LIMPING ALONG AND LAGGING BEHIND: THE LAW AND EMERGING GENE TECHNOLOGIES

JAI A DENTON* AND CHRISTOPHER S REYNOLDS**

ABSTRACT

It took Australia almost 20 years to develop a legislative regulatory system for genetically modified organisms, but with technology that changes so quickly, legislation that relies heavily on definitions can quickly become obsolete. Here we highlight two emerging technologies, CRISPR-mediated genome editing and infecting mosquitos with Wolbachia to reduce their disease transmission. We discuss their regulation, and regulation generally, with a focus on the current Australian system. Both of these technologies have fallen into a grey zone with regulators, leaving them uncertain how to act, and developing regulations that have been cobbled together. In the hope of providing a more versatile and effective path to regulation for technology stake holders, while maintaining public confidence and protecting the environment, this paper explores future legislative strategies to replace the existing regulatory model with a model that is 'outcome-based'.

I INTRODUCTION

> [L]aws and institutions must go hand in hand with the progress of the human mind. As that becomes more developed, more enlightened, as new discoveries are made, new truths disclosed, and manners and opinions change with the change of circumstances, institutions must advance also, and keep pace with the times.[1]

Although written more than 200 years ago, like much of Thomas Jefferson's wisdom, this statement has a long, broad reach and remains compelling. Jefferson recognized that the world is constantly developing and that the law needs to develop with it. New technologies can also create new hazards. While some of these are easily managed, others pose hazards that are clear potential risks to the environment and the community. These require careful management and effective regulatory oversight, typically via licensing requirements and mandated standards. Yet these are slow to develop, with multiple stages, reports, committees of inquiry, lobbying by special interest groups, and changes of government all adding years to the process of developing appropriate regulatory regimes. Too often, the regulatory vacuum is filled, if at all, by practices like self-regulation, civil litigation, or the application of unsuitable and outmoded existing regulatory frameworks, designed to respond to other problems.

Every new development presents similar concerns about the speed at which it can be regulated. This includes technologies that currently lack adequate frameworks such as

* Jai Denton BSc, PhD, GCert CS, LLB is a researcher in the Genomics & Regulatory Systems Unit at the Okinawa Institute of Science and Technology studying evolution, molecular biology and GMO regulation. Please address any correspondence to jai.denton@oist.jp.

** Chris Reynolds LLB, PhD, GDip Public Health is an Adjunct Associate Professor School of Public Health, University of Adelaide.

[1] Letter from Thomas Jefferson to Samuel Kercheval Monticello, 12 July 1816 in *American History* <http://www.let.rug.nl/usa/presidents/thomas-jefferson/letters-of-thomas-jefferson/jefl246.php>

commercial use of drones,[2] self-driving cars,[3] space exploration[4] and computing[5]. The need for regulation of these technologies is perhaps more apparent due to their novelty, but this novelty highlights the need for whole new frameworks. However, what happens when technological developments are not entirely novel, but also no longer comfortably fit within their existing regulatory frameworks?

The primary justification for government intervention through regulation is market failure, in which the 'market', typically an industry, is unwilling or unable to protect the public or the environment from its impacts through self-regulation, resulting in unacceptable risks. Regulation that establishes mandatory requirements backed by penalties is the most obvious example of government intervention to pursue a policy or achieve an aim, in this case protecting health and safety from risks associated with new technologies.

There are other forms of regulation designed to control an activity: governments can establish expert advisory bodies or vest decision makers with discretionary powers to monitor and regulate activities. They can also oversee preparation of compulsory codes of conduct and 'co-regulate' the area with industry. Governments can also use taxation as an incentive to change behaviours or achieve a goal. None of these options are mutually exclusive and in technical and high-profile areas where there is often a range of competing stakeholders and much public interest, such as food, agricultural chemicals or GMOs, a complex regulatory framework can be the result.[6]

A traditional approach to legislative regulatory frameworks tends to rely on strict definitions that focus on specific activities to define what falls within the purview of the legislation.[7] Therefore, these frameworks are prone to shuttle specific technologies down particular regulation pathways based on the nature of the technology, rather than upon outcomes and impacts of its use. This definition-based approach means that even if a regulatory framework is found for an emerging technology, it may not be the best suited to mitigate deployment risk, or alternatively, it may place an unnecessary regulatory burden on the technology's use.

