Tropical Crops and Biocommodities, Queensland University of Technology which specialises in the genetic modification of tropical crops such as sugarcane, bananas, tobacco, papaya and taro.[70] According to FSANZ, Professor Dale is listed as an inventor on 9 granted patents or patent applications.[71]

Dr Andrew Granger

Dr Granger is the Australian Director of Research of Plant and Food Research – a New Zealand company that specialises in the "commercialisation of research-based innovation"[72] and has a number of gene technology patents.[73]

Dr Roger Hellens

Dr Hellens is a former science group leader in genomics at Plant and Food Research and is currently a Professor of Agricultural Biotechnology at Queensland University of Technology. He is listed as an inventor on several granted gene technology related patents or patent applications.[74]

Professor Bernard Carroll

Bernard Carroll is Professor of Molecular Genetics at the School of Chemistry and Molecular Biosciences, University of Queensland. He specialises in gene expression, silencing and epigenetics and is listed as an inventor on a number of gene technology patents.[75]

Professor Peter Waterhouse

Peter Waterhouse is Professor of Molecular Genetics at Queensland University of Technology. He specialises in gene silencing and RNA interference and is listed as an inventor on numerous gene technology related patents.[76]

Dr Allan Green,

Dr Allan Green was Deputy Chief of CSIRO Plant Industry when the workshops took place. He has a background in plant breeding and genetics, and his main research activities have been the genetic modification of oilseed crops.[77]

The CSIRO has numerous gene technology related patents, including patents in gene silencing, and is conducting field trials with genetically modified cotton, safflower, wheat and barley.[78] The organisation also has strategic partnerships with the GM crop companies Monsanto and Bayer CropScience the details of which remain confidential.[79]

Two other panelists **Dr Rob Defeyter** and **Dr Bill Taylor** were the Intellectual Property Manager and Business Development Manager respectively for CSIRO Plant Industry when the workshops took place.

None of these panelists appear to have any expertise in toxicology, ecology or risk assessment. This expertise is vital in order to properly determine whether these new techniques should be considered as GM in the context of a safety assessment.

Furthermore, the vast majority of panelists have personal patents or work for institutions with gene technology patents or contractual relationships with biotech companies. Despite this, FSANZ appears to have deliberately misled the Senate in response to Senate questions in stating that:

> *"FSANZ is not aware that any members of the expert panel have potential conflicts of interest such as a commercial interest or patents in any of the listed breeding techniques. Some members of the panel have been, or are currently, engaged in research using some of the listed techniques."*[80]

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.[81] This conclusion is in marked contrast to biosafety assessments commissioned by other governments which found that new GM techniques require the same or similar safety evaluations as commercialised GMOs.[82] Table 2 contrasts the findings of FSANZ's expert panel compared with those of reviews commissioned by other governments.

Table 2: The findings of FSANZ's expert panel compared to those of reviews commissioned by other governments

TECHNIQUE	FINDINGS OF FSANZ'S EXPERT PANEL	FINDINGS OF OTHER GOVERNMENT COMMISSIONED REVIEWS
Oligo-directed mutagenesis (ODM)	*"...changes introduced using such techniques would be typically small and definable and have predictable outcomes. Such techniques would therefore be similar to traditional mutagenic techniques used in conventional plant breeding and food derived from these plants should not be regarded as GM food."*[83] *"There are no identified safety concerns associated with the use of ODM, both in terms of the nature and extent of the specific changes that it can introduce to target plants as well as potential unintended effects."*[84]	*"...neither the efficiency nor the specificity of the ODM technology can be sufficiently controlled. The efficiency for inducing specific mutations in plant cells is lower than for other target cells, e.g. animal cells."*[85] *"...unless more experimental evidence elucidates the mechanisms by which these molecules function, robust investigation about possible unintended effects will remain marginal."*[86]
Zinc finger nucleases (ZFN)	*"The changes introduced using ZFN-1 and ZFN-2 [using zinc-finger nuclease to delete, substitute or insert a few base pairs] will be small, definable and the outcomes predictable. Food derived from plants modified using ZFN-1 and ZFN- 2 would be similar to food produced using traditional mutagenic techniques, and should therefore not be regarded as GM food."*[87]	*"...even small molecular changes may result in pronounced effects on the expression of respective genes and/or their functions in a specific crop."*[88] *"ZFNs are resulting in significant off-target activity and therefore higher levels of cellular damage."*[89] *"Even if targeting is specific, the outcome of repair at the double strand breaks induced by SSNs can be very diverse (e.g. point mutations, sequence/gene deletion, integration of non-native sequences, inversions/ translocations of chromosomal sections). According to the nature of the outcome, an appropriate range of unintended effects need to be taken into account."*[90] *"...comprehensive untargeted profiling methods (such as omics) should be applied in order to detect and identify unintentional mutations in the entire host genome."*[91]
Other site-directed nucleases (TALENs, CRISPR, meganucleases, triplex-following oligonucleotides)	*"When used to introduce small changes only, such techniques do not present a significantly greater food safety concern than other forms of mutagenesis. Providing any transgenes have been segregated away from the final food producing lines, derived foods would be similar to food produced using traditional mutagenic techniques. Such foods should therefore not be regarded as GM."*[92]	*"Approaches to targeted mutagenesis by SSNs [site-specific nucleases] are subject to a number of possible unintended effects. According to the current lack of knowledge on the details of the involved mechanisms, significant uncertainties are associated with an assessment of unintended effects."*[93] *"The respective risk issues thus need to be addressed by a comprehensive molecular characterisation, taking into account the experiences from risk assessment of GMOs."*[94]

