Introductory remarks

CSIRO has supported the current Gene Technology Scheme. However, it is timely to re-evaluate the Scheme to ensure the level of regulation is still commensurate with the risk.

Since the Scheme began, much experience has been gained regulating the products and practices of gene technology. This experience is valuable for informing risk assessment for currently un-regulated practices, regulated gene technology and new techniques. CSIRO supports reducing the level of regulation for those techniques and product types that have previously been extensively assessed.

New scientific techniques are being developed faster than the Scheme is being reviewed and any changes legislated. Consequently the review needs to investigate new mechanisms to increase the responsiveness of regulation. Possible new mechanisms could include:

i. differently defined regulation trigger
ii. risk tiering
iii. granting the regulator more flexible legal mechanisms to respond to new technologies

Without change, there is a risk of decreasing regulatory harmonisation around a world with diverse regulatory responses to developing techniques, which could potentially impact on trade.

In this submission we have not addressed the questions relating to Social and Ethical Issues. These are however areas that CSIRO sees as vitally important if benefits from the technology are to be realised. We will continue to work across our innovation system to contribute to public understanding and awareness of the risks and benefits of genetic technologies.

Theme 1 - Technical Issues

Please note responses to questions are not mandatory - you are invited to respond only to those questions that relate to your area of interest.

The Review of the Gene Technology Scheme 2017 is considering legislated definitions and their applicability to existing, recent and on the horizon techniques, in order to ensure definitions within the GT Act remain fit for purpose:

What technological advances can be foreseen that might pose regulatory challenges for the Scheme?

Whilst the Scheme uses a process trigger there will continue to be regulatory challenges around the ability of aging definitions to accommodate new techniques and processes. These challenges can be minimised in a variety of ways. For example by:

i. exploring ways to introduce more flexible legal mechanisms for more rapidly introducing changes to definitions within any revised Scheme

ii. giving the Regulator more discretion to determine whether to regulate or exempt new technological developments, and to exempt technologies on the basis of experience and new information
iii. codifying policy principles that express the intent of the Act, and the technological changes it intends to cover
iv. moving to a product-based trigger rather than process-based trigger, or some hybrid model combining elements of both process and product

Technologies are emerging that challenge the current process trigger, others are likely to follow, highlighting the need for increased flexibility. Specific examples we believe are being described by other submissions in detail include:

i. the potential to alter the epigenetic marks on DNA using catalytically dead Cas9 enzymes fused to chromatin modification or DNA methylation or de-methylation enzymes
ii. Cas9 variations fused with deaminases to allow base changes at specific sites, without cutting DNA
iii. ribonucleoproteins gene editing via a transient system without use of a DNA template or genetic integration

What are the potential impacts of the capability to make small edits in the DNA of an organism using no foreign DNA?

Use of small DNA editing techniques could have considerable positive impacts e.g. in agriculture, medical therapy and research applications[1,2]. Since these new techniques can be applied more precisely than mutagenesis, they present potentially much greater efficiency and utility. CSIRO supports the recent OGTR Technical Review's decision to exempt such organisms from regulation under the existing Scheme.

Very minor edits are analogous to changes resulting from mutagenesis. Therefore, they should pose no greater risks than those resulting from mutagenesis, which are currently unregulated, examples include loss/impaired gene function through deletions or amino acid substitutions without using a DNA template.

Small edits using a guide DNA to direct repair, altering an organism's genetics to identical sequences found in reproductively compatible species, may be considered comparable to combined use of mutagenesis and breeding in both plants and animals. Organisms generated without using any DNA from non-reproductively compatible species should be considered similar to mutagenesis. The risks of this second category of edited organisms should be more easily assessed than classical GMOs (with large sequences introduced from non-reproductively compatible organisms).

For all modified organisms the specific phenotype and product characteristics produced will determine their actual risk level, examples of characteristics include altering:

i. toxicity
ii. allergenicity

[1] Kamburova et al., 2017: Genome Editing in Plants: An Overview of Tools and Applications. Int J Agron 2017, Article ID 7315351, 1-15
[2] D. Carroll (2016) Genome editing: progress and challenges for medical applications. Genome Medicine 8:120

iii. pathogenicity
iv. invasiveness

This is why risk assessments are conducted on phenotypes rather than processes. Therefore, serious consideration of a move towards a product-based regulatory trigger for gene technology products, before release in Australia, is warranted.

