**CSIRO Symposium on the use of Gene Drive Technology in Controlling Pests and Diseases**

**29 June 2016 – CSIRO Discovery Centre, Black Mountain Laboratories, Canberra**

**Notes**

*Key Points*

s22

- s22 – Island Conservation
  - Islands present a unique testing environment for early field use of gene drives, particularly in their application to rodents.
  - Islands are one way to alleviate concerns regarding the 'global gene drive' concept – once a gene drive is released; it's out there for good.

s22

Professor Anne Kelso AO
Chief Executive Officer
National Health and Medical Research Council
GPO Box 1421
Canberra City
ACT, 2601

Anne

Dear Professor Kelso

Thank you for your letter of 8 February 2017 regarding the principles for funders of gene drive research.

The Department is responsible for the United Nations Convention on Biological Diversity. The Parties to the Convention lead negotiations on how the international community may view, define and regulate synthetic biology and by extension gene drives in the context of the objectives of the Convention.

While we can see the merit in supporting the principles proposed in the attachment to your letter, we would recommend support for these principles does not lead to endorsement of the associated paper *Gene Drives on the Horizon*. This publication, for example, identifies a need for international regulation of gene drives and implies the Convention and its sub-Protocols may be a vehicle in which to do this. This approach would be difficult and resource intensive for the Australian Government to implement and may be contrary to some existing whole of government negotiating positons, legislative instruments and policy frameworks.

Should you or your offices wish to discuss these matters further please contact Ms Emma Campbell on (02) 6274 2501.

Yours sincerely

Kylie Jonasson
First Assistant Secretary
Biodiversity Conservation Division
21 February 2017

cc. s22 , ED, Evidence Advice and Governance

FOI 180412
Document 7

s22

**From:** s22
**Sent:** Friday, 2 June 2017 10:01 AM
**To:** s22 @environment.gov.au>
**Subject:** AG briefing Principles for sponsors of gene drive research [SEC=UNCLASSIFIED]

s22

Thanks for your assistance. I should be grateful for your comments on the revised text – in track changes in the attached or if you're reading on Good:

- The Department of the Environment and Energy is responsible for the United Nations Convention on Biological Diversity. The Parties to the Convention are leading negotiations on how the international community may view, define and regulate synthetic biology and, by extension, gene drives in the context of the objectives of the Convention. The Department has advised the NHMRC that, while we can see merit in supporting the principles, we recommend that support does not lead to endorsement of the associated paper *Gene Drives on the Horizon*.

s22

Regards

s22

s22
Director, Environmental Biosecurity
Department of the Environment and Energy

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s22 @environment.gov.au

FOI 180412
Document 7a

| NATIONAL BIOSECURITY COMMITTEE | MEETING No: 25 |
|---|---|
| | LOCATION: Darwin, NT |
| | DATE: 7 JUNE 2017 |
| AUSTRALIAN GOVERNMENT BRIEFING | ITEM: 10 |

## PRINCIPLES FOR SPONSORS OF GENE RESEARCH

**DESIRED OUTCOME**

- The NBC **NOTES** that the National Health and Medical Research Council and CSIRO have become signatories to the principles for funders of gene drive research.

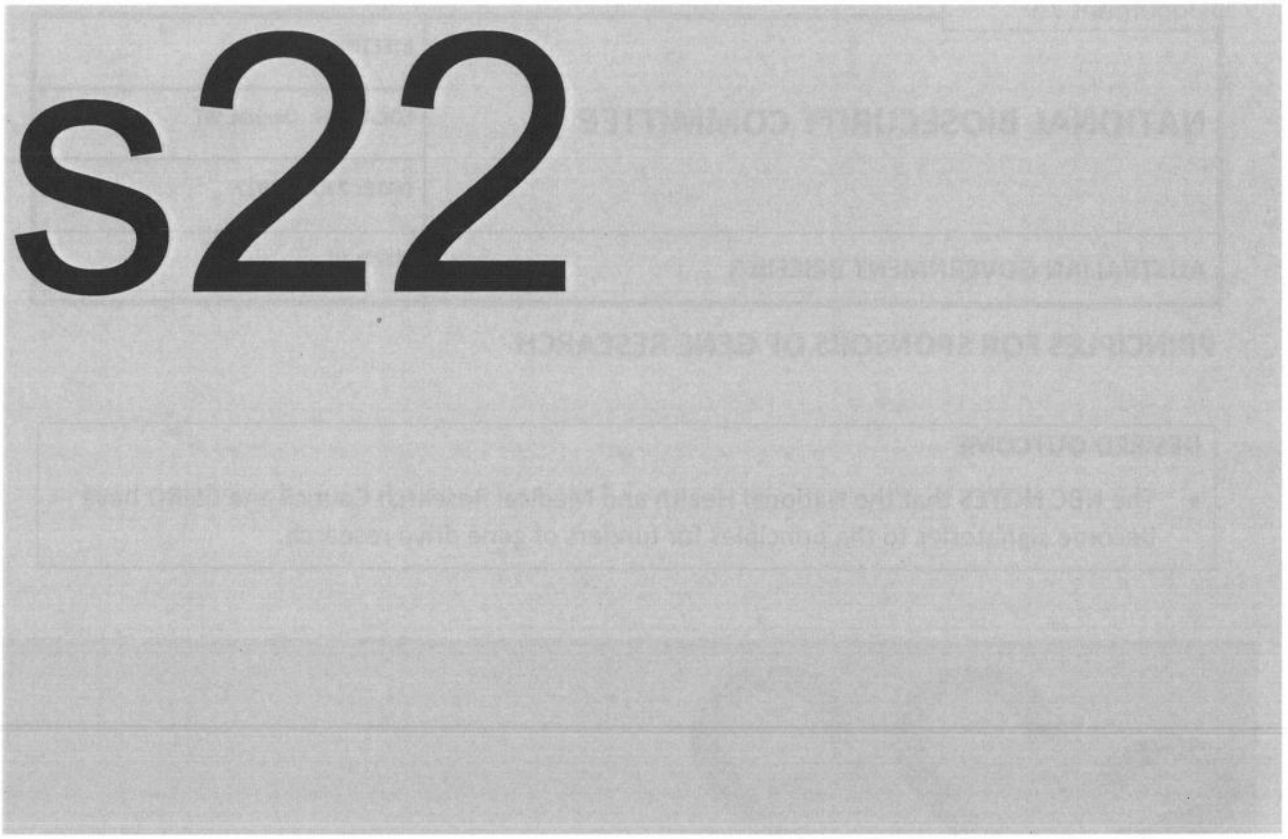
s22

**POSITION OF OTHER MEMBERS**

s22

- The Department of the Environment and Energy is responsible for the United Nations Convention on Biological Diversity. The Parties to the Convention lead negotiations on how the international community may view, define and regulate synthetic biology and, by extension, gene drives in the context of the objectives of the Convention. The Department has advised the NHMRC that, while we can see merit in supporting the principles, we recommend that support does not lead to endorsement of the associated paper *Gene Drives on the Horizon*s22

s22




| | | | |
|---|---|---|---|
| SES Clearing Officer: | Kim Ritman | Contact Officer: | s22 |
| Telephone: | 02 62724671<br>0409841442 | Telephone: | 02 s22 |

Date: 13 Feb 2017

Australian Government
Department of the Environment and Energy

To: The Legislative and Governance Forum on Gene Technology

*Submission with respect to the third review of Australia's Gene Technology Scheme from the Department of the Environment and Energy*

The Department of the Environment and Energy (Department) welcomes the opportunity to make a submission with respect to the 2017 review of Australia's Gene Technology Scheme (the Scheme).

The Department considers that the Scheme has operated successfully since its conception, assessing and managing the risks to human health, safety and the environment. Based on the defined Terms of Reference for the 2017 Review, the Department has performed a horizon scan of issues that could be considered during the review. These issues include:

- International developments in the regulation of gene technology, and the relevance of these to the operation of the Scheme in Australia
- Explore options to ensure that the approach to environmental risk assessments of GMO releases is efficient and commensurate with the level of identified risk. A large amount of experience has accumulated in dealing with certain kinds of GMOs and this is one aspect that could be considered when reviewing the efficiency of the risk assessment process, particularly in relation to genetic modifications of plants that have been the subject of a number of previous risk assessments.
- Consideration of the systems and processes that are in place for the reporting of adverse impacts of GMOs.
- Advances in biotechnology (such as gene drives) provide tools that could be used for germ-line manipulation of species. There are a wide range of potential applications for these technologies ranging from eradication of pests (e.g. mosquitos or rodents) to protection of threatened species (e.g. protecting Tasmanian Devils from facial tumours). The scope of the review should consider ethical questions concerning germ-line manipulation of species.
- Evaluating Australia's regulatory framework for Genetically Modified Products (as distinct from Genetically Modified Organisms) to ensure that interactions between regulatory schemes are efficient and effective.

The Department believes that the current Scheme has built and maintained public confidence in its ability to deal with the health and environmental risks of GMOs.

Additionally Australia has made a number of relevant submissions, drawing on input from a range of Australian Government agencies, to the United Nations Convention on Biological Diversity (CBD) which we have attached for reference.

Consideration of the above issues and attached submissions will help position the Scheme for the future.

James Tregurtha
Acting First Assistant Secretary
Environment Standards Division
Department of the Environment and Energy

21 September 2017

# CONVENTION ON BIOLOGICAL DIVERSITY (CBD) NOTIFICATION 2015-013

## Submission of Information on Synthetic Biology

## Submission by Australia

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**NOTE: All information provided in this response has been drawn from Australian Government agency inputs only. No consultation with State and Territory governments was possible for this notification due to the deadline for the response.**

## Notification 2015-013: Submission on Synthetic Biology

Australia is responding to the invitation to Parties to the Convention on Biological Diversity (the Convention) other Governments, relevant organisations and indigenous peoples and local communities to submit information relevant to the Ad Hoc Technical Expert Group (AHTEG) on Synthetic Biology as referenced in decision XII/24. Australia thanks the Secretariat for the opportunity to provide input on this issue.

It is Australia's view that:

- synthetic biology, and any organism that is produced by this means, would be covered by definitions in the Cartagena Protocol on Biosafety, as well as, Australia's gene technology legislation.
- current risk identification and assessment methodology as outlined in the Cartagena Protocol and Australia's Risk Analysis Framework is equally applicable and adequate to assess risks from synthetic biology.

***Introductory remarks***

Australia acknowledges that the term 'synthetic biology' is being used more widely in science to differentiate between the conceptual approaches used by synthetic biologists versus that of the more traditional biotechnologists. There are also arguments which suggest that synthetic biology is qualitatively different from modern biotechnology. However, given the large overlap in techniques and applications, Australia questions whether this is the case.

Australia reiterates its view, as submitted at SBSTTA 18 and COP12, that synthetic biology does not meet the criteria of a new and emerging issue, but is willing to engage in discussions anchored in sound science to explore whether there are synthetic biology applications capable of posing inherently different risks to biological diversity that fall outside of the Cartagena Protocol.

Australia also reiterates that it is important to distinguish between synthetic biology techniques undertaken in containment and environmental release of organisms derived from synthetic biology. Most applications of synthetic biology in the near future are confined to laboratory research or contained manufacturing. While it is difficult to predict how soon products of synthetic biology may be ready for wider environmental release, it is unlikely commercial applications of synthetic biology (especially organisms) would be proposed in the near future that would not be categorised and regulated as gene technology and genetically modified organisms (GMOs) in Australian and other national legislation or modern biotechnology and living modified organisms (LMOs) in the Cartagena Protocol on Biosafety[1].

**a- Information that is relevant to the work of the AHTEG, including views on:**

***Relationship between synthetic biology and biological diversity***

*i- How to address the relationship between synthetic biology and biological diversity;*

The majority of current synthetic biology applications in development are for contained use (research or manufacturing) and are therefore somewhat removed from a direct impact on the environment and biological diversity. From a process point of view, large scale manufacturing using a synthetic organism would be similar if not the same as other more traditional manufacturing processes using wild type (or modified) organisms (e.g. large scale fermentation), including the sourcing of input materials and treatment of process wastes. Therefore, it is important to identify causal pathways by which the use of synthetic organisms might impact on biological diversity, and whether any of those causal pathways are inherently different from those identified for wild type or LMOs and their products.

[1] For simplicity, the acronym 'LMO' used from this point forward is taken to also encompass 'GMO's, as defined under Australian national legislation.