Cisgenics	*"in the case of cisgenesis and intragenesis, a simplified form of food safety assessment may be warranted because the transferred genes will be derived from the same or a closely related species which is likely to be commonly used as food and have a history of safe use"*[95]	*"cisgenic plants cannot be assessed on the basis of reduced data requirements only because of a relatively 'safe' choice of the inserted gene alone. Other factors like method of insertion, place of insertion and possible accompanying (unintended) changes in the genome and physiology of the recipient plant should be taken into account. The exact data requirements will have to be determined on a case-by-case basis, as is the case for transgenic GM crop varieties."*[96] *"Characteristics which may cause potential adverse effects may either be the new genetic elements inserted or deletions and rearrangements of plant genomic DNA resulting from the genetic modification technique used (mainly Agrobacterium-mediated transformation). As the latter are the same as for transgenesis there is no difference regarding the possibility of unintended effects…Therefore a comprehensive molecular characterisation…is indispensable."*[97]
GM rootstock grafting	*"in the case of GM rootstock grafting, the majority of foods will not contain any novel genetic material or have altered characteristics and therefore should only require a simplified food safety assessment."*[98] *"the presence of novel gene products in the scion, should it occur, would typically not alter the characteristics of the food."*[99]	*"the understanding on the molecular level of the influence non-GM rootstocks exert on scions is still rather limited."*[100] *"it is known that upon grafting proteins and metabolites can be transported from the rootstock to the scion through the graft junction and vice versa. Thus effects on gene expression and phenotype in the respective other plant part (rootstock or scion) are possible."*[101]
Reverse breeding	*"There does not appear to be any particular hazards associated with the GM component of the reverse breeding technique."*[102]	*"unintended adverse effects, e.g. transmittable off-target regulatory effects need to be considered. This requires a thorough phenotypic assessment of the breeding product in case molecular evidence cannot exclude off-target effects."*[103]
Seed Production Technology	*"food produced using this technique should not be regarded as GM food as a genetic separation exists between the early GM ancestor (known as the GM maintainer line) and the non-GM parents of the final food-producing line, which does not contain the genetic modification."*[104]	*"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."*[105]
Accelerated breeding	*"it was concluded the final food producing lines would be comparable to those developed using a conventional plant breeding approach. Derived food products should therefore not be regarded as GM food."*[106]	*"unintended adverse effects, e.g. transmittable off-target regulatory effects need to be considered. This requires a thorough phenotypic assessment of the breeding product in case molecular evidence cannot exclude off-target effects."*[107]
Agroinfiltration	*"there are no significant food safety concerns"*[108]	*"any plant materials including seeds originating from agroinfiltration and agroinfection applications need to be tested rigorously for presence of transgenic Agrobacteria, transgenic virus and plasmid sequences and presence of T-DNA constructs."*[109]

CONCLUSION

Whilst the GM crop industry races to commercialise these new GM techniques, scientists are still arguing over their mode of action, let alone beginning to assess their potential risks to human health and the environment.

Meanwhile, our regulators are failing to protect our safety and right to know. Both the OGTR and FSANZ seem all too happy to accept industry claims of safety and to deregulate these techniques without any kind of public debate.

