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16th December 2016

Dr Raj Bhula
Gene Technology Regulator
Regulations Review
Office of the Gene Technology Regulator
GPO Box 9848
Canberra ACT 2601

Re: Options for Regulating New Technologies

Dear Dr Bhula,

The La Trobe Institutional Biosafety Committee (LTIBC) appreciates the opportunity to provide this submission in response to the Discussion Paper on Options for Regulating New Technologies.

The LTIBC values input into Australia's gene technology regulatory system and is committed to providing appropriate governance and oversight to biosafety across the University's teaching, research and development portfolio. The LTIBC believes that clarification and certainty is required in the assessment and management of New Breeding Technologies (NBTs) across the diversity of current and future applications.

Yours Sincerely,

Dr Carl Ramage
Chair, La Trobe Institutional Biosafety Committee
Ethics and Integrity, Research Office
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La Trobe Institutional Biosafety Committee Submission

Introduction

La Trobe University has a fine history as an excellent university with an enduring social conscience. As part of our 'Future Ready' strategy, our plan is to grow and develop La Trobe's traditional leadership in areas of research, scholarship and learning that matter to the Australian community. Having taken a detailed investigation of our capabilities and strengths, we have identified five Research Focus Areas (RFAs) and seven Disciplinary Research Programs (DRPs). La Trobe University's RFAs are:

- Securing food, water and the environment
- Sport exercise and rehabilitation
- Understanding disease
- Building healthy communities
- Transforming human societies.

La Trobe University conducts research using gene technology and potentially harmful biological material in a safe, secure, ethical and environmentally responsible framework. This framework helps us meet the needs of national legislative schemes and the Australian community.

At La Trobe University, all activities involving hazardous biological materials and genetically modified organisms (GMOs) or gene technologies must be assessed and approved by the LTIBC. LTIBC must apply a set of principles as outlined in the Australian Standard for Microbiological Safety in Laboratories AS/NZS 2243.3:2010, the *Gene Technology Act 2000* (the *'Act'*)and *Gene Technology Regulations 2001* and any amendments that govern biosafety, biosecurity, the classification of dealings with GMOs, the containment of hazardous biological materials and dealings with GMOs and the conduct of people whose work involves hazardous biological materials, recombinant DNA or gene technology. Activities involving hazardous biological materials, GMOs or gene technologies must not commence prior to the receipt of written approval by the LTIBC. The LTIBC assesses activities to ensure that any real or potential hazards concerning biological materials and dealings with GMOs are identified and managed appropriately, research environments conform to internal and OGTR certification rules and informs the OGTR of relevant dealings with GMOs at La Trobe University.

The LTIBC welcomes this opportunity to respond and comment on the *Discussion paper: Options for regulating new technologies*.

LTIBC Response to Consultation Questions

1. **Which Option(s) do you support, and why?**

The LTIBC supports **Option 4** that proposes to exclude organisms from regulation as GMOs if the genetic changes they carry are similar or indistinguishable from the outcomes/products of other mutagenesis processes (e.g. chemical and radiation mutagenesis methods and natural mutations). It is the view of the LTIBC that Option 4 provides clarity to the scope of the Gene Technology Regulations in relation to the outcomes/products of new technologies in a manner that is consistent with the original scope and intent of the regulatory scheme (i.e. exclusion from

regulation of techniques with a history of safe use). Further, Option 4 is consistent with the principle consideration that organisms created using gene technologies should be regulated in a manner that is commensurate with the biosafety risks they pose to human health and safety and to the environment.

The mutagenesis techniques based on cellular DNA repair (SDN-1, SDN-2 and ODM techniques) included in Option 4 have been used in several research and product development applications for the targeted mutagenesis of endogenous genes to induce the loss of gene function, modulate activity or alter function. At La Trobe University, the techniques are a valuable tool for the study of important areas with direct community impact across all RFAs.

Option 4 enables the same regulatory treatment of products developed with new technologies and those that can similarly be obtained with various "conventional" tools – such as use of the allelic variation within an organism, spontaneous mutations, or traditional chemical or radiation induced mutagenesis. The application of DNA repair mechanisms, such as mutagenesis, have a long safe history of use in the development of useful agricultural traits particularly in plants including, for example, herbicide tolerance, changed nutritional composition, and resistance to biotic (e.g. disease) and abiotic stresses[1].