Even closely related regulatory frameworks tend to have very different origins and guiding philosophies, such that key concepts may be applied to one technology, but not to closely related ones. This regulatory unevenness increases uncertainty and needs to be rectified, both for risk management and technological development. How can we simultaneously minimize risk, maintain public confidence, and allow development of new technologies?

This problem lies at the heart of Australia's legislative regulatory framework for genetically modified organisms (GMOs), those incorporating DNA from another

[2]Gbenga Oduntan, 'The Age of Drones Has Arrived Quicker Than The Laws That Govern Them', *The Conversation*, 10 September 2015 <https://theconversation.com/the-age-of-drones-has-arrived-quicker-than-the-laws-that-govern-them-47024> (accessed March 13, 2018).

[3]Nathan A. Greenblatt, 'Self-Driving Cars Will Be Ready Before Our Laws Are', *IEEE Spectrum*, 19 January 2016 <https://spectrum.ieee.org/transportation/advanced-cars/selfdriving-cars-will-be-ready-before-our-laws-are> (accessed March 13, 2018).

[4] Timothy G. Nelson, 'Billionaires Race For Space, But Just Who Owns The Cosmos?' *CNBC (online),* 29 August 2016 <https://www.cnbc.com/2016/08/29/private-exploration-moving-faster-than-law-in-new-space-race.html> (accessed March 13, 2018).

[5] Vivek Wadhwa, 'Laws and Ethics Can't Keep Pace with Technology' *MIT Technology Review*, 15 April 2019 <https://www.technologyreview.com/s/526401/laws-and-ethics-cant-keep-pace-with-technology> (accessed 16 March 2018).

[6] Christopher Reynolds, *Public and Environmental Health Law* (The Federation Press, 2011), 139-52.

[7] Arie Freiberg, *The Tools of Regulation* (The Federation Press, 2010), 20-21.

organism, which is now nearly 20 years old.[8] We argue that this framework, lacks the scope to regulate emerging technologies effectively.

Development of the first GMO, in 1973, initiated a novel technology with its risk to humans and their environment recognized almost immediately by the scientific community.[9] Yet it still took considerable time for legislative instruments to be developed. The foundational Australian legislation, the *Gene Technology Act 2000* (Cth) ('GT Act'), was over 20 years in the making, during which time, gene technology continued to develop.

In the context of GM legislation this paper explores the problem of the law lagging behind new and emerging technologies. To do this, we describe two such technologies, focusing on the inability of existing regulatory mechanisms to properly respond to them, so as to offer oversights and safeguards that the community has a right to expect. Finally, we explore options that offer a new and more versatile approach to this problem, one that exhibits a heightened emphasis on technological *outcomes* rather than fixed definitions, and that aims to provide a more general solution to the regulation of existing and emerging technologies.

II Example of the Technology

We have chosen to highlight two specific technologies that, in our opinion, demonstrate regulatory gaps within existing Australian frameworks. Specifically, we provide an overview of a method of genome editing, CRISPR, and a bacteria-mediated method for insect population transformation, *Wolbachia* infection.

A *Case Study – CRISPR*

The discovery of a bacterial immune system called Clustered Regularly Interspaced Short Palindromic Repeats (generally referred to as CRISPR) has ushered in a new wave of GMOs. By harnessing the components that make up this immune system, novel techniques for genetic modification of potentially all organisms has been developed. This has ushered in a new era of GMO production. By introducing the CRISPR system to an organism, quick and precise modification of the organism's genetic code can be effected. Although the technology has been developed for additional applications, our focus will be on its capacity to change the genetic code, which governs the properties of every organism, in the most minute ways.