Those government agencies overseas that have considered the biosafety risks posed by these techniques have concluded that there is insufficient knowledge regarding their risks. 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. [110]

There is zero tolerance for unapproved GM content in many of Australia's major export markets. That makes it essential to have prior assessment of not just the environmental and human health impacts, but also the economic impacts of any use of GMOs. As a major agricultural exporter, if Australia were to exempt any of these techniques from regulation it could result in serious trade implications.

Products derived from these techniques also need to be labelled so that the choices of consumers, farmers and the food industry are protected.

Australia's GMO regulations should be interpreted in their intended sense, to encompass all modern biotechnological processes that directly modify genomes. Otherwise, the Australian Government will be failing its citizens.

Friends of the Earth is calling for:

- These new GM techniques and the products derived from them to be subject to a comprehensive case-by-case risk assessment, including full molecular characterisation and independent safety testing to minimise any potential risks to human health and the environment;
- All products derived from new GM techniques to be labelled to protect choice for farmers, producers and consumers;
- The precautionary principle to be enshrined in both the Gene Technology Act and the Food Standards Australia New Zealand Act, given the experimental nature of these technologies and the risks associated with them;
- The Government to impose strict liability on all dealings with GMOs licensed by the OGTR, so that liability for GM contamination and the resultant losses and costs rests fully on the licensees and the owners of GM patents;
- A moratorium on the commercialisation of these new GM techniques until our regulatory system for GMOs is adapted to deal with the potential risks posed by them.

APPENDIX 1: THE TECHNIQUES

Oligo-directed mutagenesis (ODM)

This involves introducing short DNA fragments (oligonucleotides) into cells which trigger the cell to modify its own DNA to match the introduced DNA fragments - allowing targeted changes to be introduced.[111] This technique can change, insert or delete one or a few base pairs of DNA.[112]

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).[113]

According to a recent review commissioned by the Norwegian Environment and Development Agencies, there is still scientific dispute regarding how these techniques even work and there is evidence that the different types of oligonucleotide molecules may trigger distinct cells responses.[114] To complicate matters still further, a wide range of terms have been used to describe these techniques.[115]

Regulatory approval has already been given in North America for the commercialisation of a herbicide-tolerant canola variety developed using ODM.[116] ODM has also been used to genetically engineer herbicide resistance in maize, wheat, rice, tobacco, canola and banana.[117]

Specific risks

A review by the Austrian Environmental Agency concluded that "neither the efficiency nor the specificity of the ODM technology can be sufficiently controlled" and observes that ODM may lead to off-target mutations.[118] The review notes 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."[119]