The scientific literature consistently report that new breeding technologies such as SDN-1, SDN-2 and ODM, present no greater risk to human health safety and the environment than those posed by conventional mutagenesis techniques (Supplement 1). Further, the weight of evidence supports a key benefit of new technologies namely their precision and the enhanced predictability of off-target effects compared to conventional random mutagenesis techniques. As such, and with due consideration of the Pro's and Con's presented within the OGTR discussion paper, the LTIBC recommends **Option 4**.

Option 1 is not supported as it would provide no clarity for the LTIBC in dealing with such technologies going forward and poses a risk that uncertainty will lead to inconsistency in application of the Regulations (i.e. across institutions) and will be difficult for IBCs to monitor, provide appropriate advice and governance in a scientifically robust manner.

Options 2 and 3 are also not supported since they would impose unnecessary regulation on techniques that are functionally equivalent to other mutagenesis techniques. This is an undesirable outcome for academia, industry, the public, and government and does not align with the principles outlined in The Australian Government Guide to Regulation[2].

The LTIBC would like to note that it received commentary from and considered the views of two LTU stakeholders that favoured **Options 2 or 3** and not **Option 4.** The stakeholders did not fully accept the argument that the new technologies are unlikely to pose risks and therefore this should not mean they are exempt from being regulated, particularly in non-plant systems. Further, the stakeholders highlighted concern over the use of successive rounds of new technologies that could lead to substantial change (i.e. as discussed in the Discussion Paper). Although not backed by scientific evidence, these views emphasise the importance of engagement by the Regulator with all stakeholders and need for leadership in addressing public uncertainty around perceived biosafety risk.

[1] The FAO/IAEA Mutant Variety Database (https://mvd.iaea.org)
[2] Australian Government Guide to The Regulation (www.cuttingredtape.gov.au)

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

The LTIBC recognises the challenges of broadly applying Option 4 to all organisms, for example, pests or disease-causing organisms where exclusions may not be commensurate with the level of risk posed by these techniques. The LTIBC believes there is sufficient scope within the current regulatory framework to develop or amend existing Schedules to provide guidance for IBCs and researchers in applying regulation to such applications. For example, regulation could be applied to applications whereby the outcome/product is immunomodulatory, a pathogenic determinant, oncogenic or increases the likelihood of establishment and persistence in the environment.

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

The LTIBC is of the view is that products developed through technologies such as SDN-1, SDN-2 and ODM should not be differentially regulated if the products are like or indistinguishable from those that could have been produced through established conventional mutagenesis techniques. The literature provided in Supplement 1 provide peer reviewed scientific support to this notion. Further, any application/addition of regulation should adhere with the principles outlined in The Australian Government Guide to Regulation.

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

The LTIBC is of the view that any additional regulatory impost should be based on the risks inherent to the outcome/end-product, not the process used to develop that outcome/product. The scientific literature demonstrates that technologies such as SDN-1, SDN-2 and ODM offer potentially lower risk to human health safety and the environment than traditional mutagenesis techniques that have a long history of safe use.

The LTIBC advocate that if the adoption of either Options 2 or 3 are considered then the information and data requirements for undertaking a biosafety risk assessment should be commensurate with the lower level of risk that has been demonstrated with the use of these technologies.

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

Item 1 of Schedule 1A states: "*Mutant organism in which the mutational event did not involve the introduction of any foreign nucleic acid (that is, non-homologous DNA, usually from another species).*"

This item is incongruent with other definitions within the *'Act',* such as:

> ***gene technology:*** any technique for the modification of genes or other genetic material
>
> ***genetically modified organism***: an organism that has been modified by gene technology

There is a need to provide more definitions around mutagenesis as well as providing consistency in the definitions with other government agencies (e.g. FSANZ).

The LTIBC sought guidance from the OGTR with respect to governance over dealings with modified genes where no 'foreign DNA' was introduced (i.e. interpretation of Item 1 with respect to new techniques).

Based on OGTR advice, dealings with old and new technologies that modify genes and genetic material (other than those listed in Schedule 1A) have been considered as genetically modified organisms and regulated in accordance with the *'Act'.*

Given the current uncertainty, the LTIBC has taken a precautionary and conservative approach to new technologies and advises researchers to seek IBC assessment and approval for applications that will utilise any new technologies. This has been met with some resistance from several researchers citing the lack of regulatory consistency with other mutational techniques. However, the use of new technologies is typically part of much broader research programs that require assessment and approval under the current regulatory framework. As such, the current "in lab" burden is minor, but it is expected that as the costs associated with the technologies reduce and opportunities for products to have a commercial value increase so too will the regulatory burden.