1 CRISPR Technology

CRISPR protects bacterial cells against invading viruses. When a virus infects a bacterium, the cell is capable of recognizing the invading virus and generates a guide sequence, essentially instructions allowing the identification of specific targets, that the cell then uses to specifically attack the invader.[10] By the careful design and introduction of a specific guide, CRISPR can be used to edit any desired genomic sequence in animal, plant, or fungal cells.[11] This potential to modify existing genetic structures has changed how GMOs are developed and has impacted most fields of biology.

---

[8] *Gene Technology Act 2000* (Cth).
[9] See, eg, Paul Berg et al, 'Summary Statement of the Asilomar Conference on Recombinant DNA Molecules (1975) 72(6) *Proceedings of the National Academy of Science USA* 1981-1984.
[10] Eric Lander, 'The Heroes of CRISPR' (2015) 164 *Cell* 18-28.
[11] See, eg, Martin Jinek et al, 'RNA-programmed genome editing in human cells' (2013) 2(e00471) *eLIFE*.

In CRISPR's simplest application, a bacterial enzyme, Cas9, can attack a genetic sequence that matches the guide sequence provided. A cell then recognizes this alteration of the genetic code and repairs the damage. This attack and repair cycle can continue until, by chance, a repair mutation occurs, and the guide no longer matches the targeted genetic code. This simple form of editing the genetic code does not insert any foreign genetic material, and can be used to inactivate a specific cellular process. However, the CRISPR system has been used for targeted insertion of foreign genetic code into an organism (similar to existing GMOs). Although this and other more complex applications of CRISPR are extremely interesting, this report will focus on simple editing of the genetic code.

2 *New Crops & Their Regulation*

Beyond some of the more polarizing examples of GMO crops, such as the Monsanto produced RoundUp Ready varieties, there are less well-known GMOs, like the ringspot virus-resistant papaya. Deployment of this papaya strain increased Hawaiian papaya production and potentially provided a buffer for non-GMO papaya.[12] These GMO examples rely on insertion of foreign genetic code into the organism in question. However, changes to an organism's existing code are already being used to great effect in the development of novel agricultural strains.

One example of CRISPR technology involves white button mushrooms, which normally have a short shelf life due to browning. A small CRISPR-induced deletion in the genetic code of an enzyme associated with mushroom browning has significant commercial value to growers.[13] It is also of significance for consumers and potentially for public health and safety too, yet the technique appears to operate within a regulatory vacuum, both in Australia and elsewhere.

In 2016, the creator of this mushroom variety, Dr. Yinong Yang from Penn State University, wrote to the Animal and Plant Health Inspection Service ('APHIS') of the United States Department of Agriculture ('USDA'), requesting confirmation that the mushroom was not considered a regulated article.[14] The APHIS deputy administrator confirmed that the novel CRISPR-created mushroom variety would not be regulated as a GMO, as it contained no foreign DNA, nor as a plant pest, as the modification would likely not increase the risk of its acting as a pest.[15] This absence of regulatory oversight, although not unexpected based on previous developments, has concerned some commentators.[16] This U.S. regulatory oversight occurred primarily because the U.S. uses plant pest legislation to regulate GMO plants. Therein regulated articles are confined to those that involved introduction of foreign DNA into target plants, rather than a broad definition.[17]

[12] Dennis Gonsalves, 'Control of Papaya Ringspot Virus in Papaya: A Case Study' (1998) 36 *Annual Review in Phytopathology* 415-437.
[13] Emily Waltz, 'Gene-edited CRISPR mushroom escapes US regulation' *Nature News (online)*, 14 April 2016 <http://www.nature.com/news/gene-edited-crispr-mushroom-escapes-us-regulation-1.19754> (accessed 18 March 2018).
[14] Letters between Yiong Yang and Michael Firko, 13 April 2016 and 30 October 2016, <www.aphis.usda.gov/biotechnology/downloads/reg_loi/15-321-01_air_response_signed.pdf>.
[15] Ibid.
[16] Ibid.
[17] 7 CFR §340.1 (1997).