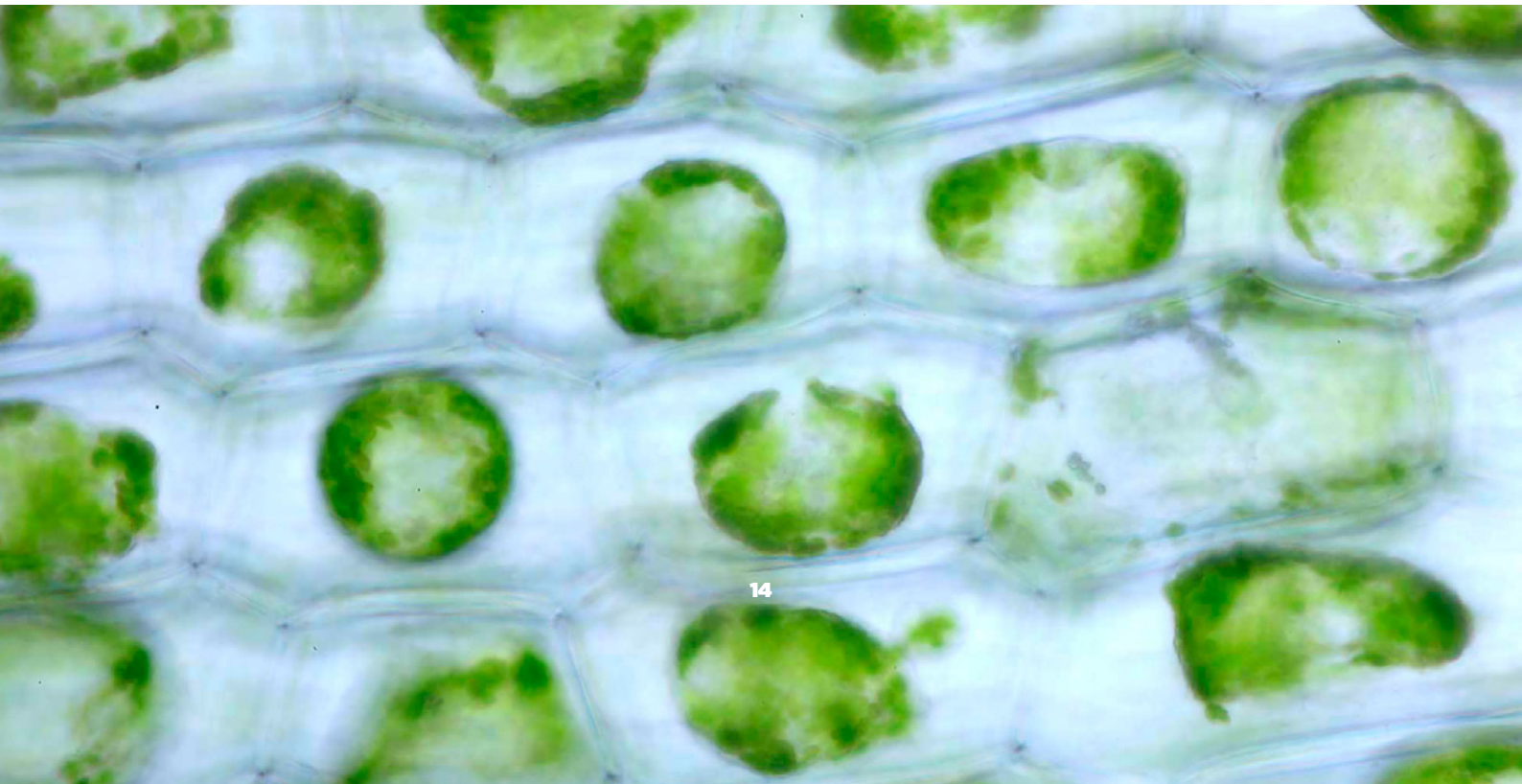
According to a recent review commissioned by the Norwegian Environment and Development Agencies most of the published ODM studies use animal cells and there is a:

> *"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."*[120]

The review also notes that there have been no studies looking at the unintended impacts of ODM in plants.[121] Unintended effects associated with ODM in animal cells include cell death and unpredicted mutations.[122] The authors argue that until more studies determine exactly how oligonucleotides function, it will difficult to conduct any research into possible unintended effects.[123]

The Austrian Environmental Agency warns of the possibility of the following unintended effects with ODM[124]:

- 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)[125] - 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 cells.[126]

These techniques can be subdivided into three different subcategories[127]:

- 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;[128]
- SDN-2 cuts the DNA and provides a DNA template (donor DNA) containing the desired mutations i.e. a 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.[129]

- **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;
  - This technique has been used to genetically engineer herbicide tolerance in maize and tobacco.[130]
- **Transcription activator-like nucleases (TALEN)**
  - These enzymes are similar in structure in ZFNs but have longer DNA binding sites;[131]
  - In August 2012, a German newspaper revealed that big agro-chemical companies such as Syngenta, Monsanto and Bayer Crop Science already have licenses to use TALEN technology.[132]
- **Meganucleases/homing endonucleases**
  - These are naturally occurring DNA cutting enzymes that have been isolated from a range of organisms including yeast and green algae;[133]
  - There seems to have been little interest in using these enzymes to develop commercial GM crops.[134]
- **CRISPR/Cas-Nucleases**
  - These are synthetic enzymes developed from a bacterial enzyme that is part of the bacteria's immune system and is used to recognise and destroy foreign DNA;[135]
  - 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'.[136]

Specific risks

A recent review by the Austrian Environment Agency 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.[137]

A recent 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."*[138]

According to the Austrian Environmental Agency[139] 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.[140] 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 cannot be assumed that these changes will not be heritable.[141]

A recent review by the Austrian Environment Agency found that ZFNs result in significant unexpected mutations.[142] This is also an important problem for the TALEN technique and, according to a recent review, can result in severe side effects.[143] 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 look at.[144]

Studies suggest that CRISPR results in even more off-target mutations than ZFN and TALENs.[145] For example, a recent study found that CRISPR-Cas9 can result in hundreds of unexpected mutations.[146]

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[147], therefore:

> *"comprehensive untargeted profiling methods (such as omics) should be applied in order to detect and identify unintentional mutations in the entire host genome."*[148]

Cisgenesis and intragenesis

These terms refer to genetic engineering where the introduced traits/genetic material are from the same or closely related species.[149]. Cisgenics involves the transfer of complete genes, whereas intragenesis combines fragments of genes from the same or related species.[150]

Cisgenesis and intragenesis are not new GM techniques per se and differ only in source material from older genetic engineering techniques - although SDN-3 type gene-editing techniques can be used to produce cisgenic and intragenic plants.