Examples of how the LTIBC currently provides governance to new technologies is provided below. The recommended classification of dealings is dependent on the type of Site Directed Nuclease application used. For example:

- the propagation of plasmids with the non-specific CRISPR-associated endonuclease (CAS9) gene and the targeted guide RNA (gRNA) is considered an Exempt Dealing with a Host/Vector system Bacteria/non-conjugative plasmid
- the introduction of the CRISPR/Cas9 system for Non-Homologous End Joining (NHEJ) and homology directed repair (HDR), (and for HDR, the template 'donor' or guide DNA), in cell culture is considered an Exempt Dealing with a Host/Vector system, Tissue culture/non-conjugative plasmid or Tissue culture/none (non-vector systems). Tissue culture can, for example, be *C. elegans* cells, cell lines or early non-human mammalian embryos cultured *in vitro*
- if, for example, a modified animal embryo is implanted into an animal or a culture or tissue is used to regenerate into a whole plant then the dealing is deemed capable of generating a whole animal or plant and NLRD classifications are considered (other than for *C. elegans* which remains Exempt). For example, NLRD PC1 1.1 (a) for edited mice, NLRD PC2 2.1 (b) for edited plants and NLRD PC2 2.1 (a) for other edited animals.
- All edited dealings that utilise a lentivirus system are classified as NLRD PC2 2.1 (l).

The LTIBC recommend that Item 1 should be clarified or removed and that Schedule 1 be revised to provide the framework whereby the regulation of new technologies is commensurate to the risks (i.e. only applicable when applied to pests or disease-causing outcomes).

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

The LTIBC has no comment on the use of gene drive.

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

The LTIBC provides oversight for several programs that utilise RNA interference. Principally it is used as a tool for the targeted down regulation of gene expression in a research and development context. This process is highly conserved in plants, insects, fungi, nematodes, and animals.

Current activities are undertaken under containment conditions as assessed on a case by case basis. This may not be commensurate to the risk to human health and safety or to the environment. RNA interference has been used to develop several commercial products that are consumed by humans and animals. Over 130 food and feed approvals exist in 16 countries for biotech crops using siRNA[3]. In Australia, the bi-national government agency, Food Standards Australia New Zealand (FSANZ), which evaluates food safety requirements from biotech foods stated, "*There is no scientific basis for suggesting that small dsRNA present in some GM foods have different properties or pose a greater risk than those already naturally abundant in conventional foods*"[4]. FSANZ has assessed and approved for human consumption several products that use RNA interference[5].

Based on the large number of international assessments and approvals there appears to be a global regulatory consensus that consumption by humans and animals of RNA including RNA transcripts, such as dsRNA and siRNA, is safe. Therefore, the level of containment and oversight ascribed to RNA interference should be re-examined.

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

The LTIBC proposes three additional amendments to the *Gene Technology Regulations*:

1. That zebrafish (*Danio rerio*) be considered similarly to laboratory animals listed in Schedule 3 Part 1.1(a) for which a PC1 level of containment is considered sufficient, unless the nature of the donor DNA warrants a higher level of containment (e.g. Donor DNA is a pathogenic determinant, oncogenic or immunomodulatory). Our reasons for requesting this include:
    a. Unlike mice, rats or rabbits, zebrafish have not become, and do not appear able to become, feral in the Australian environment and are not able to cross-breed with Australian native species.
    b. Zebrafish gametes or embryos cannot survive for lengthy periods under sub-optimal environmental conditions and therefore there is a negligible risk that any genetically modified zebrafish will escape into the Australian environment[6]

[3] ISAAA 2015–Brief 51: 20th Anniversary (1996 to 2015) of the Global Commercialization of Biotech Crops and Biotech Crop Highlights in 2015
[4] FSANZ 2013–Response to Heinemann et al on the regulation of GM crops and foods developed using gene silencing
[5] http://www.foodstandards.gov.au/consumer/gmfood/applications/Pages/default.aspx
[6] Spence R, Gerlach G, Lawrence C, Smith C. The behaviour and ecology of the zebrafish, *Danio rerio*. Biological Reviews. 2008;83:13–34.

c. Appropriate containment conditions for aquatic organisms that are infected with, or which may contain, hazardous or infectious microorganisms, will be detailed in the revised AS2243.3 Aquatic Organisms Section.

d. Changes to the current restrictions on GMO work with zebrafish that are commensurate to the risks to human health and safety and to the environment could mean that the aquaria that house them may not be subject to expensive over-designed containment facilities and conditions in order to deal with them.