***Similarities & Differences***

*ii- The similarities and differences between living modified organisms (as defined in the Cartagena Protocol) and organisms, components and products of synthetic biology techniques;*

In Australia's view, the term 'synthetic biology' has increasingly been used to describe a subset of biological research in which the tools of gene technology are used to apply engineering principles to the fundamental components of biology. That is, using the knowledge and tools of biotechnology to reduce biology to its most basic functional units (genes, proteins and pathways) then modify and reassemble them to produce a novel organism capable of efficiently producing the required outcome. This can be carried out *in vitro,* using modern biotechnology, or *in silico,* with the designed genome being chemically synthesised and used to create the organism (also a modern biotechnology technique). The term synthetic biology is being used to separate this, ground up, additive approach (synthesis), from the more traditional deletion or transfer approach (modification). Some synthetic biology applications may also involve the use of artificial amino acids or nucleic acids (xenobiology), though these are still at a very early stage of development and are a long way from commercialisation or release.

The broad and interdisciplinary nature of approaches described as 'synthetic biology' makes similarities and differences between synthetic biology products and living modified organisms problematic to describe categorically. As with much other contemporary scientific research there is a continuum of work being undertaken with synthetic biology representing an evolution of biotechnology towards the application of multidisciplinary engineering / systems approaches in which scientists and engineers think of DNA and proteins as parts, devices, and systems. These components can then be used and combined in new ways to achieve different outcomes.

However, in all cases the end result is a modified organism with intentional changes to its biology. The outcome of these changes can be predicted and the potential for risks or benefits from these organisms can be assessed through already established risk assessment processes used for LMOs.

The Cartagena Protocol defines 'modern biotechnology', which is part of the definition of an LMO, as follows:

*"Modern biotechnology" means the application of:*

> *a. In vitro nucleic acid techniques, including recombinant deoxyribonucleic acid (DNA) and direct injection of nucleic acid into cells or organelles, or*
>
> *b. Fusion of cells beyond the taxonomic family,*
>
> *that overcome natural physiological reproductive or recombination barriers and that are not techniques used in traditional breeding and selection.*

The use of 'including' in part (a) of the definition indicates that the list of techniques which follows is a selection of examples of *in vitro* nucleic acid techniques, rather than a definitive list. Therefore, it is arguable that synthetic biology, in each of its various manifestations, can be described as part of modern biotechnology.

Current biotechnology applications labelled as synthetic biology, such as the production of food ingredients (e.g. vanilla flavouring) or cosmetics (e.g. rose fragrance), involve the modification of existing organisms through the addition of genes coding for entire biosynthetic pathways and/or the modification of existing genes and gene pathways to allow the production of new molecules. If such organisms are described as products of synthetic biology due to the addition of one or more biosynthetic pathways, they are very similar to some LMO plants that are considered products of modern biotechnology and, therefore, currently regulated. In these cases a parent organism and/or donor organisms can be identified and their known characteristics used in the assessment of the properties of the new 'synthetic' organism. Science-based risk assessment of these organisms is possible within the existing regulatory frameworks.

For extensively modified organisms, the scale of changes may impact on the usefulness of the parent organism as a comparator. Further information may also be required for the assessment of organisms using novel nucleic acids (xenobiology), including their ability to persist outside of laboratory conditions and their capacity to transfer genetic material to other organisms. However, the production, commercialisation and release of the potential products of xenobiology are a long way off. This expected development time and process should allow for better understanding of any scientific and regulatory gaps, including where these products might diverge from those encompassed by current regulatory instruments, including the Cartagena Protocol.

***Current best practice & Adequacy of existing regulation***

*iii- Adequacy of existing national, regional and/or international instruments to regulate the organisms, components or products derived from synthetic biology techniques;*

*vi- Best practices on risk assessment and monitoring regimes currently used by Parties to the Convention and other Governments, including transboundary movement, to inform those who do not have national risk assessment or monitoring regimes, or are in the process of reviewing their current risk assessment or monitoring regimes;*

Australia reiterates its previous submission to CBD Notification 2014-090, that current synthetic biology applications for research and commercial purposes involve the modification of existing organisms in ways that would be captured by regulatory schemes which cover LMOs. End products which are not themselves LMOs may be captured by other existing product regulators, such as those responsible for regulating therapeutic goods, agricultural chemicals or industrial chemicals.

In Australia, organisms created via synthetic biology would be regulated under the *Gene Technology Act 2000* (the GT Act) and applications for release into the environment would be subject to a science-based, case by case assessment. The GT Act and corresponding state legislation are administered by the Gene Technology Regulator, supported by the Office of the Gene Technology Regulator (the Office). The GT Act includes definitions of 'gene technology' and 'genetically modified organism'. Based on these definitions, known and proposed synthetic biology applications would be regulated in Australia under the GT Act. Australia maintains a watching brief on synthetic biology. The Australian gene technology regulatory scheme undergoes periodic review to ensure that it keeps pace with technology developments and scientific knowledge regarding risks. In this context, the Gene Technology Technical Advisory Committee (Technical Committee) provides scientific and technical advice to the Regulator on biosafety and gene technology.

Certain products arising from synthetic biology may also be regulated by other Australian agencies if they meet relevant definitions in the associated legislation such as, for therapeutic goods (the Therapeutic Goods Administration - TGA), veterinary and agricultural products (Australian Pesticides and Veterinary Medicines Authority - APVMA), industrial chemicals (National Industrial Chemicals Notification and Assessment Scheme - NICNAS), and foods or food packaging (Food Standards Australia New Zealand - FSANZ). The Gene Technology Regulator also has the ability to impose licence conditions relating to GM products, this could occur where end products are not regulated by other agencies, and a risk requiring management has been identified.

Other international best practice, such as good laboratory practices (GLP) and good manufacturing practices (GMP), would guide both research and commercial scale synthetic biology applications.

In Australia, research involving synthetic biology is subject to the same general requirements as all other research, including avoiding harm to human health or the environment. Access to funding under the Australian Research Council requires adherence to the *Australian Code of Conduct for Responsible Research* developed by the National Health & Medical Research Council, the Australian Research Council and Universities Australia https://www.nhmrc.gov.au/guidelines-publications/r39.

Import of organisms not native to Australia, and biological products would require authorisation from the Department of Agriculture under the *Quarantine Act 1908* http://www.agriculture.gov.au/import. Import of GMOs requires additional authorisation under the GT Act.

***Definition***

*iv- An operational definition of synthetic biology, comprising inclusion and exclusion criteria;*

Australia notes that there is no agreed definition of synthetic biology, internationally or scientifically. Synthetic biology is a very broad, umbrella term encompassing and/or applied to a wide, and varied, range of techniques and potential applications and end products. Many techniques described as synthetic biology may equally be described as techniques of modern biotechnology, gene technology or genetic engineering, in particular those applications that are closest to commercial scale application. We reiterate that, given the current debate over organisms currently classified as LMOs and those that would be described as the products of synthetic biology, existing tools and approaches for environmental risk identification and assessment are equally applicable to organisms and products derived from synthetic biology techniques. Australia recognises work being undertaken by other national and international bodies (for example, the European Commission) to develop a working definition of synthetic biology and recommends that any Convention work in this area should be in collaboration with these fora to avoid any contradictions in the definition developed.

Because of the breadth of techniques and applications which may be included in the term, agreement of a sensible definition for synthetic biology may be problematic and/or elusive. Time may be better spent in identifying/cataloguing applications referred to as synthetic biology that do not fall within the existing broad definition of "modern biotechnology" and LMOs contained within the Cartagena Protocol. These applications can then be assessed to determine whether they might pose inherently different risks to biological diversity that need to be managed.

However, should the parties to the Convention decide to move forward in developing a definition, care should be taken that the effort/time taken to develop the definition does not exceed the value of such a definition. Focus should be on developing a definition that is useful for determining which, if any, aspects of synthetic biology fall outside of current regulation and result in actual risks to biological diversity.

***Risks and Benefits***

*v- Potential benefits and risks of organisms, components and products arising from synthetic biology techniques to the conservation and sustainable use of biodiversity and related human health and socioeconomic impacts relevant to the mandate of the Convention and its Protocols;*

Given the overlap between modern biotechnology and synthetic biology, the risks and benefits arising from synthetic biology are expected to be similar to those arising from other novel organisms and their products.

Additionally, synthetic biology based work carried out entirely within containment (research, development and manufacturing) would have little or no direct contact with the environment and its biodiversity. Risk identification would need to demonstrate a clear and viable linkage between the contained work and any potential adverse environmental impact. It would also need to demonstrate that any risks identified as arising from synthetic biology are inherently different from those posed by similar uses of wild type or LMOs in order to require different management/regulation.

Australia supports a case by case, science-based risk-assessment of synthetic biology applications to identify actual risks to biodiversity and related human health. Management of identified risks (if any) should be consistent with relevant international obligations and current regulatory frameworks for LMOs.

One of the greatest potential benefits of synthetic biology would be the capacity to engineer microorganisms to be able to produce any naturally occurring molecule (e.g. flavours, scents, dyes or pharmaceuticals) and thereby eliminating the need to cultivate large monocultures of the original source plants or animals. This would also reduce the amount waste produced during extraction and purification

from the original organisms. Additionally, the ability to produce novel molecules could benefit human health by producing designer pharmaceuticals. Synthetic organisms would also be able to produce desired products all year round and would not be impacted by growing seasons, weather extremes or the need to cultivate crops in both hemispheres. This could reduce the area of land required for commercial cultivation, aiding in the conservation and sustainable use of biodiversity.

A potential benefit of xenobiology is the requirement for a substance which is not found in nature. Organisms with artificial amino acids (and which do not encode a pathway enabling them to produce the artificial amino acid) would be reliant on the supply of that amino acid and would not be able to survive in environments where the amino acid is not present. Organisms with artificial nucleic acids would not be able to exchange DNA with wild type organisms, as the recipient organism would not have the ability to replicate or translate the novel sequences. This would prevent any engineered or novel genes from 'escaping' into the natural pool of biodiversity, and again may be self-limiting, if an artificial substance is required for the production of the new nucleotides. Therefore, there would be minimal potential for harm arising from an intentional or accidental release of these organisms.

***Current effectiveness?***

*vii -The degree to which the existing arrangements constitute a comprehensive framework in order to address impacts of organisms, components and products resulting from synthetic biology relevant to the objectives of the Convention on Biological Diversity and its Protocols, in particular threats of significant reduction or loss of biological diversity;*

Currently, Australia is not aware of any synthetic organisms or novel products of synthetic biology ready for release into the environment. Nor is Australia aware of any evidence that current synthetic biology applications would result in inherently different risks to biological diversity that might be posed by wild type organisms or LMOs.

Contained work is covered by codes of responsible conduct which allow for research and developmental work to be carried out safely and sensibly. National and international biosafety and biosecurity legislation and/or codes of conduct provide for organisms to be contained in a manner which minimises exposure of people and the environment to potentially dangerous microorganisms.

**b- Information on measures undertaken in accordance with paragraph 3 of the decision, including the identification of needs for guidance; and**

Currently, all work with synthetic organisms in Australia would require authorisation under the GT Act. Contained work, including large-scale manufacture, must be carried out in facilities certified by the Regulator as being suitable for the work to be carried out. The certification of facilities covers both structural and behavioural aspects of containment.

Regulation of genetically modified organisms under the GT Act is underpinned by case by case, scientific risk assessment. For all proposed environmental releases of genetically modified organisms (including synthetic organisms), the Regulator must prepare a comprehensive risk assessment and risk management plan and consult with relevant State and Territory Government(s), The Australian Minister for the Environment, the Technical Committee, other regulatory agencies, Local Government and the public. Licences impose conditions to manage any risks to human health and the environment. Non-compliance with the GT Act or licence conditions carries significant penalties. Products of synthetic biology which do not meet the criteria to be GMOs are regulated by other product regulators, as identified in the answer to (iii) above.

To date, Australia has not received any applications for the intentional release of a synthetic organism into the environment. Work involving the large scale production or manufacture of synthetic organisms is also not being conducted in Australia at present.

**c- Further information on the components, organisms and products resulting from synthetic biology techniques that may have impacts on the conservation and sustainable use of biological diversity and associated social, economic and cultural considerations.**

Australia is not aware of any additional information to add at this stage.