Cisgenic approaches appear to hold appeal for some GM scientists as a means to 'invent around' the existing regulatory scrutiny of GM products.[151] Scientists have also expressed the hope that there may not be as much consumer resistance to GM crops if the genes used are derived from the same crop or a closely related species.

The commercial development of cis- and intragenic plants is quite advanced in the EU, the US and New Zealand and field trials are being undertaken in potatoes, apples and barley.[152]

Specific risks

It has been suggested that cisgenic GM plants do not carry the same risks as transgenic GM plants because the components are derived from the same or closely related species.[153] However, the genetic engineering process is identical for cisgenesis, intragenesis and transgenesis (where the genes are from an unrelated species), regardless of the origin of the inserted genes. Therefore, the concerns regarding unintended genetic changes and unforeseen genomic interactions - that could have an adverse effect on human health or the environment -remain the same.

Gene insertion can cause unintended genomic alterations in the same way as transgenesis. For example, multiple copies of the gene can be inserted and the genetic engineering process can result in the deletion or rearrangement of plant DNA around the intended genetic insert.

In both cisgenesis and intragenesis, the expression pattern (i.e. when and where expression occurs) of the inserted gene may be different due to its changed location on the genome (position effects)[154].

Thus, cisgenesis and intragenesis could still alter plant biochemical pathways in similar ways to transgenesis, potentially giving rise to unexpected effects.

A review by the Austrian Government observed that when *Agrobacterium*-mediated transfer is used to transfer DNA this can result in bacterial DNA being incorporated into the plant genome. This can result in the formation of potentially harmful fusion proteins.[155] The authors argue that molecular data is therefore important to substantiate claims that crops are cis- or intragenic.[156]

Cisgenesis and intragenesis also allow for genetic material from within the same species to be so significantly rearranged that the result could be genetic constructs and traits equally as foreign as when donor DNA from outside the species is used. As Professor of Genetics and Molecular Biology at Canterbury University, Jack Heinemann, points out:

> *"The cisgeneticist is confined to no minimum string length for manipulation and thus, from the raw building blocks common to all genomes, can create strings just as "foreign" to that same genome as any that came from a different species. Any gene from a human being could be rearranged to become 2%, 50% or 70% different from itself and as different as the average gene from a human was to the average gene from a single-celled soil microorganism."*[157]

The Austrian Environment Agency review[158] summarises the potential risks associated with cis- or intragenic plants as follows:

- Proteins may be expressed in cisgenic plants that have never been part of the human or animal diet;
- Increased gene expression may affect food and feed safety via altered biochemical properties;
- The random insertion of the genes may disrupt the plant's genes leading to changes in its chemical composition.

All of these factors can have a potential impact on the toxicity and allergenicity of products derived from the plant.

GM rootstock grafting

This technique involves grafting the vegetative part of a non-GM plant onto the rootstock of a GM plant.[159] A 2012 workshop hosted by FSANZ concluded that since "a grafted plant can essentially be regarded as a single organism, a plant with a GM rootstock should therefore be regarded as GMO."[160]

Currently, no plants grafted onto GM rootstock are commercially available. However, some field trials with GM rootstock have already taken place in the EU with grape vine, apples, peas and oranges. In China field trials have been conducted with poplar and in Korea with watermelon.[161]

Specific risks

Since GM rootstock grafting involves the use of older GM techniques, the concerns regarding unintended genetic changes and unforeseen genomic interactions - that could have an adverse effect on human health or the environment - remain the same.[162]

For example, multiple copies of the gene can be inserted and the genetic engineering process can result in the deletion or rearrangement of plant DNA around the intended genetic insert. Furthermore, the expression pattern (i.e. when and where expression occurs) of the inserted gene may be different due to its changed location on the genome (position effects).