Off target edits are a possible result of gene editing, although these are unlikely to be any greater than in organisms produced through conventional mutagenesis and breeding. Gene editing technology is rapidly improving in its specificity. Unintended edits would be segregated away from any desirable edits during subsequent breeding, at least in crops, as is normally required for induced mutations.

Under what circumstances might it be practical, efficient or appropriate to regulate gene editing under the GT Act when, from an enforcement perspective, it may not be possible to distinguish the products of gene editing from the products of conventional methods?

In most instances it would not be practical, efficient or appropriate to regulate the final commercial products of gene editing that are indistinguishable from those derived from conventional methods (natural variation, mutagenesis and breeding approaches), particularly the domesticated species used in agriculture and food production. Exceptions might be made for organisms whose phenotypes had animal welfare, human health or environmental concerns. These would likely also trigger assessment by other agencies.

However, CSIRO supports regulation of early stage gene editing research conducted as contained dealings, while the potential risks of those edits have not been fully evaluated or if a substantive risk is identified requiring management before release. Early stage contained gene editing research, e.g. under NLRD or DNIR, could be efficiently regulated in a similar manner to low risk classical genetic modification under the current Scheme. Regulating research at this early stage could conceivably delay the need to thoroughly assess the risks of releasing an edited organism, assuming that this was a requirement of any implemented revised Scheme. Many research applications of gene technology never reach the stage of being released, therefore imposing an in-depth risk assessment at an early stage may be inefficient.

While the majority of intentional gene edits will be completely harmless, there may be some categories with greater risk (e.g. edits to genes for allergens, toxins and virulence factors). In the event a small number of events were identified with a substantive risk (locally or globally), it may be practical to require testing for those events (e.g. to assure that they were removed from food crop seeds, or animal breeding stocks). In such circumstances it could be practical to generally deregulate the class of edited organisms, capturing risk through a schedule of higher risk events or type of targets (e.g. product resembling an allergen), subject to stricter regulation. The method of production is a secondary issue to their identification and removal from germplasm/breeding stock to ensure that they were not inadvertently present in food production.

Although detection may be possible for some edits, e.g. identifying the specific sequence within a gene known to have been edited elsewhere, a more general screening test for all possible editing events would likely be impractical and potentially unnecessary if our

systems were harmonised with those of our trading partners. A Scheme that has different triggers or specific exemptions for low risk classes of intentionally modified organisms that pose little or no risk to health or the environment would reduce the instances where screening of difficult to detect gene edited products would be required.

As gene edited organisms become more common, and possibly deregulated in other jurisdictions, Australian produced organisms may be unequally regulated due to the impracticality of identifying edited organisms crossing the border. This outcome would likely render regulation by a process trigger both inefficient and ineffective.

The emerging applications, and their definitional implications for research purposes, are another area the Review will consider:

Do these applications of gene technologies present unique issues for consideration? If so, how might these issues be best addressed by the Scheme?

The development and application of each new technology will potentially challenge any definitions in current and future legislation.

Keeping a broad definition of what is captured at the contained research phase would build on a proven system of managing gene technology in a transparent way, where the regulatory burden is somewhat lower than dealings involving release.

Adoption of a hybrid system of triggers and product based assessment (described below) would facilitate transition of research products from the laboratory to use.

Gene drives potentially pose higher risks, due to their potential to spread quickly through unmanaged populations. While these risks are investigated, carefully contained research will be important. CSIRO supports the OGTR Technical Review decision to regulate gene drive research as DNIRs, until their potential impacts are better understood. However, over time these potential risks may not be evident with experience. As considerable benefits may be realised for the environment and human health from proposed applications of this technology (e.g. in feral animal, insect pest and pathogen control) the regulations should permit a release process subject to careful risk assessment.

The Review is seeking further input on the prospect of the intentional release of a GMO or organism with changed characteristics, delivered by one of the new breeding technologies, into the environment:

What are the potential implications of the release of a GMO targeting an invasive species in Australia? What are the technical issues to consider in the scenario of a GMO used to target an introduced plant, vertebrate or invertebrate pest?

The Australian environment has many exotic invasive plants and animals that continue to alter the Australian environment. Large amounts of money is spent trying to reduce their impact and further costs are incurred from their damage. These new technologies should be investigated for potential solutions.