# CONVENTION ON BIOLOGICAL DIVERSITY (CBD) NOTIFICATION 2017-025

## Submission of information on synthetic biology and nomination of experts to participate in the Open-ended Online Forum on Synthetic Biology

## Submission by Australia

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**NOTE: All information provided in this response has been drawn from Australian Government agency input only.**

**Notification 2017-025 Submission of information on synthetic biology and nomination of experts to participate in the Open-ended Online Forum on Synthetic Biology**

Australia is responding to the invitation to Parties to the Convention on Biological Diversity, other Governments, relevant organisations and Indigenous peoples and local communities to:

(b) submit information and supporting documentation relevant to the Ad Hoc Technical Expert Group (AHTEG) on Synthetic Biology as referenced in paragraph 10 of decision XIII/17, and

(c) nominate experts to participate in the Open-ended Online Forum on Synthetic Biology.

Australia thanks the Secretariat for the opportunity to provide input on these matters.

***Introductory remarks***

Australia reiterates key points from its previous submission on synthetic biology (2015-013). In particular, it is Australia's view that:

- current synthetic biology applications are not qualitatively different from modern biotechnology
- synthetic biology, and any organism that is produced by this means, would be covered by definitions in the Cartagena Protocol on Biosafety, as well as Australia's gene technology legislation
- current risk identification and assessment methodology, as outlined in the Cartagena Protocol and Australia's Risk Analysis Framework 2013, is equally applicable and adequate to assess risks from synthetic biology
- it is important to distinguish between synthetic biology techniques undertaken in containment and environmental release of organisms derived from synthetic biology
- Australia supports a case-by-case, science-based risk assessment of synthetic biology applications to identify plausible risks to biodiversity and related human health. Management of identified risks (if any) should be consistent with relevant international obligations and current regulatory frameworks for LMOs
- synthetic biology does not meet the criteria of a new and emerging issue, but Australia is willing to engage in discussions anchored in sound science to explore whether there are synthetic biology applications capable of posing inherently different risks to biological diversity that fall outside of the Cartagena Protocol.

> (a) submit information and supporting documentation relevant to the Ad Hoc Technical Expert Group (AHTEG) on Synthetic Biology as referenced in paragraph 10 of decision XIII/17.

In response to those elements detailed in paragraph 10 of decision XIII/17, Australia wishes to submit the following information:

*(a) Research, cooperation and activities noted in paragraph 9 of decision XIII/17*

For two decades, Australia's Commonwealth Scientific and Industrial Research Organisation (CSIRO), the principal agency for scientific research in Australia, has conducted benchmark research on the development of genetic based biological control technologies for invasive species management, both plant and animal. These include:

i) insertion of gene constructs to manipulate sex expression in invasive species in the context of meiotic gene-drives based on Mendelian inheritance (so called "daughterless" or "sonless" approaches)

ii) immuno-contraception, which involves the use of an animal's immune system to prevent it from fertilizing offspring for the control of vertebrate pests like mice and foxes, through the genetic manipulation of specific viruses as delivery mechanisms

iii) the use of RNA interference creation and delivery to regulate gene expression to reduce fitness of pest organisms and

iv) initial studies of the potential of CRISPR gene-drive approaches.

As the authority responsible for the regulation of work with LMOs in Australia since 2001, the Gene Technology Regulator (the Regulator) has applied Australia's Risk Analysis Framework to produce scientific risk assessments for the conduct of the above research, and all work with LMOs in Australia. The Regulator uses these risk assessments and associated risk management plans to guide decisions on whether or not to authorise work with LMOs and to identify relevant conditions which should be imposed. This has enabled the safe research and work with LMOs in Australia.

CSIRO has many peer reviewed publications that can be supplied to support the pre-deployment research, scientific risk analysis, management strategies and post-deployment analysis of the use of these approaches. Synthetic biology provides new opportunities to develop biological control systems, through gene edited living organisms or LMOs containing synthetic gene drives, which substantially change the impact of an invasive organism. CSIRO is building on its 100 year history in the development of classical biological control solutions for managing invasive species causing environmental harm to understand the best approaches and scientific risks of synthetic biology based biological control.

In addition, CSIRO has a new research initiative that has established a series of Future Science Platforms (FSP) including one for synthetic biology. The Synthetic Biology FSP acts as a collaboration hub supporting synthetic biology research both within CSIRO and across Australia through university research partners. Activities include projects focused on developing synthetic biology based solutions to protect the environment and biodiversity, as well as projects feeding into risk assessment, including modelling ecological responses to interventions. The Synthetic Biology FSP is also developing a research program in understanding social, ethical, regulatory and legal issues related to synthetic biology.

The Australian Council of Learned Academies (ACOLA) is currently developing a report entitled 'The future of Synthetic Biology in Australia'. The report has been commissioned through the Office of the Chief Scientist and will be delivered by June 2018 for consideration by the Prime Minister's Commonwealth Science Council.

*(b) Evidence of benefits and adverse effects of synthetic biology vis-à-vis the three objectives of the Convention*

Although there is no hard data evidence from work conducted by CSIRO to support the above aims, experience gained from work conducted by the University of Queensland and Monash University introducing new strains of the bacterium *Wolbachia* into *Aedes* mosquitoes in an effort to reduce their potential to be efficient vectors for *Dengue Fever Virus* may provide insights on the risks, benefits and management of organisms containing engineered gene drives.

*(c) Experiences in conducting risk assessments of organisms, components and products of synthetic biology, including any challenges encountered, lessons learned and implications for risk assessment frameworks*

CSIRO has developed a risk analysis platform for understanding the scientific risks of releasing living modified organisms and funded projects to conduct risk assessments of both gene drive containing LMOs (in the first instance, the mouse) and the use of externally applied biological agents (namely small RNA to effect transient RNA interference effects). CSIRO is involved in international discussions and collaborations to advise and inform the risk assessment frameworks to better fit the issues of concern in the release of gene drive containing LMOs.

The Regulator has not received any applications for work with organisms badged as synthetic biology organisms. However, the Regulator has produced risk assessments for genetically modified viruses containing substantial percentages of genetic material from multiple organisms, whereby comparison to a single parental organism is not practical. Australia was able to adapt current risk assessment procedures to perform an assessment based on the total risk posed by the LMO rather than assessing potential risks arising from differences between the LMO and its parent organism. It is expected that this approach will be able to be applied to risk assessments for synthetic organisms for which there is no relevant parent organism.

*(d) Examples of risk management and other measures that have been put in place to avoid or minimize the potential adverse effects of organisms, components and products of synthetic biology, including experiences of safe use and best practices for the safe handling of organisms developed through synthetic biology*

The Regulator has a rigorous scheme in place for the regulation of all living modified organisms, including synthetic biology organisms. This includes requirements for containment and safe handling of LMOs not authorised for release, and provisions to impose licence conditions if LMOs are being released into the environment.[1] Recently, the Regulator also issued Guidance on the Regulatory requirements for contained research with GMOs containing engineered gene drives.[2] This includes information on the current regulation of organisms containing gene drives as well as advice on appropriate containment levels and measures. It is also important to note that the OGTR has developed different physical certification requirements tailored to different types of organisms. For example, the containment features and work practices required for a Plant Facility will be different to those for a Invertebrate Facility (e.g. for work with insects) or an Animal Facility (e.g. for work with mice), with the differences taking account of the different biology of the subject organisms.[3] The OGTR has guidelines for a range of different facility types and these are available from the OGTR website.[4] It should also be noted that Institutional Biosafety Committees play an important role in the Australian regulation of contained GMO research, both in the correct classification of approvals required and in 'on the ground' oversight of adherence to containment and other risk management requirements. It should be further noted that OGTR undertakes monitoring of lab-based research for compliance with regulatory requirements with a focus on higher risk activities, for example higher level containment facilities.

Laboratory-based research relating to synthetic biology within CSIRO is conducted at Physical Containment level 2 (PC2) as a minimum. Minimum containment requirements for work with GMOs are set by the Gene Technology Regulations 2001 or through specific licence conditions imposed by the GT Regulator.

Through dialogue between research organisations and regulators regarding the conduct of synthetic biology, research in the field of gene-drives is to be conducted using the conditions set by the GT Regulator and, if needed, supplemented by controls suggested in peer review articles. In particular, the genetic control by the use of "split gene-drive" components, artificial genomic targets and laboratory strains of animal rather than wild strains. When a unified gene-drive is being considered in a non-laboratory strain of animal, CSIRO has proposed that this would be conducted at PC3 level containment.

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[1] http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/section-working-with-gmos

[2] http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/53139D205A98A383CA257D4F00811F97/$File/OGTR%20guidance%20on%20gene%20drives.pdf

[3] http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/FacilTypesv1-2-htm

[4] http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/cert-pc2-1
http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/cert-pc3-1
http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/cert-pc4-1

CSIRO is the managing body for the Australian Animal Health Laboratory, with animal facilities that operate at this highest level of physical containment. Work of this nature is not yet underway nor are funds yet assigned for such work.

*(e) Regulations, policies and guidelines in place or under development which are directly relevant to synthetic biology*

As referenced above, the Regulator has legislation, regulations and guidelines in place that regulate all LMOs including synthetic biology. Please see the Australian Government submission to notification 2016-041 for further information on Australia's scheme and requirements - http://bch.cbd.int/database/record.shtml?documentid=110410

CSIRO is funded by the Australian Government and has a role as trusted advisor in areas of particular scientific expertise. CSIRO and other organisations work closely with national regulators to provide impartial advice relating to the potential benefits or risks of synthetic biology-based technologies and for the development of guidelines, policies and regulations pertaining to developments in synthetic biology and their impacts on environment and health. CSIRO only provides advice in this area and has no formal responsibility.

*(f) Knowledge, experience and perspectives of indigenous peoples and local communities in the context of living in harmony with nature for comparison and better understanding of the potential benefits and adverse effects of synthetic biology*

Through the recently establish Synthetic Biology Future Science Platform and its re-instigated Gene Technology Working Group, CSIRO will continue to build capability in the areas of scientific risk analysis. In addition to this, CSIRO has specific liaison with Indigenous peoples groups and will continue to work closely with them where synthetic biology activities have applications or implications for the natural environment.

| |
|---|
| (b) nominate experts to participate in the Open-ended Online Forum on Synthetic Biology. |

Names redacted

Names redacted

# CONVENTION ON BIOLOGICAL DIVERSITY (CBD) NOTIFICATION 2017-035

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Risk Assessment and Risk Management

Cartagena Protocol

Submission by Australia

Australian Government

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NOTE: All information provided in this response has been drawn from Australian Government agency input only.

## Australia's Submission to CBD Notification 2017-035

**Notification 2017-037 - Digital Sequence Information on Genetic Resources**

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Australia thanks the Secretariat for the invitation to submit views and relevant information requested in decision VIII/12 on Risk Assessment and Risk Management, as communicated in notification 2017-35 Ref.:SCBD/SPS/DC/MPM/MW/86376 of 12 April 2017.

In addition to the information provided in the annex to this submission, Australia wishes to draw to the attention of the Secretariat a number of documents produced by Australia's Office of the Gene Technology Regulator (OGTR) which provide guidance relevant to the risk assessment and risk management of Living Modified Organisms (LMOs) that may be of use to Parties. Australia shares this information in line with decision VIII/12 paragraph 4.

*Risk Analysis Framework*

The *Risk Analysis Framework* (RAF) is a key explanatory document that provides guidance on how the Gene Technology Regulator (the Regulator) and staff under the Regulator's direction in the OGTR approach the risk analyses of LMOs. The RAF incorporates risk assessment, risk management and risk communication and provides guidance on how to characterise and deal with uncertainty. The RAF may provide guidance to other countries establishing and implementing risk assessment processes for LMOs. The current version of the RAF was published in July 2013 is available on the OGTR website at http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/risk-analysis-framework.

*Risk Assessment and Risk Management Plans (RARMPs)*

The Regulator's assessment of each application to release a LMO into the environment involves the preparation of a Risk Assessment and Risk Management Plan (RARMP), which includes a critical assessment of data provided by the applicant together with a thorough review of other relevant national and international scientific literature. The risk assessment takes account of risks to human health and safety and the environment posed by the dealing and the risk management plan determines how those risks can be managed. The principles and approach set out in the RAF are put into practice in the RARMP.

Copies of RARMPs and licence conditions are publicly available through the Record of GMO dealings on the OGTR website at http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/ir-1.

*Application forms*

Information relevant to guidance on risk assessment is contained in application forms for environmental release of LMOs in Australia.

The detailed application forms provide guidance to applicants and outline the type of information considered necessary to prepare a RARMP for each application to release an LMO into the Australian environment. Application forms have been developed for the experimental and commercial release of plants into the Australian environment, as well as a more general form for the release of other LMOs including animals, bacteria and therapeutics. These forms contain specific questions to elicit information necessary to address important considerations relevant to each LMO application.