3 *CRISPR Regulation in Australia and Beyond*

Some commentators have suggested that simple genome editing should not be regulated in the same way as conventional GMOs that contain foreign DNA.[18] The Australian GMO regulatory authority, the Office of the Gene Technology Regulator ('OTGR'), has not remained silent on the matter. Its advice last year concluded that under the broad definition in the *GT Act*[19] CRISPR-based genome editing would be considered a GMO.[20] However, the OTGR has recently released its response to their inquiry into the function of the *GT Act* and has recommended several changes.[21] Significantly, the OTGR has recommended separating the classification of site-directed nucleases ('SDN'), like CRISPR, that induce DNA changes based on the nature of the resulting change. SDNs, like the simple CRISPR system, were classified as SDN-1 and were determined to have the same risk as random DNA changes, since any alteration of the code was random and did not depend on a guide. On the other hand, SDNs that directed specific changes to the code via inclusion of a guide, classified therein as SDN-2, are recommended to remain as GMOs.

In the European Union ('EU') there is the suggestion that because their regulatory framework focuses on the end result, CRISPR genome-edited organisms like the mushroom would not be regulated.[22] A recent EU opinion on mutagenesis (the practice of damaging an organism's DNA, usually with chemical mutagens or radiation), reaffirmed that this practice is not regulated under the EU GMO directive.[23] However, this opinion did not expressly mention CRISPR; thus, it failed to suggest how this technology will be regulated. This issue is far from settled as both the EU and member states, such as Germany, are still debating the effectiveness of their current regulation and the need for new frameworks.[24]

Regulation of CRISPR is unlikely to be settled quickly, since stakeholders and government agencies continue to discuss and debate the details. Regardless of what happens, it is likely that in time, many jurisdictions will regulate CRISPR simple genome modifications in a manner similar to GMOs that contain foreign DNA, despite the fact they can be indistinguishable from strains that contain naturally occurring changes. Effectively many simple genomic modifications brought about by CRISPR have more in common with traditional plant breeding than with GMOs. This may result in situations in which a company developing strains could pass off CRISPR-modified varieties as having been developed through natural breeding. This point was also emphasized in the OTGR response and is likely a factor in their recommendation to exempt CRISPR, in its simplest form, from GMO status.[25]

---

[18] See, eg, Tyne Logan, 'Gene editing is different to genetic modification, so should its regulation be relaxed?', *ABC News* (Online), 24 March 2017 <http://www.abc.net.au/news/rural/2017-03-24/gene-editing-is-different-to-genetic-modification/8383278>

[19] *Gene Technology Act 2000* (Cth), s 10.

[20] Office of the Gene Technology Regulator, 'General advice from the Regulator on coverage of new technologies' 18 December 2016 <http://www.ogtr.gov.au/internet/ogtr/publishing.nsf /Content/newtechnologies-htm> (accessed 16 March 2018).

[21] Office of the Gene Technology Regulator, 'Updating Gene Technology Regulation in Australia: Regulation Impact Statement for consultation' December 2017 <http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/39DB72B3BB9AA790CA25823B00812B73/$File/Regulation%20Impact%20Statement%20for%20consultation.pdf> (accessed 19 November 2018)

[22] Rene Custers, 'The Regulatory Status of Gene-edited Agricultural Products in the EU and Beyond' (2017) *Emerging Topics in Life Sciences* ETLS20170019.

[23]Court of Justice of the European Union, 'Press Release no 04/18' 18 January 2018 <https://curia.europa.eu/jcms/upload/docs/application/pdf/2018-01/cp180004en.pdf> (accessed 16 March 2018)

[24] Nature Editorial, Gene Editing In Legal Limbo in Europe (22 February 2017) 542 *Nature* 392.

[25] General advice from the regulator on coverage of new technologies (n 20) 10.

B *Case Study — Australian Release of Wolbachia Infected Mosquitos*

Dengue fever is a serious mosquito-borne disease. It is estimated that 500,000 people with severe fever 'require hospitalization each year, and about 2.5% of those affected die'.[26] In 2011, the World Mosquito Program, formerly known as "Eliminate Dengue" commenced a strategy in Australia to infect the *Aedes aegypti* (*A aegypti*)[27] population, the vector primarily responsible for spreading the disease, with a bacterium called *Wolbachia* (resulting in a novel association referred to as *wA aegypti*). As *Wolbachia* has been shown to reduce disease transmission[28] transforming the existing mosquito population to one hosting this bacterium has the potential to reduce disease burden.