2. That *Drosophila melanogaster* (the vinegar fly) be considered similarly to laboratory animals listed in Schedule 3 Part 1.1(a) for which a PC1 level of containment is considered sufficient, unless the nature of the donor DNA warrants a higher level of containment (e.g. Donor DNA is a pathogenic determinant, oncogenic or immunomodulatory). Our reasons for requesting this include:

   a. The PC2 containment levels in Australia are out of step with other modern countries conducting research with GM flies (e.g. US, UK, Europe), where work is conducted at a PC1 level, unless the nature of the genetic modifications has an inherent higher risk and warrants PC2.

      In the United States, almost all transgenic Drosophila research is considered at Biosafety Level 1, the least restrictive containment level under the NIH Guidelines (http://osp.od.nih.gov/sites/default/files/NIH_Guidelines.html). However, when the nature of the Genetic Modifications constitutes a real risk to human health and safety, then a higher level of containment is required. For example, flies expressing prion sequences or gene drive constructs.

   b. *Drosophila melanogaster* is an experimental species that has been used for genetic research since 1909. There is a very low level of inherent risk to the environment and human health with this species because:

      i. It is already an established species in Australia, and is found throughout the world.

      ii. It is not a disease carrying vector like mosquitoes, Tsetse fly, etc.

      iii. It does not bite or sting

      iv. It is not a crop pest.

      v. Although *D. melanogaster* is often called a fruit fly it is not a true fruit-fly such as the family Tephritidae. Therefore, it does not affect any agricultural crop. It should also be distinguished from the spotted winged Drosophila species *Drosophila suzukii* that is a fruit pest species.

   c. Laboratory-kept Drosophila are disadvantaged and do not survive or persist outside of controlled laboratory conditions. In the literature, studies have shown that when wild Drosophila are brought into a laboratory setting and cultured under standard laboratory conditions they rapidly adapt to a 'laboratory life' and lose inherent advantages such as tolerances to abiotic stress or lose the traits required to survive and successfully reproduce in the wild[7] [8].

[7] Hoffmann, A. A., R. Hallas, C. Sinclair, and L. Partridge. 2001. 'Rapid loss of stress resistance in Drosophila melanogaster under adaptation to laboratory culture', Evolution, 55: 436-8.
[8] Sgro, C. M., and L. Partridge. 2001. 'Laboratory adaptation of life history in Drosophila', Am Nat, 158: 657-8.

3. The following techniques, when applied to plants, should not be classified as genetic modification:

    a. The generation and use of null-segregants. There is no scientific basis for organisms that are derived from GMOs that no longer contain a functional DNA insert that was integrated into the genome to be regulated under the *'Act'*. Null segregants are no longer a transgenic event due to loss of the transgene by segregation following conventional breeding with a sexually compatible plant that did not contain the transgenic event. These organisms do not contain any elements of the transgenic event and therefore cannot be identified as being a GMO, or derived from one, using molecular detection tools. Null segregants are therefore indistinguishable from that obtained through conventional breeding methods and should not be regulated.

    b. Cisgenics. Cisgenic plants are characterised by using donor DNA cassettes (i.e. protein coding genes and non-coding regulatory sequences) that originate from the species being modified or a sexually compatible species (i.e. from the wider sexually compatible gene pool for the species). The resulting plants could, in principle, be developed using conventional breeding techniques.

    This is consistent with the conclusion reached by the GMO Panel of the European Food Safety Authority that cisgenic and conventionally bred plants share similar hazard profiles[9]. The types of changes that may occur in the genome due to cellular DNA repair mechanisms during conventional breeding are also expected to occur at the integration site in cisgenic plants, but only at that locus[10].

4. Allow IBCs greater powers and flexibility in the management of containment facility certification. The suspension and reinstatement of Physical Containment (PC) certification is largely an administrative process for the OGTR with on the ground oversight already provided by IBCs. Amendments to PC certification is an unnecessary burden on the OGTR and risks significant delays to research and business continuity at the institutional level. This is further compounded by the promotion of larger and fewer certification areas that limits future flexibility in the PC certification composition of an area, without research impost. Currently, this is largely managed through lab processes such as spatial and temporal separation of GM and non-GM activities.

    The LTIBC advocates greater responsibility for IBCs to manage the suspension and reinstatement of PC certification.

[9] European Food Safety Authority Panel on Genetically Modified Organisms (2012) Scientific opinion addressing the safety assessment of plants developed through cisgenesis and intragenesis, EFSA Journal 10: 2561.
[10] European Food Safety Authority Panel on Genetically Modified Organisms (2012) Scientific opinion addressing the safety assessment of plants developed through cisgenesis and intragenesis, EFSA Journal 10: 2561.

Supplement 1 – New Breeding Technology Literature Reviewed

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