Applicants must provide comprehensive information about the proposed dealings with the LMO including possible risks posed by the dealings and proposed ways each risk could be managed. All responses must be supported by appropriate data and literature citations. Additional data relevant to the application may be

sought during the risk assessment process. Application forms are available from the OGTR website at http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/forms-1.

*Biology documents*

Risk assessments identify risks attributable to gene technology by considering the risks posed by a particular LMO in the context of the risks posed by the unmodified parental organism in the receiving environment. The OGTR has prepared biology documents for a number of species that provide an overview of baseline biology information to support comparative risk assessments. The biology documents may be of use to other countries conducting risk assessments on relevant GM species and are available on the OGTR website at http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/biology-documents-1.

ANNEX 1

## FORM FOR THE SUBMISSION OF INFORMATION REQUESTED IN DECISION VIII/12 ON RISK ASSESSMENT AND RISK MANAGEMENT

*A. Country information*

| | |
|---|---|
| **Country name:** | Australia |

***B. Please indicate your country's needs and priorities for further guidance on specific topics of risk assessment of living modified organisms (LMOs)***

| | **Needs and priorities for further guidance on risk assessment of LMOs** | **Notes** |
|---|---|---|
| 1 | | Australia does not support the development of separate guidance documents for the risk assessment of specific types of LMOs under the Cartagena Protocol on Biosafety. Australia supports developing a single, practical and generic guidance document based on current risk assessment practices that could be used to assess all types of LMOs. |

***C. Please propose possible criteria that may facilitate the selection of topics for the development of further guidance on specific topics of risk assessment of LMOs, including a technical justification for each of the criterion proposed****

| | **Criteria for the selection of topics** | **Notes and technical justification** |
|---|---|---|
| 1 | **Need** - Is there evidence that commercially viable LMOs of that type have been/are being developed for release into the environment | The Secretariat should focus efforts on aiding in the assessment of actual commercial products rather than experimental ideas that may never make it out of the lab. |
| 2 | **Scope of existing guidance** - Is there scientific evidence that LMOs of that type could realistically cause harms that could not be identified and assessed under the generic guidance | Well-designed generic risk analysis guidance should allow for the identification and assessment of all plausible pathways to actual harm that could reasonably be expected to result from the intentional environmental release of LMOs. |

| | | |
|---|---|---|
| 3 | **Expertise** - Does the on-line forum contain enough experts in the relevant fields to be able to produce sensible and practical guidance on the topic | Practical guidance can only be produced by those with the knowledge and experience to be able to identify the areas of reasonable concern. |
| 4 | **Adoption of existing guidance** - Is there any relevant existing guidance that could be used to meet the need | Australia notes many countries and organisations are active in the field of the environmental risk assessment of biological organisms, both modified and wild type, and does not support unnecessary duplication of effort. |
| 5 | **Adaption of existing guidance** - Is there any existing environmental risk assessment guidance produced for other purposes that could be easily adapted to fit the need | Risk assessment guidance and processes used for assessing the risks involved in releasing wild type biological control or bioremediation agents, control of invasive alien species or indigenous use of threatened species may be able to be adapted to LMOs. |

*D. Please share your views on perceived gaps in existing guidance materials*

| | Perceived gaps | Views |
|---|---|---|
| 1 | | Australia notes the complexity of the current guidance document and supports the development of simple, practical and generic guidance capable of enabling Parties to conduct the risk assessments required under the Cartagena Protocol. |

# CONVENTION ON BIOLOGICAL DIVERSITY (CBD) NOTIFICATION 2017-037

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## Digital Sequence Information on Genetic Resources

Submission by Australia

Australian Government

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NOTE: All information provided in this response has been drawn from Australian Government agency input only.

**Notification 2017-037 - Digital Sequence Information on Genetic Resources**

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Australia thanks the Secretariat for the invitation to submit views and relevant information on any potential implications of the use of digital sequence information on genetic resources for the three objectives of the Convention and the Nagoya Protocol, as communicated in notification 2017-37 Ref.:SCBD/SPS/DC/VN/KG/jh/86500 of 25 April 2017.

**Key Points**

The objectives of the Convention are:

1. the conservation of biological diversity;
2. the sustainable use of its components; and
3. the fair and equitable sharing of the benefits arising out of the utilisation of genetic resources.

"*Genetic resources*" as defined under the Convention and the Nagoya Protocol means genetic material of actual or potential value.

"*Genetic material*" as defined under the Convention and the Nagoya Protocol means any material of plant, animal, microbial or other origin containing functional units of heredity.

Digital Sequence Information on genetic resources is not defined under the Convention. For the purposes of this submission Australia defines "*digital sequence information on genetic resources*" as electronically held sequence information which represents the biological composition of "*genetic material*" as defined under the Convention.

Australia considers digital sequence information on genetic resources and the physical genetic resources and material as distinct entities. This distinction aligns with the outcome of lengthy debate in the establishment of the Nagoya Protocol. To consider digital sequence information a genetic resource under the Convention and the Nagoya Protocol would require a renegotiation of the Convention and the Nagoya Protocol to redefine 'genetic material' noting information does not contain 'functional units of heredity' or genes.

Australia does consider that digital sequence information on genetic resources has a role in supporting Parties to meet the objectives of the Convention in line with Articles 3, 15(6) and 15 (7).

> ***3*** *States have, in accordance with the Charter of United Nations and the principles of international law, the sovereign right to exploit their own resources pursuant to their own environmental policies, and the responsibility to ensure that activities within their jurisdiction or control do not cause damage to the environment of other States or of areas beyond the limits of national jurisdiction.*
>
> ***15(6)*** *Each Contracting party shall endeavour to develop and carry out scientific research based on genetic resources provided by other Contracting Parties with the full participation of, and where possible in, such Contracting Parties.*
>
> ***15(7)*** *Each Contracting Party shall take legislative, administrative or policy measures, as appropriate, and in accordance with Articles 16 and 19 and, where necessary, through the financial mechanism established by Articles 20 and 21 with the aim of sharing in a fair and equitable way the results of research and development and the benefits arising from the commercial and other utilization of genetic resources with the Contracting Party providing such resources. Such sharing shall be upon mutually agreed terms.*

There is a broad range of types and quality of sequence information relating to genetic resources that may be stored and/or transmitted digitally. Different types of sequence information include DNA, RNA and protein sequences as well as information on epigenetic factors such as methylation and glycosylation sites. The quality of information can range from raw sequence data through to fully annotated, characterised and codon optimised sequences complete with information on relationships to other sequences, including from multiple source organisms.

Open access to digital sequence information deposited in the public domain is the common standard in the global scientific community. Digital sequence information is found in many publicly available databases that can be considered data hosts not data owners. For example, GenBank (including Barcode of Life database of reference sequences from vouchered specimens of species) is an open access sequence database that contains nucleotide sequences for more than 300,000 organisms with supporting biological and bibliographic annotation.

Access to, and use of, digital sequence information is fundamental to modern biotechnology. The identification of useful information from within raw sequence data relies upon vital contextual information provided through existing public databases of characterised and annotated digital sequence information.

The generation and open sharing of digital sequence information on genetic resources provides benefits through increased scientific information and discovery that enable Parties, to meet the objectives of the Convention and the Nagoya Protocol. The use of digital sequence information on genetic resources increases the value of biological diversity and enables scientific progress and innovation.

Australia finally notes a number of multilateral discussions are in progress regarding whether and how regulatory mechanisms that apply to physical resources should be extended to digital sequence information. Outside the Convention and Nagoya Protocol discussions include:

- Multilateral System of the International Treaty for Plant Genetic Resources in Food and Agriculture (genomic sequence of germplasm);
- World Health Organisation (genetic sequence data from influenza viruses with pandemic potential); and
- Biodiversity Beyond National Jurisdiction discussions under the UN Convention on Law of the Sea (digital information from marine genetic resources).

Co-ordinated and non-duplicative consideration of this crosscutting issue is required to ensure consistency across these fora. We call on the CBD Secretariat to ensure the continuation of this collaboration as we consider this to be critical to inform the work being progressed through the CBD.

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National Health and Medical Research Council

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Dr Raj Bhula
Gene Technology Regulator
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CC: Samantha Martinek (Regulatory Practice Section, Regulatory Practice and Compliance Branch, OGTR)
Samantha.Martinek@health.gov.au

Dear Dr Bhula

As Chief Executive Officer of the National Health and Medical Research Council (NHMRC) and a member of Heads of International Research Organisations (HIROs), I have been asked to consider signing onto a set of principles for funders of gene drive research (see attached document).

You will be aware that gene drive technology promotes the preferential inheritance of a gene of interest, thereby increasing its prevalence in a population. The applications of gene drive technology include controlling vector-borne diseases and invasive species. However, the technology raises challenging ethical, safety and other issues that must be considered by researchers, funders and regulators. For this reason, the US National Academies of Science, Engineering and Medicine published a study in 2016[1] that outlined recommendations for a strategy to advance gene drive research safely and responsibly. The attached principles were developed by HIROs members in response to the recommendations in this study.

I am writing to you to inform you of my intention to sign onto the principles as a way of making a public statement about NHMRC's intent to pursue best scientific and ethical practices in the oversight of gene drive research related to human health. Before doing so, I wanted to provide you with an opportunity to advise me of any implications for your agency that may preclude me from signing up or require qualification in support.

I would be very grateful for your advice by 13 February 2017 as the attached principles will be submitted for publication in mid-February.

Yours sincerely

Professor Anne Kelso AO

Chief Executive Officer, NHMRC
25 January 2017

Attachment: Emerson *et al.*, *'Principles for funders of Gene Drive Research'* (Draft).

[1] https://www.nap.edu/catalog/23405/gene-drives-on-the-horizon-advancing-science-navigating-uncertainty-and


DISCUSSION PAPER

# SYNTHETIC GENE DRIVES IN AUSTRALIA: IMPLICATIONS OF EMERGING TECHNOLOGIES

AUSTRALIAN ACADEMY OF SCIENCE MAY 2017


DISCUSSION PAPER

# SYNTHETIC GENE DRIVES IN AUSTRALIA: IMPLICATIONS OF EMERGING TECHNOLOGIES

AUSTRALIAN ACADEMY OF SCIENCE MAY 2017

## Acknowledgements

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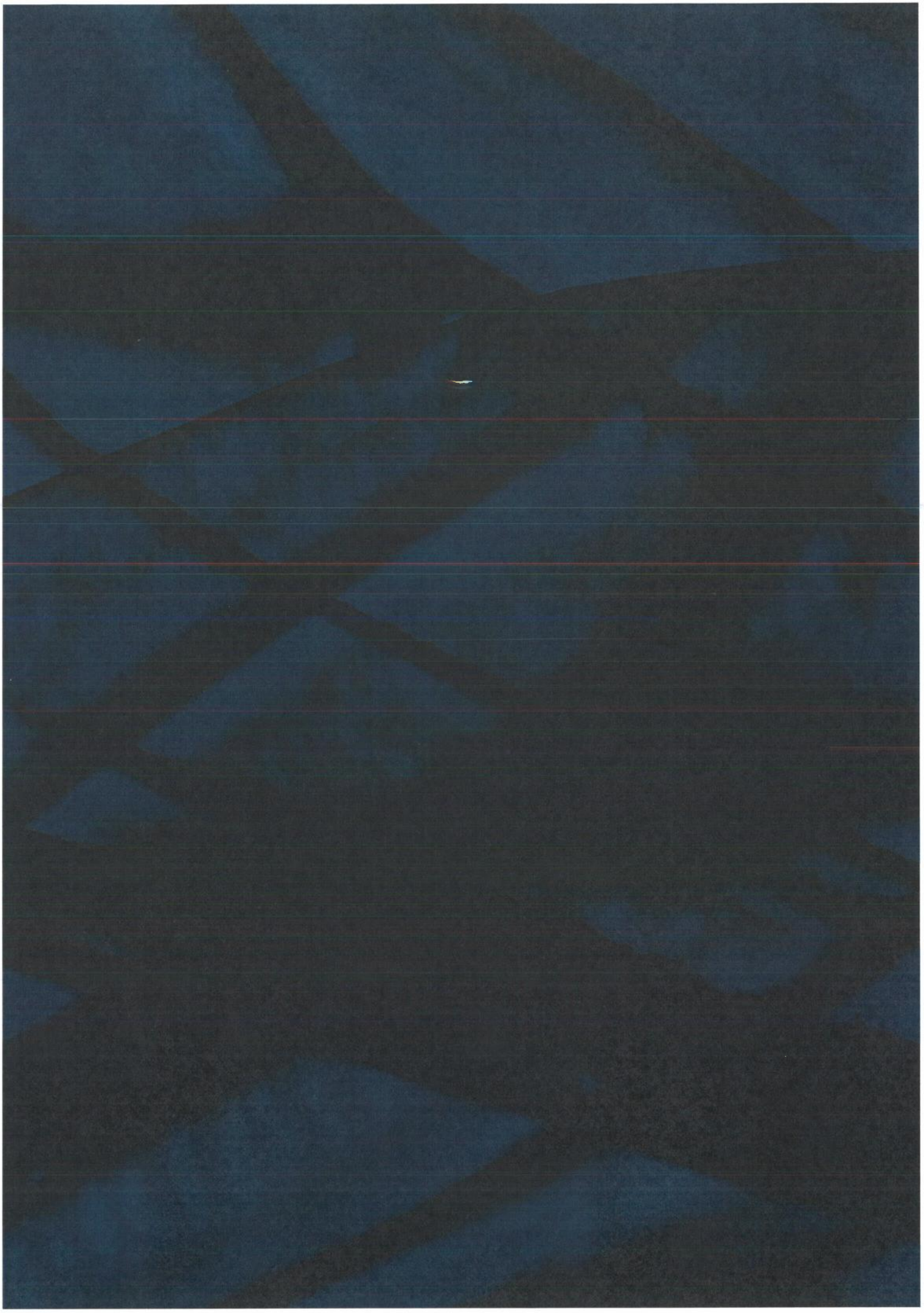