1 *Wolbachia*

Wolbachia, a bacterial genus, is a common pathogen in arthropods[29] and some nematodes.[30] First identified in the mosquito, *Culex pipientis*, *Wolbachia* is predicted to have a wide distribution across all continents, except the Antarctic, and it infects 65% of all insects on the planet.[31] It forms complex relationships with its hosts, ranging from strong parasitism, a one-way relationship where *Wolbachia* only takes from its host, to strong mutualism, a reciprocal relationship in which both organisms benefit.[32] Although these complex ecological dynamics are interesting, perhaps the most fascinating aspect of *Wolbachia* biology is its manipulation of the host life cycle.

Female insects infected with *Wolbachia* pass the infection to all of their offspring in what is called vertical transfer. This is rather unremarkable, but what is remarkable is the male's role in infection transmission. The males do not pass *Wolbachia* to their offspring, but if an infected male mates with an uninfected female this renders her offspring inviable. As most female insects mate only once, infected male/uninfected female mating is a reproductive dead end for the female. Over time this means that, from a few infected females, *Wolbachia* can spread through a population until all individuals are infected.

An *wA. aegypti* mosquito transmits the dengue virus at a lower rate.[33] Proposed mechanisms for this reduced transmission are twofold: first, *Wolbachia* infection reduces the life span of the mosquito (older mosquitoes spread the disease more easily); and secondly, *Wolbachia* is reported to strengthen the mosquito immune system, thereby reducing the viral load per insect.[34] This suggests that if all individuals of an *A aegypti* population carried the *Wolbachia* infection, disease vectoring to humans would be reduced along with the suffering these diseases cause in human populations.

Due to occasional outbreaks of dengue fever in Queensland, several sites in the state were chosen for release of *Wolbachia*-infected *A aegypti* mosquitos as a trial to test the effectiveness of the strategy. However, dengue is not common in the area, so the trial

---

[26] World Health Organisation, *Dengue and Severe Dengue Fact Sheet*, April 2017 <http://www.who.int/mediacentre/factsheets/fs117/en/>.

[27] *A. aegypti* is a common mosquito that vectors several human diseases including dengue fever, malaria and zika virus. It is also widely dispersed in Northern Australia.

[28] See, eg, TP Walker et al, 'The wMel Wolbachia strain blocks dengue and invades caged *Aedes aegypti* populations' (2011) 476 (7361) *Nature* 450-53.

[29] Arthrods are a diverse group (phylum) of animals that includes insects, arachnids and crustaceans.

[30] John Werren, Laura Baldo and Michael Clark, '*Wolbachia*: Master manipulators of invertebrate biology' (2008) 6(10) *Nature Reviews Microbiology* 741-51.

[31] Ibid.

[32] Ibid.

[33] Walker (n 28) 450-53.

[34] Ibid.

was more focused on testing the spread of *Wolbachia* than on the epidemiological efficacy of the system. Since these original releases, mosquito populations in the release zones have been monitored for the spread of *Wolbachia*. It was determined that Wolbachia is now stable in the population and that there have been no dengue outbreaks in the release zones.[35] However, to even commence this trial, several regulatory steps needed to be overcome.

2 *Wolbachia Regulation in Australia*

An article by De Barro *et al*[36] detailed the process the Australian Eliminate Dengue team went through to obtain regulatory approval. This was a complex process since the regulatory landscape in Australia was not equipped for the release of *Wolbachia*-infected *Aedes aegypti*. Several steps were attempted in the regulation:

1. The initial proposal was the release of *Wolbachia*-infected mosquitos as a biological control agent under the *Biological Control Act 1984* (Cth). However, as the authors note, this Act primarily deals with mediating between potentially conflicting interests for a release. For example, it provides the opportunity for parties that might potentially suffer loss due to the biological control of specific targets to file submissions.[37] As most targets for control do not produce this sort of conflict, most biological control systems were regulated under the Commonwealth *Quarantine Act 1908* (Cth), in conjunction with the *Environmental Protection and Biodiversity Conservation Act 1999* (Cth). However, the *Quarantine Act* has since been repealed and replaced with the *Biosecurity Act 2015* (Cth). The Commonwealth Departments of Agriculture, Forestry and Fisheries (DAFF), which manage the *Quarantine Act*, and Sustainability, and Environment, Water, Population and Communities (SEWPAC), which manage the *Environmental Protection and Biodiversity Conservation Act*, also deemed the *Wolbachia*-containing mosquitoes outside their regulatory purview.[38] This was due to the fact that both *Wolbachia* and *A. aegypti* are already present in Australia, albeit independently, and the law does not cover novel organismal associations.[39]
2. The next regulatory path described by De Barro *et al* was to consider the infected mosquitoes as a GMO and have them regulated as such under the *GT Act*. However, that Act is concerned with organisms and their offspring that have been modified with gene technology and, according to the interpretation of the *GT Act*, infecting *A. aegypti* with *Wolbachia* does not constitute gene technology. A primary reason cited by De Barro et al is that GMOs involve the integration of recombinant DNA into the genome of a target organism, whereas this is not the case for *Wolbachia* as it is free living and can be lost from the organism.[40] This closed another avenue for regulation of *Wolbachia* infected mosquitoes.
3. To obtain a ruling regarding regulation of the system The Eliminate Dengue Program made a submission to the Primary Industries Ministerial Council

[35] See eg AA Hoffmann et al, 'Stability of the wMel *Wolbachia* Infection following Invasion into *Aedes aegypti* Populations' (2014) *PLoS Neglected Tropical Diseases* 8(9): e3115.
[36] Paul De Barro et al, 'The proposed release of the yellow fever mosquito, Aedes aegypti containing a naturally occurring strain of Wolbachia pipientis, a question of regulatory responsibility' (2011) 6(S1) *Journal für Verbraucherschutz und Lebensmittelsicherheit* 33-40.
[37] *Biological Control Act 1985* s17.
[38] De Barro, (n 38) 35.
[39] Ibid.
[40] Ibid.

('PIMC') to determine the best way to proceed. As part of this process the submission was circulated through various Federal agencies including the Australian Pesticides and Veterinary Medicines Authority ('APVMA').

4. The APVMA determined that the *Wolbachia* release could be considered a veterinary chemical product, since the *Agricultural and Veterinary Chemicals Code Act 1994* (Cth) provides that anything that modifies the physiology of a plant or pest can be considered an agricultural chemical product[41]. As part of the submission, legal advice was given by an APVMA member that the *Wolbachia*-infected mosquitos were consistent with this definition.

Although a previous risk assessment of *wA aegypti* existed,[42] the APVMA, with assistance from SEWPAC, undertook an additional risk assessment that specifically focused on environmental impacts.[43] Subsequently the release of *wA aegypti* was given Australian regulatory approval as an agricultural veterinary drug.

3 *Was this sufficient?*

This regulatory journey from development to release of a novel technology application, affords considerable insight into the Australian regulatory landscape. *Wolbachia*-infected *A aegypti* was held not to be a GMO, as it was not the product of Gene technology, but it may be argued that the mosquito now harbors foreign DNA. It does not simply harbor a single piece of foreign code, like many GMOs, but an entire organismal genome. If the risk of a single foreign gene in a GMO requires considerable assessment and time, how does one determine the risk posed by a complete foreign genome? However, in answering this question one must consider that novel bacterial associations are common. All organisms are colonized by numerous microbes that can either aid or harm. Regulation is further complicated because this particular novel association between *A. aegypti* and *Wolbachia*, has the potential to transform the entire mosquito population. If the system works as expected, the current *A aegypti* population, without *Wolbachia*, will be replaced by the novel *Wolbachia A aegypti* association. Clearly, this has an impact on regional biodiversity, though most people would welcome at least its promises of disease control. Moreover, the World Mosquito Program has been exceptional in its community engagement and in seeking risk assessments even though under the current regulatory framework it had no obligation to pursue such approval.