Invasive species

Potential implications of the release of a GMO reducing populations of invasive species would likely include:

1. Benefits from reduced invasive species impacts
2. Ecological disruption e.g. loss of an abundant food source
3. Environmental impact if the trait transferred to another untargeted species
4. Economic disruption if an invasive species is also of economic use
5. Potential escape to another country
6. Effectiveness breaking down over time

Technical issues

Assessment of a GMO to target pests could include the following:

1. Can the release be removed from the environment if harms eventuate?
2. Is the trait able to be transferred to other species e.g. related species?
3. What role does the target organism play in the environment and for humans?
4. How persistent are the released organisms/traits likely to be?

It may be difficult experimentally, or early on in a release program, to assess loss of invasiveness if the introduced GMO doesn't cause death/sterility, e.g. detoxified cane toads may over time lead to reduced invasiveness through increased predation.

Theme 2 - Regulatory Issues

Please note responses to questions are not mandatory - you are invited to respond only to those questions that relate to your area of interest.

The Review is considering the issue of regulatory triggers, and how best to undertake future policy design processes with both process and product trigger considerations in mind.

What do you think is the most appropriate regulatory trigger for Australia in light of extensions and advancements in gene technologies?

A decision tree based hybrid system (process and product trigger) and tiered evaluation are worth consideration for intentional releases and commercialisation. Principles guiding this hybrid system could include:

i. don't regulate widely used technologies that are currently unregulated (i.e. no increase in regulation)
ii. evaluate new technologies (focus regulatory effort on applications with less knowledge/experience and whose risks have not yet been thoroughly evaluated)
iii. use accrued evidence to allow classes of products to be moved to lower levels of regulation, or higher if evidence indicates additional risks

Hybrid system structure

1. The trigger could be defined around either the introduction (via transgenesis or gene editing) of "foreign DNA" from a species that is not reproductively compatible with the target organism and hence not accessible by conventional breeding or crossing methods AND/OR a phenotype outside the range of reproductively compatible species.

2. Exempt in regulations those technologies with a history of safe use* (e.g. GM traits/species that have been used for 30 years or more without unintended impacts) and/or that are not currently regulated (e.g. mutagenesis, simple gene edits not involving DNA from a reproductively incompatible species).
3. After initial assessment, a range of pathways could be envisaged. For example an application:
    a. With great similarities to previous applications and for which no new risks are identified (low risk), a shortened/modified assessment should be initiated.
    b. Involving new processes, phenotypes, or species-trait combinations, an evaluation similar to current practice including broad consultation should be initiated.

    At any time during (a), identification of a new risk reaching a risk threshold, a short track application should be transferred to the comprehensive assessment process.

*To facilitate greater ability for the regulator to make determinations and move technologies/traits/etc. between regulated/non-regulated, or tiers of regulation, some tools need to be developed. For example "A history of safe use" or "A long history of safe use" are frequently used terms. If an evidence-based process or set of criteria was defined that met this hurdle, the regulator would have a basis on which to exclude and tier applications based on accumulated evidence. To a small degree the use of a thorough analysis of horizontal gene transfer, selectable markers and commonly used transformation techniques are referred to and not analysed in detail in the risk assessment and management plans prepared recently for intentional releases of genetically modified plants.

A combination of more flexible legal mechanisms and a continuously developing tool kit based on previous assessments and research would increase the ability of a new scheme to respond to developing technology.

What factors need to be taken into account in the design of a product-based or a hybrid process/product regulatory scheme?

i. Definition of the product trigger needs to be clear and unambiguous. Lack of clarity may present an unnecessary barrier to innovation. How different must the phenotype of a new organism be to what has gone before to be captured? Using the definition (1) above as a phenotype that does not exist outside the range of reproductively compatible species could overcome this.
ii. Using a product trigger to assess the consequences of release would bring regulation of genetically modified organisms in line with other Australian regulators (FSANZ, APVMA, and TGA). It is important not to duplicate or increase the total overall regulatory burden to maintain efficiency and to ensure regulation remains commensurate with risk.
iii. It is critical that no greater or new uncertainty is introduced into the assessment of potential products. Lack of certainty could greatly impact investment decisions, potentially reducing research efforts, ultimately reducing Australian competitiveness and efficiency gains.

Phase one consultations identified a number of functional efficiencies that could be applied to the Scheme. The Review is exploring these issues from perspective of the existing process-based regulatory scheme:

Are there any 'fixes' the scheme needs right now to remain effective? How would you streamline the existing scheme? What efficiencies could be gained through adjusting the interface between the Scheme and other regulators?