# INTRODUCTION

Gene drive mechanisms (or gene drives) cause a gene to spread throughout a population at a rate higher than would normally occur. Scientists have been observing examples of biased inheritance generated by natural gene drive mechanisms for many years. However, significant advances in genetic and molecular tools for genome editing have brought synthetic gene drive technology within the reach of many more researchers, and research has accelerated greatly in recent years. Since 2015, scientists have published four proof of concept studies in yeast, mosquitoes and the fruit fly *Drosophila* to demonstrate the feasibility of using synthetic gene drives for purposes such as combating vector-borne disease, suppressing pest populations, or for introducing desired characteristics into target organisms. As with many new technologies, the potential applications and benefits are far reaching, as are the potential impacts—both intended and unintended—on public health, conservation and ecology. This rapidly developing area represents an additional method of manipulating populations alongside traditional and other methods (Table 1).

The pace at which the gene drive research is moving has triggered international discussion (for example, Nuffield, 2016; NAS, 2016a). The scientific community has raised concerns as to when organisms modified with synthetic gene drives should be released, and there is significant discussion amongst scientists regarding best practice and strategies to manage and mitigate any hazards involved (Akbari et al., 2015; Oye et al., 2014).

To inform government and community consideration of these issues, this discussion paper by the Australian Academy of Science considers synthetic gene drives in a specifically Australian context and highlights the potential benefits and hazards of possible applications, emphasising the need to eventually consider these within a risk assessment framework. The paper discusses environmental hazards, social and economic issues (including trade implications) and how the technology can be managed within Australia's governance arrangements. Our unique Australian environment generates a number of issues specific to our country; the Academy intends this discussion paper to complement the international discussion underway and to inform Australian governments and our community about gene drives in Australia.

**Table 1: Description of various methods of biological manipulation of populations.**

| Method of manipulation | Description |
|---|---|
| Biological control | A method of controlling invasive weeds and pests using their own natural predators or parasites against them. Successful Australian examples include the control of prickly pear and skeleton weed. This approach is itself not without risk, as demonstrated by the well-known case of the cane toad in northern Australia. |
| Plant breeding | A systematic method of selecting plants with desirable characteristics for further breeding. It may include crossing closely related plant species to produce new crop varieties, or the use of chemicals or radiation to randomly generate mutants that happen to display desirable traits. |
| Animal breeding | As for plant breeding, this method aims to establish a line of animals with specific traits based on selective breeding, although related species are less commonly crossed and animals are less commonly exposed to radiation and mutagenic chemicals for this purpose. |
| Gene technology | This is a broad term that includes a variety of genetic manipulation techniques that are used to alter an organism's DNA. |
| Gene therapy | An application of gene technology involving the introduction of corrective genes to replace defective or missing genes to treat genetic disorders, usually in humans. |
| Synthetic gene drive | An application of gene technology that increases the prevalence of a genetic variant within a population. Natural gene drive mechanisms are also known; these are sometimes harnessed for manipulating populations without the use of gene technology. |

The Australian Academy of Science recommends that:

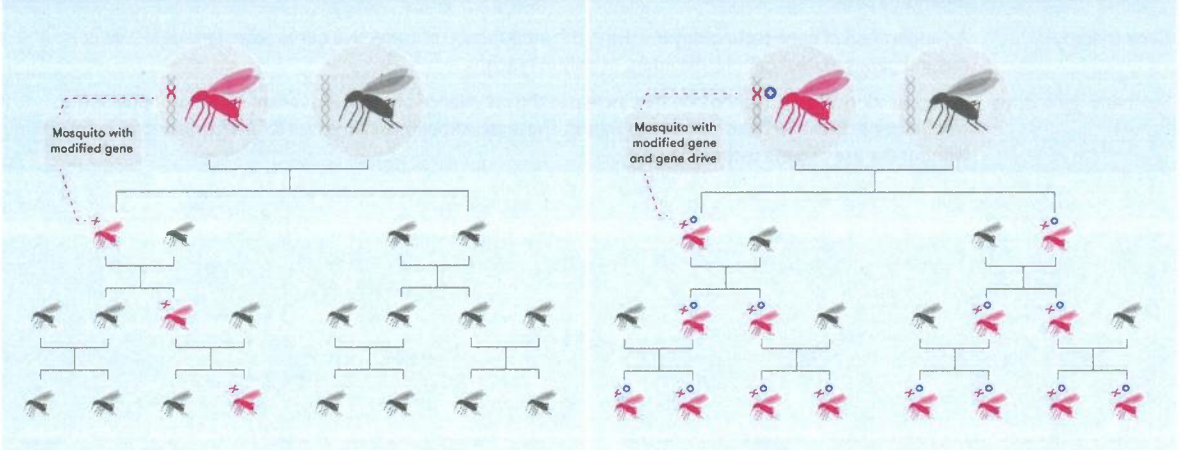
1. There continues to be clear and transparent communication of governance arrangements regarding regulation of synthetic gene drives.
2. Resources be provided to study synthetic gene drives in isolated laboratory populations with sample sizes and time frames that are large enough and/or long enough to observe processes such as selection, resistance evolution, population structuring and transmission distortion, together with the intended and potentially unintended consequences that these process may lead to.
3. Stringent, multiple containment measures be taken when researching synthetic gene drives.
4. Any decision to release a synthetic gene drive continues to be made on a case-by-case basis following a comprehensive environmental risk assessment which includes ecological and evolutionary modelling.
5. There be clear communication and consultation with the public through appropriate channels from the earliest stages of gene drive research, particularly with affected communities.
6. The wider implications of synthetic gene drives (e.g. trade implications) be considered.

# BACKGROUND

Gene drives produce a biased form of inheritance. They overcome normal Mendelian inheritance, where one copy of a gene is inherited from each parent, and greatly increase the chances of an allele passing from a parent to its offspring (Figure 1). This results in the preferential increase in the frequency of a specific genotype over many generations and the entire population may eventually come to possess only that genotype.

Synthetic gene drives are being developed to influence a target population via two primary methods: population suppression or population alteration. A synthetic gene drive that is designed to suppress a population would, over many generations, reduce the number of individuals within a population following its introduction—possibly to zero. A synthetic gene drive designed to alter some characteristic of a population would involve a modified genetic element

**Figure 1: An idealised illustration of Mendelian versus gene drive inheritance rates. Through standard Mendelian inheritance (left), offspring have a 50% chance of inheriting a modified gene carried by one of their parents. With a gene drive mechanism (right) the modified genes are eventually inherited by 100% of the offspring, allowing the gene to spread rapidly through the population. Images from Nova: Science for curious minds, modified from 'CRISPR, the disruptor', www.nature.com**



that is then spread throughout the population, for example to confer resistance or immunity to a certain parasite or disease.

A number of basic criteria are required for a synthetic gene drive to work. Firstly, the organism must reproduce sexually. This means that viruses, bacteria, many plants and some animals which use other means to reproduce cannot be altered in this way. Secondly, to be practical, the organism must reproduce rapidly. Elephants and trees with long generation times are therefore not ideal targets whereas insects, some plants and small vertebrates such as rodents and fish could be successful candidates. In addition, the organism must also be able to be transformed, and the trait of interest must have a simple genetic basis.

Whilst synthetic gene drives could technically be used in humans, we are unlikely candidates due to the combination of the complex ethical issues this would raise and the lack of efficacy from a practical perspective. Our long generation times would mean a gene drive-mediated change would take hundreds of years to spread throughout a human population. In most jurisdictions any research in this area would also be heavily regulated by existing legislation; in Australia extensive coverage would be provided by the *Research Involving Human Embryos Act 2000* and the *Prohibition of Human Cloning Act 2002*.

# GENE DRIVE MECHANISMS

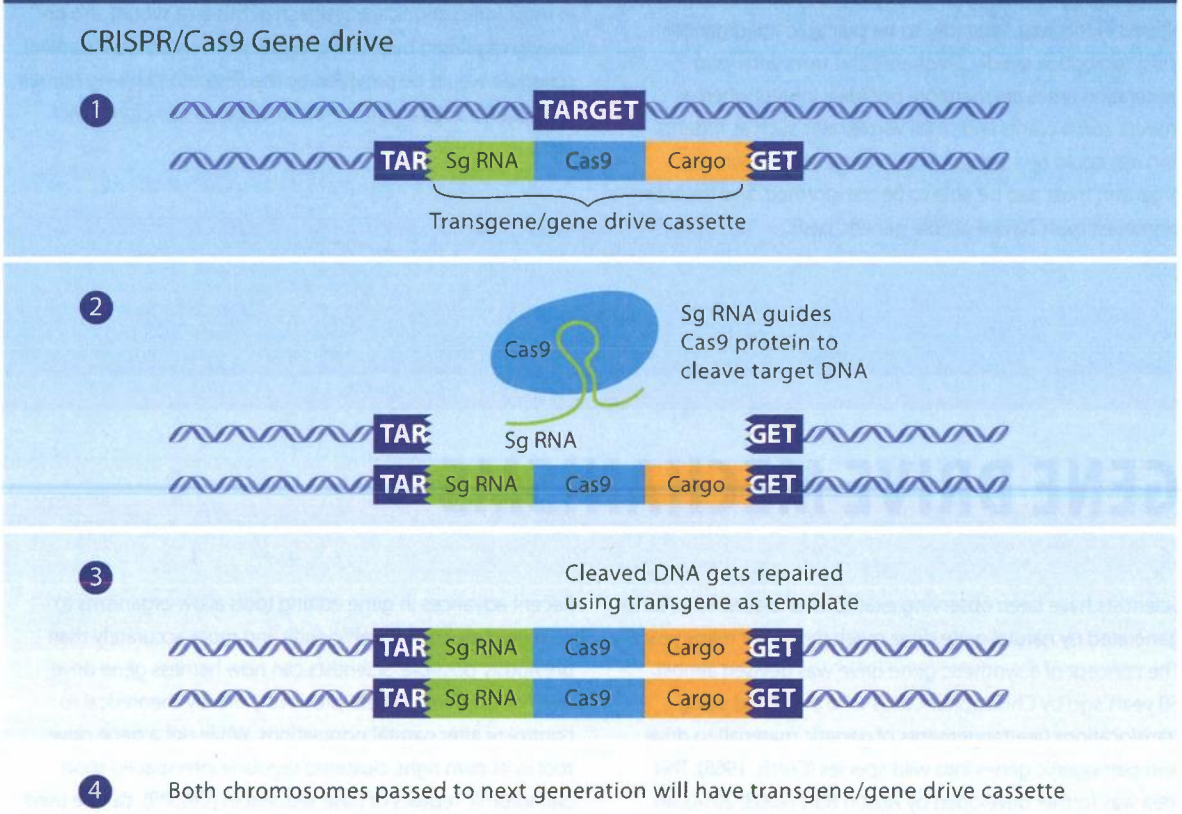
Scientists have been observing examples of biased inheritance generated by natural gene drive mechanisms for many years. The concept of a 'synthetic gene drive' was devised almost 50 years ago by Christopher Curtis who proposed using translocations (rearrangements of genetic material) to drive anti-pathogenic genes into wild species (Curtis, 1968). This idea was further developed by Austin Burt (2003; 2014), an evolutionary geneticist, who discussed how a synthetic gene drive could be used to prevent insects spreading diseases such as malaria.