III The Australian Pathway to GMO Regulation

The *Wolbachia* field trial was able to proceed and achieve its aims, while the CRISPR technology offers innovative ways to make plants and animals better adapted to changing needs and environments. However, the approval and oversight that should have accompanied them was inadequate, because the current regulatory framework simply was not fit for purpose. This is despite the fact that GMOs have perhaps one of the most complex regulatory frameworks. Although far from straightforward, community concerns about genetic modification have driven development of intricate regulatory frameworks in a comparatively short period of time. These frameworks need to govern diverse practices including farming, scientific research, food consumption and labelling, and pharmaceutical production, while minimizing risks posed to the

[41] *Agricultural and Veterinary Chemicals Code Act 1994* (Cth) s 4.
[42] De Barro (n 38), 37-38
[43] Ibid.

environment, to scientists, consumers, patients, and the public at large. Achieving a balance between stakeholders for any regulatory system is subjective and fraught with difficulty but the difficulty is compounded when the regulatory subject changes rapidly. To mitigate some of this difficulty, many regulatory frameworks employ principles as general guides in their use. Principles allow regulatory administrators to employ a more purposive approach to regulation and bypass regulatory gaps.

Australia's pathway to GMO regulation prior to the implementation of a legislative framework is a fascinating tale of concern begetting industry-based regulation, but justice cannot be done to this tale here.[44] In 2000, the *GT Act* was passed, bringing the OTGR into existence.[45] Consistent with s 27 of that act, the *Gene Technology Regulations 2001* (Cth) were put in place. These two instruments established the GMO regulatory landscape in Australia for nearly two decades and will likely remain its foundation. It is difficult to succinctly describe all aspects of these instruments, but there are key sections that cement this framework as the highest standard for the regulation of Australian biotechnology.

Any discussion of a specific GMO regulatory framework needs to begin with that framework's functional definition. The *GT Act's* GMO definition, quoted above, was carefully formulated to ensure that the law is as broad as possible without being unduly restrictive. In submission 51 to the Senate inquiry into the Gene Technology Bill 2000 (Cth) (called 'A cautionary tale: Fish don't lay tomatoes'), the Friends of the Earth (Fitzroy) group suggested that the GMO definition include:

> (d) any biological entity capable of replication or transfer of genetic information, and includes plants, animals, bacteria and all other kinds of micro-organisms, cell cultures (prokaryotic or eukaryotic) created and propagated as such, viruses, and plasmids and other kinds of vectors, in which the genetic material has been altered in a way that does not occur naturally, by means of cell or gene technology. [46]

However, the problem with a highly specific definition such as this, lies in what it excludes, allowing a GMO that fell outside the definition to escape regulation.[47] The definition of *gene technology,* namely 'any technique for the modification of genes or other genetic material', limits the capacity of this Act to cover new technologies. However, some exceptions to this are either spelt out in the definition (sexual reproduction and homologous recombination) or in the Regulations. According to the Act, *genetically modified organisms* are more precisely defined to include:

> (a) an organism that has been modified by gene technology; or
>
> (b) an organism that has inherited particular traits from an organism (the initial organism), being traits that occurred in the initial organism because of gene technology; or
>
> (c) anything declared by the regulations to be a genetically modified organism, or that belongs to a class of things declared by the regulations to be genetically modified organisms;
>
> but does *not* include:
>
> (d) a human being, if the human being is covered by paragraph (a) only because the human being has undergone somatic cell gene therapy; or

[44] See, eg, Jim Pittard, 'A short history of the regulation of genetically modified organisms (GMO) in Australia' (2010) 122(1) *Transactions of the Royal Society of* Victoria xxxvi-xxxix.
[45] *Gene Technology Act 2000* (Cth) pt 3.
[46] Committee for Reviewing the Gene Technology Bill, *A cautionary tale: Fish don't lay tomatoes*, (2000) 2.68.
[47] Ibid 2.69.

(e) an organism declared by the regulations not to be a genetically modified organism, or that belongs to a class of organisms declared by the regulations not to be genetically modified organisms.