- Within the current Scheme using a process trigger, efficiencies may be gained by assessing applications through a fast/slow track process e.g. fast track applications for a trait/ trait class which have previously been fully assessed. This would have the effect of introducing some minor risk tiering.
    - For example herbicide tolerance traits in cotton and canola. No adverse risks have been identified over many years of use. Introducing a new herbicide tolerance trait into these crop species is not going to present any new risks beyond those already evaluated for existing commercial GM traits. Use of a different herbicide should still be assessed by regulators e.g. APVMA. However, use of previously released herbicide resistance traits (used on millions of hectares world-wide) into a new crop species may potentially present new risks. For example new crop species could have additional weediness or containment risk. The safety of these traits/herbicides to humans and animals will remain the same, so a detailed regulatory package for toxicity/allergenicity assessment should not be required.
- Where multiple regulators require applications, shared application forms and data standards should be developed to avoid inefficiencies.

The Review is exploring whether greater alignment of regulation with risk should be further developed for environmental releases:

What support exists for a regulatory framework providing for tiered risk? What examples exist of licence applications to the Regulator that could be 'fast-tracked', under a risk tiering system, with evidence of scientific and technical integrity that the aims of the Scheme (protection of human health and the environment) will be delivered? Under a regulatory framework to tier risk for environmental release, what efficiencies might be delivered to regulated stakeholders? How could efficiency gains to the Regulator be quantified?

CSIRO supports moving to a regulatory Scheme with tiering of GMO release assessments commensurate with potential risks to human health and the environment.

How do new applications essentially reusing very similar technologies, previously thoroughly assessed many times, benefit from another full risk assessment and broad consultation? For example, in Australia over the past 20 years many limited and commercial intentional release applications have been made for several herbicide traits in cotton and canola. No new risks have been identified through decades of commercial use, with GM crops being grown on hundreds of millions of hectares around the world. CSIRO sees little value in the preparation of applications, risk assessments and detailed consultation presently undertaken for applications demonstrated through experience to be low risk.

Introduction of a tiered assessment system would focus regulatory effort on less thoroughly assessed technologies/traits, potentially creating efficiencies for the regulator and applicants.

The Review is exploring whether a distinction can be made between classes of organisms so the necessary controls can be applied to the highest risks, rather than applying a one size fits all approach:

What justification is there to regulate animals, plants or microbes differently? In what way might different applications be treated differently (e.g. medical, agricultural, industrial, environmental, etc.)? How might the Scheme accommodate the DIY-biology movement? What measures might be warranted to identify potential long-term or 'down-stream' effects of gene technologies on humans and the environment? What opportunities are there for principles-based regulation in the Gene Technology Scheme? What advantages could be gained from doing this? What drawbacks are there from such an approach to regulation? Are there any non-science aspects that would enhance the object of regulation, that do not place unnecessary burdens on the regulated community? How might these be considered?

Differential regulation of Animals, Plants and microbes

There has been significant experience with plants and their commercial releases, in Australia and globally, without a substantive risk being identified. However, to date no GM animals have been released in Australia (although GM Atlantic salmon have been released into aquaculture in Canada). Accumulated experience provides sufficient evidence to allow regulation to be moderated, at least for some plant species. If similar experience is gained releasing GM animals, we would also support moderating regulation.

Were the Scheme amended to allow risk tiering, then differentiation based on organism type would not be required, as high or unknown risk organisms would be thoroughly assessed. CSIRO is supportive of a risk tiering approach to ensure regulation is commensurate with risks posed by specific modified organisms or classes of modifications based on a scientific assessment of those risks and accumulated experiences with their release into the environment. In practice this could function somewhat similarly to the current practice of generating biology documents for certain species, e.g. a dossier could be compiled reviewing risks of GM herbicide tolerant Canola as a class.

The Review is exploring the practical implications to the Scheme of harmonising Australian regulation with the regulatory needs of trade partners:

What are the potential impacts on market access for exporters of animal or plant derived food products?

In Practice, exporters must meet the requirements in all markets resulting in a multiplied regulatory burden. Regulatory harmonisation could potentially reduce barriers to exporting to harmonised markets.

Theme 3 - Governance Issues

Please note responses to questions are not mandatory - you are invited to respond only to those questions that relate to your area of interest.