There are many different types of natural gene drive mechanisms (Appendix 1). These can be characterised by attributes such as the rate of spread, species specificity, fitness cost, susceptibility to resistance, removability and reversibility (Champer et al., 2016). The rate of spread is an important consideration. So called 'high threshold' gene drives would only spread if the number of individuals with the drive genotype reaches a high level. These types of drive systems could be confined to local areas and breeding populations by controlling the number of individuals with and without the drive. In contrast, 'low threshold' gene drives, which are considered invasive, would spread with a low initial release, requiring only a small number of gene drive-carrying organisms to be released to spread. Natural *Wolbachia* infections provide examples of drives with high and low thresholds (Nguyen et al., 2014; Hoffmann et al., 2011). It is worth noting that no synthetic gene drives have yet been released into wild populations so the concepts discussed here are untested to date on such systems.

Recent advances in gene editing tools allow organisms to be edited much more efficiently and more accurately than previously possible. Scientists can now harness gene drive mechanisms which were previously merely theoretical to control or alter natural populations. While not a gene drive tool in its own right, clustered regularly interspaced short palindromic repeats of base sequences (CRISPR), can be used as part of a system to produce a synthetic gene drive. When CRISPR is paired with a guide RNA and with specific proteins, such as Cas9 (CRISPR associated protein 9) that cuts DNA, it can be used to efficiently edit genetic material. In natural prokaryotic systems, CRISPR/Cas9 is produced by host bacteria to remove viral DNA by targeting repeats associated with viral insertions, as a kind of immune system to combat infections. For gene editing purposes, the Cas9 protein and guide RNA are injected into the cell to cut the DNA at a sequence complementary to the RNA guide. For synthetic gene drives, the target organism is transformed with a construct that includes the gene for the Cas9 protein, a guide RNA that is complementary to the sequence at the insertion site, and the 'cargo' gene controlling the desired trait (Figure 2). The guide RNA directs Cas9 to produce a double stranded cut in the DNA at the target site in the other chromosome. This triggers the cell's repair mechanism, which copies the entire construct (Figure 2). If germ cells are targeted, the new sequence can then be passed on to offspring ensuring the editing changes can occur in each generation. A CRISPR-based gene editing technique was used in all four synthetic gene drive proof-of-concept studies in 2015. These studies generated laboratory-

based gene drives in yeast *Saccharomyces cerevisiae* (DiCarlo et al., 2015), fruit fly *Drosophila melanogaster* (Gantz & Bier, 2015) and two mosquito species *Anopheles stephensi* (Gantz et al., 2015) and *Anopheles gambiae* (Hammond et al., 2016).

**Figure 2: A synthetic CRISPR/Cas9 gene drive. Sg RNA is the guide RNA, Cas9 is an endonuclease which cuts the DNA and cargo is the desired genetic material added. When all three elements are present in a gene drive cassette this ensures that each chromosome will have the desired cargo and will be inherited by the next generation thereby spreading the gene drive.**




# POTENTIAL USES IN AUSTRALIA

Australia has a unique environment with highly diverse flora and fauna that have evolved in relative physical isolation over a long time period. A number of pests, diseases and invasive species that Australia has acquired from other parts of the world do not have close relatives in this country. This genetic differentiation and our well-established governance frameworks may make Australia an attractive setting in which to test synthetic gene drives that target pest species.

Any release of an organism containing a synthetic gene drive would be required to comply with our governance arrangements which include the requirement for a comprehensive risk assessment.

Australia has had mixed success in using deliberate biological introductions to reduce invasive and feral species populations. One success story is the control of prickly pear, a cactus which was introduced to Australia in 1788 and quickly became an invasive species spreading rapidly throughout eastern Australia. A South American insect, *Cactoblastis cactorum*, was introduced as a biological control and successfully reduced the prickly pear population. Other introductions, particularly that of cane toads to suppress cane beetles, have had far greater negative consequences than their modest positive contribution in the sugar cane fields. Mechanisms used for screening and testing biological control agents have prevented a repeat of such destructive introductions in the last few

decades, highlighting the efficacy of Australia's strong governance framework.

There are many potential local and international applications of gene drives in areas such as public health (specifically looking at interactions with pathogens), environmental conservation and agriculture, targeting both animals and plants. Gene drives can provide significant positive benefits to certain problems, especially where alternative methods are ineffective, damaging to the environment and/or costly. Australian-specific examples are described below; more detail is provided in Appendix 2.

## DISEASE APPLICATIONS

Insect-borne infectious diseases are a serious and significant global public health issue, and Australia is not immune. Malaria, dengue, Ross River fever (named after its place of discovery in Queensland) and Zika are all spread by mosquitoes and despite research efforts vaccines are still many years away from being widely available. Other methods to control mosquito populations are in jeopardy due to an increase in insecticide resistance. Current research in Australia is investigating how to suppress the transmission of dengue: a disease estimated to infect 390 million people each year worldwide (Bhatt et al., 2013) and which occurs in parts of northern Australia. Using a natural or synthetic gene drive to reduce mosquito populations, or make the mosquitoes less susceptible to becoming carriers, would help reduce the spread of this disease.

Other potential disease control applications include gene drives in vector insects to prevent the spread of livestock diseases such as blue tongue virus and systems to reduce wildlife diseases such as avian malaria that threaten endangered species.

## INVASIVE SPECIES AND THE ENVIRONMENT

Introduced invasive species can devastate native flora and fauna through predation, competition or parasitism. Gene drives may have the potential to restore native biodiversity through a number of routes, either by controlling specific invasive species or conferring competitive advantages on native animals. In Australia, suggestions to date include a synthetic gene drive to reduce the population of black rats on Lord Howe Island, cane toads in the tropics, European carp in the Murray Darling Basin and rabbits across the continent.

## AGRICULTURAL APPLICATIONS

Australian agriculture is a promising area for gene drive applications. Controlling organisms that damage important crops or carry crop diseases would provide a major boost to agricultural productivity and competitiveness. Introducing

| Disease applications | | | |
|---|---|---|---|
| **Problem** | **Examples of current solutions** | **Potential problems with current solutions** | **Potential beneficial consequences of gene drive** |
| **Insect-borne diseases** | Spraying of chemicals, vaccination, wear long sleeve clothing, mosquito nets. | Several hundred thousand humans die every year from mosquito-borne diseases. Spraying of non-selective chemicals damages the environment and kills beneficial insects. Current non-chemical solutions rely on changes in human behaviour. Many solutions are costly to implement in remote regions. | A gene drive designed to prevent a mosquito from transmitting a pathogen would have positive consequences by reducing the spread of disease. The mosquito would still be present to retain its ecological function. Suppression of populations of exotic mosquitoes and midges will likely have few detrimental effects. |

| Invasive species and the environment | | | |
|---|---|---|---|
| **Problem** | **Examples of current solutions** | **Potential problems with current solutions** | **Potential beneficial consequences of gene drive** |
| **Invasive species** | Traps and poisons, and other vector control strategies (e.g. ballast water exchange). | Invasive plants and animals predate and out-compete native Australia flora and fauna. Inaction could result in the extinction of native species. Some traps and poisons are non-selective and vector control strategies can be costly to implement. | A gene drive to control an invasive species could restore native species populations and ecosystem function. |

| Agricultural applications | | | |
|---|---|---|---|
| **Problem** | **Examples of current solutions** | **Potential problems with current solutions** | **Potential beneficial consequences of gene drive** |
| **Agricultural pests** | Spraying of pesticides. | Spraying of chemicals damages biodiversity and decreases beneficial invertebrates due to non-selective nature of many chemicals. Pesticides become ineffective when resistance evolves. | A gene drive to eliminate a weed or pest could reduce chemical spraying and potentially increase farmer's crop yields. |

genes that reverse pesticide or herbicide resistance would help farmers to continue to control insects and weeds by chemical methods.

Suppressing or modifying invertebrate pests would be valuable for farmers and land managers. Targets for suppression include fruit fly pests, which attack soft fruits and cause significant crop loss, as well as various moths, mites, thrips and other pest invertebrates which attack vegetables and broad acre crops. Pests like diamondback moths, *Lucilia* blowflies and redlegged earth mites that have developed resistance to chemical pesticides are particularly important targets for control. Synthetic gene drives might also be developed to modify insect and mite vectors to reduce their ability to transmit plant viruses.

# POTENTIAL HAZARDS AND CHALLENGES

Despite the significant benefits synthetic gene drives may provide, an unplanned or poorly managed release of a gene drive modified organism could potentially change the environmental landscape well beyond the site of its introduction.

The introduction of foreign species and their genes into a new environment is not new. With human exploration and travel we have introduced new species into different environments either inadvertently (e.g. within ships' ballast water) or consciously (e.g. new crops, garden flowers or even animals for sport hunting) for many decades. Many invasive and feral species have become established in Australia, some of which have caused ecological and environmental damage. The introduction of new genes occurs both through new mutations arising in existing populations and though the movement of genes from one population to another. For instance, insecticide resistance genes in Australian insect pests have likely arisen both locally following mutation and been introduced from overseas populations (Umina et al., 2014).

Significant technical and knowledge challenges remain which must be overcome to engineer a successful synthetic gene drive, and these challenges should not be underestimated. The four proof of concept studies published over 2015 have all been in laboratory organisms which are highly uniform and unlike wild populations. The genetic constructs produced in controlled laboratory conditions are unlikely to perform in the same way in natural environments where conditions are much more variable and unpredictable. Additionally in a wild population, a trait which reduces the biological fitness of an organism—for instance a gene drive containing a construct designed to suppress reproduction—will slow down the spread of the gene drive.

The release of a low threshold synthetic gene drive designed to spread genes throughout an entire population demands additional care. The consequences of such releases are potentially widespread, and hence international consideration and consultation may be required. The spread of genes between populations—gene flow—must be understood prior to the release of any synthetic gene drive, but this is particularly important with low threshold drives. The possible transfer of genes between distinct species must also be considered. Gene drives shouldn't be implemented in species where there is potential for introgression with non-pest native species.

There is the possibility that releases of gene drive modified organisms will lead to unpredicted and undesirable side effects. Past eradication of pest species by conventional means such as baits or sprays have in some instances allowed another problematic pest to flourish as a result of a vacated niche or the withdrawal of predation (Dutcher, 2007). We must consider equivalent problems that might arise from possible future use of gene drive modified organisms.

It is also important, however, to put the hazards presented by gene drive modified organisms into perspective. A 100% effective gene drive can only ever double in frequency with each generation inheriting the drive mechanism. Mosquitoes have an average generation time of three weeks and it would take multiple generations to spread a gene drive to a portion of a local population. By comparison, a viral pandemic would affect national and international populations in a matter of weeks. While there should be caution in regard to the use of synthetic gene drives, there would be time to react if an unintended release or unexpected effect were detected.

The potential of evolution to modify gene drives and the constructs being driven also needs to be carefully considered. Resistance to the gene drive is likely to evolve unless other DNA repair systems that organisms possess can be turned off or multiple, independently acting, drive systems are developed. Before release into the environment, likely evolutionary changes in each genetic construct and their consequences

will need to be carefully modelled and evaluated. In addition, untargeted changes in the genome associated with the creation of drives may need to be evaluated.

Hazards pertinent to the applications of synthetic gene drives relating to pathogens, invasive organisms and agricultural applications are discussed in more detail below.

## HAZARDS RELATED TO PATHOGEN CONTROL

There are several hazards associated with releasing an organism containing a gene drive which results in the extinction of an insect-borne disease. Removing one vector could allow another potentially dangerous species to take its place by competitive- or predator-release processes. Releasing a gene drive modified organism that was only partially successful could also cause a loss of herd immunity in previously exposed populations. Public health would benefit in the short term but possibly not in the longer term, because individuals within the population may become more susceptible to the disease as the vector recovers from the initial suppression.