Studies show that novel gene products (such as RNA and proteins) can move from the GM rootstock into the rest of the plant and potentially also into food products such as fruit.[163] Translocation of regulatory proteins, plant hormones or RNA from the rootstock can also affect gene regulation or gene silencing in the rest of the plant. In certain cases these changes may be stably inherited by the next generation. Scientists have also suggested that horizontal gene transfer is possible between the rootstock and the rest of the plant. [164]

Depending on the species, suckers may develop on the GM rootstock and produce leaves and fruits that are GM. This would significantly change the exposure of non-target organisms to transgenic proteins and the possibility of plant-to-plant gene flow.

Depending on the nature of the genetic modification, the interaction of GM–rootstock with the soil environment may also have an impact on soil organisms such as nematodes, which are capable of directly taking up RNA from the environment.[165]

Techniques to support breeding (TSBs)

Reverse breeding

This is actually a combination of techniques that can be used to create parental lines that when crossed recreate an elite hybrid crop. Usually it involves using genetic engineering to silence genes that initiate genetic recombination.[166] A FSANZ commissioned review which looked at this technique concluded that there are a fairly narrow range of crops for which it might be suitable and its benefits are not immediately apparent.[167]

Seed production technology

These techniques include DuPont Pioneer's proprietary seed production technology (SPT). This was developed for use in the breeding of hybrid corn varieties to avoid the need for detassling corn (removing the male flowers) to prevent self-pollination.[168] It involves using GM techniques to produce a male-sterile plant line (i.e. one that doesn't produce pollen) to reduce the possibility of self-pollination. This is then used as one of the parents to produce hybrid seed.[169]

This technology has assisted in the development of Pioneer® brand corn products that are on the US market. It is also in the early development phase for producing hybrid rice varieties and the proof of concept stage for developing hybrid wheat.[170]

Accelerated breeding (AB)

This involves using GM techniques to induce early flowering in plants to speed up the breeding process. This can be achieved by certain gene silencing techniques or by using genetic engineering to overexpress chemicals involved in the initiation of flowering.[171]

AB is still in research & development according to Schaart & Visser (2009).[172] The concept has been applied to a number of crop species, including fruit trees like apple, plum, citrus and pear trees and annual plants.[173]

Specific risks

The concept behind all TSBs is that the genetic modifications introduced to aid breeding are segregated out to create non-GM crops. However a review by the Austrian Government 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. [174]

The authors conclude that:

> *"a thorough characterisation of the final products of RB and AB is needed to exclude the unexpected presence of GM modifications."*[175]

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."*[176]

Agroinfiltration

These techniques exploit the ability of certain soil bacteria to infect host plants and introduce genetic material. This is the most common method used to create GM crops. However, in most agroinfiltration applications the intention is not to stably introduce new genes. In agroinfiltration the desired bacteria are genetically modified to carry the desired genes. The tissues of the target plant are then 'infiltrated' with a liquid suspension of the bacteria using syringes, vacuum suction, dipping plant parts into the suspension, or spraying it on. This results in high levels of expression of the transgenes in the tissues and can also be used to silence plant genes.[177]

Agroinfiltration is of commercial interest as a way of producing high value proteins such as plant made pharmaceuticals e.g vaccines, antibodies and blood proteins for use in human and animal medicine.[178]

There are a few different types of agroinfiltration:

- **Agroinfiltration sensu strictu:** plant tissues (typically leaf tissues) are infiltrated in order to locally express the desired genes;
- **Agroinfection:** this is similar but also uses a viral DNA to spread the gene through the whole plant;
- **Floral dip:** this involves exposing reproductive tissues (typically flowers) to the suspension with the aim of producing GM plants.[179]

Specific risks

Since floral dip applications are designed to produce GM crops the risks are similar to other GM techniques such as cisgenesis (see p. 16). These include unexpected effects due to the presence of non-plant DNA, gene rearrangements, multiple gene insertions and instability.

Although the intention of other agroinfiltration is not for the transgene to be incorporated into the plant, a review by the Austrian Government concluded that this possibility cannot be excluded. It is possible that transgenes may become integrated into cells selected for further propagation.

The review also concludes that applications that involve the silencing of genes may result in unexpected effects due to inheritable epigenetic effects on the regulation of both target and non-target genes.