The Review is exploring opportunities to maintain and enhance the transparency of, and trust in, the governance arrangements of the Scheme:

What will reassure the Australian public and regulated communities of the integrity of the Scheme?

CSIRO supports continuing to release information pertaining to the process of evaluation and making applications being freely available to all (except where there are grounds for commercial in confidence protection).

Maintenance of an independent regulator assures the public of a thorough, unbiased assessment process.

What mechanisms could address the challenges that making changes in the Scheme might entail: Domestically – across a federated government system experiencing different political agendas and community sentiments? Internationally – relating to other agreements, trade agreements, and harmonised regulatory approaches?

The Review is exploring how to ensure the rate of adaptation of the Scheme keeps pace with changes in technology and community values:

What principles should guide the level at which a decision is made within the Scheme? Does reviewing the Scheme every five years best address the needs of the Scheme? Is there a preferable option? Is the existing role of the Forum the most suitable way of providing oversight and guidance for the Scheme? What criteria should be used to determine what legislative amendments are minor and could be progressed without going to the Forum?

GM moratoria remain a debated element of the Scheme and the Review is seeking to understand the factors and practical implications for all stakeholders:

What evidence is there to support economic and trade advantages of GM moratoria – or indeed, the absence of GM moratoria? How could regulated stakeholders access the benefits of a national scheme, whilst ensuring jurisdictions are able to effectively trade in the international context? What other mechanisms could be utilised in order to realise the outcomes currently achieved through moratoria?

The Review is exploring how the Scheme can harness the emerging benefits of gene technology that were not anticipated at the establishment of the Scheme:

Are existing mechanisms, when used effectively, sufficient to ensure the emerging health, environmental and manufacturing benefits of gene technology that were not anticipated at the establishment of the Scheme, can be harnessed for Australians? Should other policy principles be developed that are tailored to horizon technology management? What other factors could be considered in the regulatory decision? What data sets are required to assist the regulator to consider benefits in addition to the risks?

The Review seeks to identify areas where clear policy positions could enhance the Scheme and support compliance with regulation:

What aspects of gene technology would benefit from greater policy position clarity? What other mechanisms would provide suitable policy clarity that would enhance the Scheme and support compliance?

The Review is seeking to identify any regulation gaps and overlaps at the interface of the Scheme and other product regulators:

What are the pressure points at the boundaries between regulatory schemes that are caused by regulatory gaps or overlaps? How can existing coordination functions be utilised more effectively to support the Scheme to be agile and facilitate transitions across regulatory framework boundaries? What other activities would enhance this? What amendments to the funding model would support an agile Scheme that will cope with increased future activity?

How could some aspects of the Scheme be funded through other mechanisms that will support innovation and competition in gene technology, whilst retaining public confidence in the Scheme?

Theme 4 - Social and Ethical Issues

Please note responses to questions are not mandatory - you are invited to respond only to those questions that relate to your area of interest.

It is important for the Review to identify where public understanding and confidence is strong, so this can be maintained, as well as opportunities for greater understanding:

How do we help the community to best understand the benefits and risks of a complex, science-based technology?

Response

Where does the community have confidence in the gene technology regulatory scheme? How can this be maintained?

Response

Where is there a lack of community confidence in the gene technology regulatory scheme? Why might this be, and how can confidence be built?

Response

What does the public need to know?

Response

Who is best placed to provide that information?

Response

The Review is seeking to better understand how to balance consumer choice within the scope of the Scheme:

What does the public need in order to accept the increasing availability and range of use of gene technologies? What does the public need in order to determine whether to provide social licence for the adoption and embedding of gene technology into the culture, lifestyle, economy and health sector? What are the ethical considerations for enabling access to medical treatments?

The Review is seeking to explore and better understand factors relating to choice and the potential impacts on trade, alternate farming techniques and the broader environment:

How do we ensure that information is available to the community on the value of GM and what it can do? Who is responsible for providing this, and why? Is the Scheme putting up barriers to research and development and commercialisation of agricultural applications?

<u>Barriers to research and development and commercialisation</u>

Regulation in its current form presents barriers to research, development and commercialisation. Consequently actions that responsibly reduce regulation will lower these barriers.

1. Giving the regulator the tools and freedom within the act to determine what are initially or become after time low risk activities.
2. Provide a framework in the Scheme to allow the regulator informed by experience to exempt low risk activities (traits/processes etc.), tier evaluations and change them over time.