## HAZARDS RELATED TO INVASIVE SPECIES CONTROL

Ecosystems are highly interlinked systems within which the abundance of each species is governed by the balance of births, deaths, immigration and emigration. Their dynamics are controlled by positive and negative feedback cycles that respond to external forces in ways that are often difficult to predict. Introduced non-native species, if they are successful and flourish, can alter these processes and cause significant changes to the abundance of native species, and the feedback cycles they operate within. Gene drive modified organisms offer the potential to restore impacted ecosystems by suppressing invasive species, potentially to extinction. Modified ecosystems, however, may not return to a previous (desired) state even if the drive is successful. Furthermore, species that have become reliant on the invasive species could suffer as its abundance was reduced, and other harmful species could be released from predation pressure or competitive exclusion, and thereby flourish. Regardless of the cause—be it through a gene drive, attack by an invasive species or habitat loss—extinction of species requires careful and serious consideration.

Gene drive modified organisms may also spread naturally, or through human-mediated dispersal mechanisms, to other regions and other parts of the worlds. A possible consequence of creating a synthetic gene drive aimed at eradicating European carp or rabbits in Australia could be that the drive spreads overseas where these animals have important food, cultural and/or ecological values.

## HAZARDS RELATED TO CONTROL OF AGRICULTURAL PESTS

The spread of gene drive modified organisms also poses hazards in agriculture domains. Efforts to improve agriculture in Australia using synthetic gene drives may target problem weeds such as *Echinochloa colona*, or barnyard grass. This is a damaging weed for Australian farmers but in India the seeds of this grass are used to prepare a dish consumed on festival fasting days. Consequently, if a gene drive modified organism was released to suppress the weed population in Australia it could also affect a food source in other parts of the world. Elimination of a pest species might also create an empty niche that could be filled by other pests, as in the case of redlegged earth mites that show competitive interactions with other species of earth mites.

Significant technical limitations currently exist for gene drives in weeds. Gene drives can only function if double strand DNA breaks are repaired by homologous recombination, but some plants use non-homologous end joining pathways which prevents the use of the current generation of synthetic gene drive constructs.

Another challenge for agriculturally related gene drives is to avoid the development of resistance (Fukuoka et al., 2015). Resistance alleles can prevent a gene drive from spreading in pests and weeds (Champer et al., 2016). Efforts to avoid the development of resistance include stacking traits so that there are multiple defences to target the same pests and weeds. This strategy is already used in GM crop plants with resistance to insects where multiple insecticide genes are stacked together to reduce the likelihood of insects evolving resistance.

# SOCIAL AND ECONOMIC DIMENSIONS

Based on available information, which is currently limited, there is very little public awareness of the term 'gene drives' or of the science and technology associated with this term. Negative attitudes to all genetic modification persist despite almost 30 years of GMOs being globally available, and many scientific studies providing strong evidence that there are no adverse effects to human health due to consumption of GMOs (Nicolia et al., 2014; NAS 2016b). Within Australia, there are relatively few GM products on the market compared for instance to the United States, although GM-derived vegetable oil and soy flour have been in widespread use for the past two decades.

Public opinion regarding GMOs appears to vary widely within the Australian community, although there are few scholarly studies on attitudes towards GM foods (as noted by Lea, 2005). Community attitudes to biotechnology have been monitored in Australia by the Commonwealth Government, under the auspices of Biotechnology Australia (from 1999–2007), the Department of Industry (in 2010 and 2012) and the Office of the Gene Technology regulator (in 2015).[1] These surveys show some volatility in Australian public opinion regarding GM and biotechnology. Australians are generally viewed to be less cautious than Europeans and more sceptical than residents of the USA about GM. Anti-GM activism (in the form of direct action) in Australia has been far more limited than in Europe and the United States (Hindmarsh, 2008). There continues to be popular concern about the potential for drift between GM and non-GM crops (particularly organics, for example the recent court case in Western Australia (Paull, 2015)), the use of GM in crops destined for the food supply (even when no GM material remains in the final product) and the role of multinationals in GM particularly in the developing world. In short, the key issue underlying public attitudes to GM is that competing arguments are grounded in extremely diverse understandings and assumptions, particularly about what counts as evidence (predominantly of risk or lack thereof), and how to balance risks and benefits, especially with regard to new innovations. These arguments are likely to recur in the case of synthetic gene drives.

As in the case of GMOs, the concerns of potentially affected communities need to be carefully considered in regard to gene drives. Community engagement will be important from the earliest stages of gene drive research. Community engagement around control of carp involving genetically-based approaches (Thresher, 2008) and *Wolbachia* releases (Hoffmann et al., 2011; Kolopack et al., 2015) provide case studies. Any unintentional release—even without harmful consequences—could cause widespread public distrust of scientists, transgenics and transgenic products, and the field of gene drive research more generally. Transparent information provision and policy, cultural respect and engagement with social and ethical implications of this type of research will be imperative for the possible benefits of synthetic gene drives to be realised, in alignment with best practice strategies in science engagement (see for example Department of Industry, Innovation, Science and Research, 2010) and to avoid community backlash such as occurred in the case of GM policy and regulation (Schibeci & Harwood, 2007). The potential benefits of gene drives and the consequences of inaction are also important to convey to the public. There is a risk that lack of action or continued ineffective action could cause damage to the environment and be unnecessarily costly.

The trade implications of gene drive modified organisms released in Australia must also be considered. Australian exports to an importing country with different gene technology legislation to our own could be detrimental to trade relationships and generate other economic issues. Unintended consequences of a gene drive modified organism may include increased import requirements such as increased testing and documentation. A gene drive targeting pest fruit flies may be a problem for countries such as Japan which have highly specific regulations on fruit imports. These potential trade impacts should be discussed with Australian industries prior to release to ensure they are comfortable with the risks. In addition early engagement with key importing countries for trade is highly recommended.

A significant ethical concern is commercialisation and ownership of intellectual property. A patent for the technology of RNA guided gene drives was filed by Esvelt and Smidler in 2014 (WO 2015105928 A1). There are currently two competing patents (Zhang versus Doudna) over the CRISPR gene editing technology (Egelie et al., 2016). For a synthetic gene drive with applications in public health and conservation, there may be very little scope for commercialisation. As in other areas of biotechnology, the patenting of gene editing and gene drive technologies may raise ethical and economic issues and thus present impediments to ongoing research. Conversely, intellectual property can reward innovation and allow time for new products to be developed.

1 See www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/reports-other for the OGTR 2015 survey and https://industry.gov.au/industry/IndustrySectors/nanotechnology/Publications/Pages/Public-Attitude-Research.aspx for earlier surveys.

# MITIGATION STRATEGIES

Gene drives have the potential to solve intractable problems in diverse areas of public health, agriculture and conservation but also present a range of social and environmental hazards. It is vital that the use of technology is open and peer reviewed, with research intentions made clearly transparent to the public. The Academy recommends scientists adhere to best scientific practices and follow the responsible conduct of research when investigating gene drive modified organisms[2]. Ethical consideration of both social and environmental consequences should be considered prior to commencing any research. The *National Framework of Ethical Principles in Gene Technology 2012* provides guidance on values and ethical principles in relation to gene technologies.

Such considerations should include a thorough and quantitative investigation of alternative methods to address the experimental problem. Not all problems that can be addressed by a gene drive modified organism should be: if there is an alternative available that will achieve the same outcome while presenting fewer hazards then it should be prioritised over new technologies. On the other hand, if a synthetic gene drive is the best solution it should be considered to prevent the consequences of inaction or ineffective action.

Multiple stringent confinement strategies should also be used to avoid the unintentional release of a gene drive modified organism while in development (Akbari et al., 2015; Oye et al., 2014). Molecular and physical confinement measures are described below in addition to possible safeguards that may be prepared in advance of a gene drive release.

## MOLECULAR CONFINEMENT

There are a number of options which can be considered during the design of a gene drive construct that can act as a molecular confinement measure. These include:

- using synthetic target sequences that are not in natural populations and therefore could not spread to wild organisms.
- targeting unique sequences which are very specific to the target organism to avoid a gene drive spreading to closely related species. For example targeting the toxin genes of cane toads which are not found in other amphibians
- choosing a gene drive mechanism which has a low ability to spread, known colloquially as high threshold drives—these help confine the spread of a gene drive to a local breeding population. If the threshold is not exceeded, the drive system is lost from a population. This concept is illustrated by the loss of *Wolbachia* from natural populations (Nguyen et al., 2015)
- designing a gene drive which is not self-sufficient by physically separating the elements. In the case of CRISPR/Cas9 drive technology the Cas9 and guide RNA would be separated, known as a split gene drive system. This has been tested in yeast (DiCarlo et al., 2015)
- designing a gene drive that would stop after a few generations. This would limit the capacity of the gene drive to spread. Figure 3 demonstrates this 'daisy chain' gene drive where each genetic element drives the next (Noble et al., 2016).

**Figure 3: Example of a 'daisy chain' gene drive. A daisy chain system consists of serially dependent, unlinked drive elements which are on separate chromosomes. These genetic elements drive the next element and are lost over time which limits the time and location of the gene drive spread.**


2 www.science.org.au/supporting-science/science-policy/position-statements/ethics-and-integrity

## PHYSICAL CONFINEMENT

Appropriate training of researchers in best practice and using precautions to limit human errors are very important. Other physical measures which can be implemented include:

- following the specific guidelines for work on mosquitoes as outlined within *The guidance framework for testing genetically modified organisms* (WHO, 2014)
- avoid transferring gene drive modified organisms between laboratories. Instead DNA constructs or information sufficient to reconstruct the gene drive should be sent, if required
- ensuring that all work takes place in suitably confined premises as currently defined by Physical Containment levels PC2[3] or PC3[4] (Office of the Gene Technology Regulator) or Biosecurity Insectary Containment levels BIC2[5] or BIC3[6] (Department of Agriculture and Water Resources).

## REPRODUCTIVE AND ECOLOGICAL CONTAINMENT

Options for reproductive and ecological containment include using:

- reproductive barriers, such as using a laboratory strain which cannot reproduce with wild organisms.
- ecological confinements, such as developing a gene drive in an area where there are no viable mates or an area which is only temporarily habitable for that organism.

## SAFEGUARD MEASURES

In addition to the containment measures described above, a strategy to mitigate potential ecological and environmental consequences from the accidental release of a gene drive or from unanticipated impacts of an intentional release is highly recommended. Options include:

- an immunisation gene drive to block the spread of unwanted gene drives by pre-emptively altering the target sequence thereby preventing the gene drive from spreading (Esvelt et al., 2014)
- a reversal gene drive designed in parallel with any gene drive experiment to overwrite any unwanted changes of a gene drive (DiCarlo et al., 2015)
- trialling a gene drive using a benign change to enable the effectiveness of a gene drive spread to be studied prior to a release
- ecological modelling to help predict the potential consequences resulting from a gene drive release (for example, see Unckless et al., 2017).

Wherever possible, the likely effectiveness of safeguards should be assessed in a quantitative way based on current knowledge.

# CURRENT REGULATORY STATUS

The rapid advances in gene editing and gene drive technologies present substantial challenges to current regulatory systems that are under active consideration in numerous jurisdictions (Nuffield, 2016; NAS, 2016a; Secretariat CBD, 2015). There are important differences between gene editing and gene drives. As organisms with a gene drive may spread beyond geographical borders, this raises many questions including who should, ultimately, make the final decision on a gene drive release? And who bears responsibility for any negative consequences?

The ability of gene drives to intentionally spread a trait through a population carries important implications for the governance of gene drive research, not only for the regulatory framework but also the informal processes of implementing a gene drive. The informal processes include public engagement, addressing societal expectations, communication, and mitigation strategies which have been discussed in the previous sections.

Australia has a well established regulatory framework for gene technology. Our national, integrated regulatory scheme is a process-based system that was set up to protect people and the environment by identifying and managing the risks posed by live and viable GMOs. The *Gene Technology Act 2000* (the Act) covers work with GMOs in certified contained laboratory conditions as well as intentional releases to the environment under limited and controlled conditions (field trials), through to unrestricted releases.