The review concludes that:

- The absence of modifications needs to be demonstrated in cells used for future breeding;
- Changes in the expression of the target genes as well as other likely-affected non-target genes need to be evaluated;
- The unintended release of transgenic bacterial strains into the environment can result in adverse effects as they may survive in soil and transfer transgenes to other plants or other microorganisms. The release of transgenic plant viruses from agroinfected material is a concern for the same reasons;
- Any plant materials originating from agoinfiltration and agroinfection applications needs to be tested rigorously for the presence of transgenic bacterial and viral DNA.[180]

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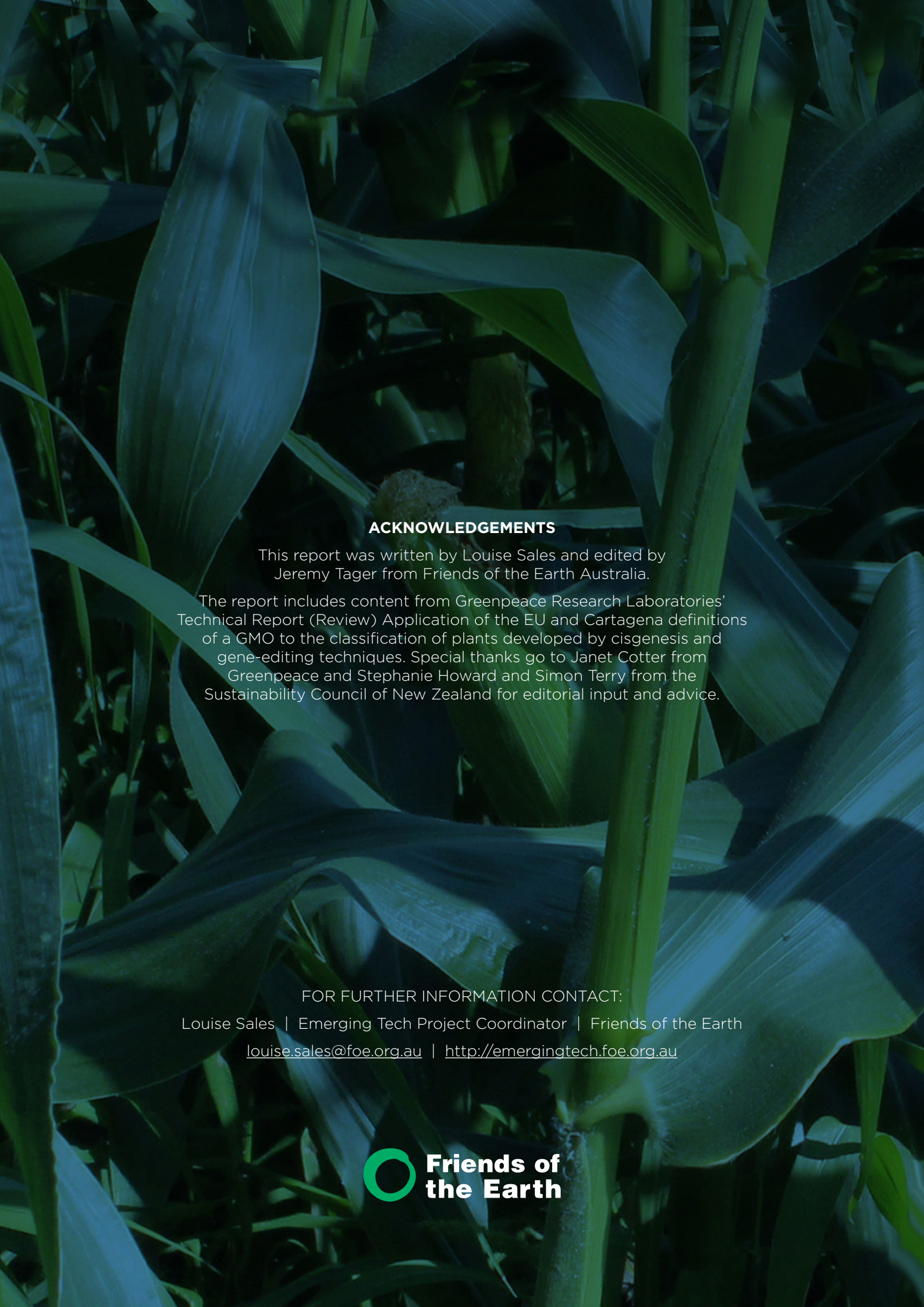

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