**3** www.ogtr.gov.au/internet/ogtr/publishing.nsf/content/PC2-4/$FILE/PC2LABv3-1-1.pdf

**4** ogtr.gov.au/internet/ogtr/publishing.nsf/Content/PC3-4/$FILE/PC3LABv3-May2012.pdf

**5** www.agriculture.gov.au/SiteCollectionDocuments/biosecurity/import/arrival/approved-arrangements/7.2-requirements.pdf

**6** www.agriculture.gov.au/SiteCollectionDocuments/biosecurity/import/arrival/approved-arrangements/7.3-requirements.pdf

| Table 2: Australian regulatory environment for GMOs | | |
|---|---|---|
| **Agency** | **Relevant legislation** | **Scope** |
| Office of the Gene Technology Regulator | *Gene Technology Act 2000* | Genetically modified organisms, including gene drives. |
| Department of Agriculture and Water Resources | *Biological Control Act 1984* | Assessment and authorisation of biological control activities. |
| | *Biosecurity Act 2015* | Assessment and management of biosecurity risks from diseases and pests. Includes provisions addressing importation of products presenting a biosecurity risk. |
| Department of the Environment and Energy | *Environmental Protection and Biodiversity Conservation Act 1999* | Protection and management of nationally and internationally important flora, fauna, ecological communities and heritage places. |
| Australian Pesticides and Veterinary Medicines Authority | *Agricultural and Veterinary Chemicals (Code) Act 1994* | Agricultural pesticides and veterinary medicines. |
| | *Agricultural and Veterinary Chemicals Administration Act 1994* | |
| Food Standards Australia and New Zealand | *Food Standards Australia New Zealand Act 1991* | Food and food technology (including food produced using gene technology). |
| Therapeutic Goods Administration | *Therapeutic Goods Act 1989* | Human therapeutics, including medicines and medical technologies. |

Where gene technology is used to introduce or create a gene drive in an organism, the resulting organism will be considered to be a GMO and subject to regulation under the Act.[7] Hence, the use of site-directed nucleases (SDNs) such as CRISPR/Cas9 to produce a gene drive modified organism would be regulated.

To enhance coordinated decision making and avoid duplication, the Act requires consultation between regulatory agencies that have complementary legal responsibilities and expertise in relation to the evaluation and use of GMOs and GM products (Table 2).

Where a synthetic gene drive modified organism targets invasive species, a range of legislative provisions may also apply. The *Biological Control Act 1984* (Commonwealth) assesses and authorises biological control activities. Each state and territory has their own version of this act (except the ACT, which is under the Commonwealth act). As such organisms can potentially cross state and territory borders, agreement across Australia will be needed for the release of a synthetic gene drive modified organism to control invasive organisms. In addition, the *Biosecurity Act 2015* targets biosecurity risks entering Australia from overseas relating to animal and plant pests and diseases so a gene drive modified organism imported from overseas would likely be subject to this act. The *Environmental Protection and Biodiversity Conservation Act 1999* (EPBC), which protects and manages nationally and internationally important flora, fauna, ecological communities and heritage places, may also need to be considered.

Some work with gene editing and gene drive technologies may be subject to control as a consequence of Australia's membership of a number of international counter-proliferation regimes. The Defence Trade Controls Act was introduced in 2012 to prevent sensitive goods and technologies that could be used for offensive purposes (known as 'dual use') going to individuals, states or groups of concern.

The regulatory environment continues to evolve in response to changes in technologies. At the time of writing The Gene Technology Regulator, the independent statutory office holder responsible for administering the *Gene Technology Act 2000*, is conducting a technical review of the Gene Technology Regulations 2001, with community consultation and engagement. This review is explicitly considering gene drive technology. The Department of Health will be undertaking a scheduled review of the *Gene Technology Act 2000* in 2017, and Food Standards Australia and New Zealand are drafting a guidance document to provide clarity regarding food produced using gene editing technologies.

Australia also works with other countries to harmonise approaches in biotechnology and new technologies in agriculture. In January 2016, Australia released a joint statement with Argentina, Brazil, Canada, Paraguay and the Unites States advocating removal of global barriers to the trade of agricultural biotechnology and promotion of science-based regulatory approaches.

**7** www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/53139D205A98A3B3CA257D4F00811F97/$File/OGTR%20guidance%20on%20gene%20drives.pdf

# RECOMMENDATIONS

Synthetic gene drives have the potential to solve seemingly intractable problems in public health, environmental conservation and agriculture. However, they also have the potential to cause negative environmental and human health effects.

The Australian Academy of Science recommends that:

1. There continues to be clear and transparent communication of governance arrangements regarding regulation of synthetic gene drives.
2. Resources be provided to study synthetic gene drives in isolated laboratory populations with sample sizes and time frames that are large enough and/or long enough to observe processes such as selection, resistance evolution, population structuring and transmission distortion, together with the intended and potentially unintended consequences that these process may lead to.
3. Stringent, multiple containment measures be taken when researching synthetic gene drives.
4. Any decision to release a synthetic gene drive continues to be made on a case-by-case basis following a comprehensive environmental risk assessment which includes ecological and evolutionary modelling.
5. There be clear communication and consultation with the public through appropriate channels from the earliest stages of gene drive research, particularly with affected communities.
6. The wider implications of synthetic gene drives (e.g. trade implications) be considered.

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# APPENDIX 1: EXAMPLES OF NATURAL AND SYNTHETIC GENE DRIVE MECHANISMS

## HOMING ENDONUCLEASE GENES

Site-specific selfish genes such as homing endonuclease genes (HEGs) can spread through populations as a gene drive due to their biased inheritance (Burt, 2003). They cleave a unique stretch of genomic DNA and as the cell repairs the hydrolysed DNA the HEG is copied into the cleaved site. Consequently the frequency of HEGs increases and they spread throughout a population.

There are other current gene editing techniques such as Zinc Finger Nucleases (ZFNs), Transcription Activator-like Effector Nucleases (TALENs) and CRISPR (Clustered regularly interspaced short palindromic repeats) which also utilise nucleases to cleave at specific sites. While not a gene drive in its own right, CRISPR/Cas9 is a gene editing tool that can be used to produce synthetic gene drives that increase the inheritance of a particular trait as outlined in the main text. Note that the vast majority of gene editing applications does not involve the creation of a gene drive.

## TRANSPOSABLE ELEMENTS

Gene drives can be generated by manipulating transposable elements, also known as jumping genes. These are small DNA segments which can excise themselves and randomly insert into different parts of the genome. This results in multiple copies within the genome. The *P*-element transposon is a type of transposable element well studied in the *Drosophila melanogaster* (Rubin & Spradling, 1982). An active *P*-element can be modified and in this way can rapidly spread the modified sequence throughout a population.

## MEIOTIC DRIVE

Meiotic drive is a gene drive mechanism interfering with meiotic processes to cause a distortion of allelic segregation compared to expected Mendelian inheritance (McDermott & Noor, 2010). This has been reported in *Drosophila melanogaster*, in the house mouse *Mus musculus* and in plants *Zea mays* and *Silene*. Within *Zea mays* the Abnormal 10 (Ab10) chromosome affects segregation of chromosome 10 and causes heterozygous chromosomal pair separation of 70% rather than the typical 50% expected with Mendelian inheritance.

## UNDERDOMINANCE

Underdominance is selection against heterozygous progeny where the homozygotes have an increased fitness and one of the homozygous forms can be driven to a high frequency. Underdominance was proposed as a method of controlling sheep blowfly in Australia several decades ago (Whitten, 1971). Current approaches for establishing underdominance have been achieved by RNA interference in *Drosophila melanogaster* to suppress an endogenous gene (Reeves et al., 2014).

## MATERNAL-EFFECT DOMINANT EMBRYONIC ARREST

Maternal-effect dominant embryonic arrest (*Medea*) can be used to suppress a population by targeting and silencing a maternal gene necessary for embryonic development. This was first discovered in a flour beetle and causes death in any offspring that lack the *Medea*-bearing chromosome (Beeman et al., 1992), allowing the *Medea* element to spread.

## CYTOPLASMIC INCOMPATIBILITY

*Wolbachia* are bacteria that manipulate the reproduction of a diverse range of arthropod hosts to their own advantage (Sinkins & Gould, 2006). They are a common intracellular microbe which can generate a gene drive in infected host individuals by triggering incompatibility between eggs and sperm or by male killing. They are maternally inherited and change the population dynamics to favour infected females. A rescue function allows eggs from infected females to develop normally when mated to infected males. Current research trials on release of mosquitoes which carry *Wolbachia* have focused on preventing the spread of viruses such as Zika and dengue whose transmission is suppressed by *Wolbachia*. However these bacteria could also be used to potentially spread genes engineered into *Wolbachia* or other maternally transmitted factors such as mitochondria.

## CYTOPLASMIC MALE STERILITY

Cytoplasmic male sterility is another form of non-Mendelian inheritance (Laughnan & Gabay-Laughnan, 1983). This condition is widespread among higher plants and results in a plant unable to produce functional pollen, i.e. male sterile, due to a sterility inducing mitochondrial gene which is maternally inherited. This is used extensively in agriculture to generate hybrid seed, these seeds usually result in larger, more vigorous plants.

# APPENDIX 2: POTENTIAL GENE DRIVE APPLICATIONS

## DISEASE

A gene drive could be used to reduce mosquito populations to help reduce the spread of diseases. Advances in gene editing techniques have led researchers to develop a CRISPR/Cas9 gene drive targeting a female sterility gene. This would lead to more male offspring than females and over multiple generations reduce *Anopheles gambiae* populations to a level where disease transmission of malaria is limited (Hammond et al., 2016). Although malaria is not an issue in Australia, we do experience other human viral diseases spread by mosquitoes, such as dengue and Ross River fever. Another approach is using *Wolbachia*, a bacterium which infects mosquitoes, to reduce transmission by *Aedes aegypti* populations in north Queensland, which is the main vector of dengue (Hoffmann et al., 2011).

## INVASIVE SPECIES AND THE ENVIRONMENT

A gene drive could be used to reduce the population of the non-indigenous mouse species *Mus musculus* on islands around the world, or specific to Australia, to reduce the population of black rats on Lord Howe Island. Introduced rodents can negatively affect an islands ecosystem by competing with native species and by destroying their habitats. Current efforts to eradicate invasive rodents have disadvantages including using toxic chemicals which can damage the environment or mechanical traps which don't discriminate between introduced or native species. A gene drive targeting a sex determining gene, *Sry*, to produce more male offspring than females could lead to a reduced population of mice after several generations (Cocquet et al., 2012).

Cane toads were first introduced to Australia in 1935 as an attempt to biologically control cane beetles which damaged sugarcane crops. Since their release in north Queensland the cane toad has spread and caused the decline of many native species. The skin of the cane toad is toxic and has poisonous glands across its back and the tadpoles are highly toxic if ingested. These toxic defences have poisoned many native Australian animals. A gene drive could detoxify the cane toad to reduce the detrimental effects of this invasive species or could control the population of cane toads directly. The cane toad is the only toad species in Australia, so a targeted gene drive could be specific to just the cane toad and not affect native frog species.

Another invasive species in Australia is the European carp. It was introduced over 100 years ago and has colonised many waterways throughout Australia causing major environmental impacts. Carp now dominate many river systems and reduce water quality, increase erosion, spread diseases and reduce native fish numbers. A gene drive to reduce the number of females and create an all-male population would be one mechanism to eradicate the European carp.

Rabbits are a classic example of an invasive, destructive species. Rabbits were introduced to Australia in 1859 for hunting but have since caused extensive damage, competing with livestock for grazing, spreading weeds, accelerating erosion and reducing biodiversity. It is estimated that rabbits cause A$200 million per year of economic damage.[8] Efforts to control rabbit populations have had mixed success in the past, namely through biocontrol programs using viruses including Myxomatosis and calicivirus. However resistance has developed in some Australian rabbits meaning the rabbit population is again on the rise. A gene drive to reduce rabbit numbers would be highly beneficial for Australian farmers and our environment.

## AGRICULTURE

Gene drive systems hold a lot of promise in controlling agricultural invertebrate pests such as fruit flies, moth pests, thrips and mites. These pests tend to have short generation times and have often become problematical to control due to the evolution of resistance to widely-used pesticides such as pyrethroids and organophosphates.

Gene drive systems may also help deal with weed issues. For instance, *Echinochloa colona*, also known as barnyard grass or jungle rice, is a damaging weed for agricultural production in Australia. It particularly affects rice, sugarcane, maize, sorghum and summer fallow crops and since 2007 several populations have developed glyphosate resistance (Thai et al., 2012). Glyphosate is a herbicide commonly used to control weeds. The production of herbicide resistant crops have dramatically changed weed control practices. However after decades of herbicide use weeds are developing resistance, reducing the efficacy of glyphosate for weed control. A gene drive to reverse herbicide resistance would be valuable especially for Australian cotton farmers.

8 www.csiro.au/en/Research/BF/Areas/Managing-the-impacts-of-invasive-species/Biological-control/Controlling-those-pesky-rabbits

Discussion paper **Synthetic gene drives in Australia: Implications of emerging technologies**