It should be noted that, in accordance with definitions in the Act, a regulator is only permitted to change the definition of *gene technology*, by excluding things or by not including them. As such, it cannot regulate new gene technologies and variations that fall outside this established definition. However, the definition of a GMO does allow for expansion by regulation.

Under the *GT Act,* environmental GMO releases need to be licensed by the OTGR.[48] As part of this licensing, the *GT Act* requires that a risk assessment of the proposed release be conducted,[49] wherein the OTGR needs to seek the advice of many stakeholders: The Commonwealth, the states and territories, the independent Gene Technology Technical Advisory Committee, prescribed Commonwealth authorities, the Federal Environment Minister, and any local council deemed appropriate.[50] This obligation for consultation establishes the *GT Act* as easily the most comprehensive regulatory device for biotechnology, but it is not beyond criticism.

In July 2017 the OGTR commenced a new review of the *GT Act,* a process also conducted in 2006 and 2011.[51] In the response to this review, they raised several critical points and proposed sensible evidence-based changes to the legislation.[52] They proposed an update to the definition of GMOs in the GT Act, but acknowledged that with respect to CRISPR, '*there is a lack of consensus among stakeholders as to how these definitions should be amended'.*[53] The report concluded that more work was needed before appropriate recommendations can be made,[54] which still leaves this technology without a clear regulatory pathway. It is worth highlighting that to ensure national consistency any legislative change would involve a lengthy process. As such, even with this considerable effort, the law is still lagging behind the technology.

A *Australian Legislation Beyond Gene Technology*

Although the *GT Act* is still the gold standard of legislation that might apply to gene and related technologies, it is not, as the *Wolbachia* case illustrates, the only regulatory act. Australia has a number of other statutes that can apply to emerging biotechnologies. Unfortunately, though, they were designed to deal with different issues, and in the case of emerging technologies, are not necessarily applied in a predictable or appropriate manner, due their age and their focus on different needs.

The *Biological Control Act 1984* (Cth) regulates the release of organisms (agent organisms) that are used to control other organisms (target organisms).[55] Rather than being a regulatory instrument the Act primarily exempts releases taken under the Act[56]

[48] *Gene Technology Act 2000* (Cth) at ss 49-54.
[49] Ibid s 50.
[50] Ibid s 50(3).
[51] Office of the Gene Technology Regulator, 'Legislation' <http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/legislation-2) (accessed 17 November 2018).
[52] Department of Health, 'The Third Review of the National Gene Technology Scheme' < http://www.health.gov.au/internet/main/publishing.nsf/Content/011C554B9847D6F0CA258169000FCBBE/$File/Final-Report-Oct2018.pdf> (accessed 17 November 2018).
[53] Ibid 24.
[54] Ibid 25-26.
[55] *Biological Control Act 1984* (Cth) s 3.
[56] Ibid s 35.

from legal proceedings[57] (although it does permit parties that might suffer loss, an opportunity to object to a release). Given Australia's famously mixed results with previous animal control strategies, of which the release of the cane toad in 1935 is the most notorious example, it might have been expected that this type of release would have had a more comprehensive regulatory framework, but this was not the case.

Australia's original biosecurity controls were in the Commonwealth *Quarantine Act 1908* (Cth). Originally it focussed on the containment of specific infectious human diseases, though this was extended to plant and animal diseases, which in practice, became its primary biosecurity concern. Given its focus on infectious diseases the quarantine regime, now regulated by the *Biosecurity Act 2015* (Cth), had no application to *Wolbachia* release or to CRISPR technology.

The *Agricultural and Veterinary Chemicals Act 1994* (Cth) ('*Ag Act*') and *Agricultural and Veterinary Chemicals Code Act 1994* (Cth) ('*AgCode Act*') establish the regulatory framework followed by the APVMA. These Acts have a rather limited regulatory impact on biotechnology. Of particular relevance to their use as the regulator of the *wA aegypti* release, is the absence of required risk assessments. Although the *Wolbachia* release had two risks assessments, there was no legislative requirement to do so. Moreover, the *Ag Act* and the *AgCode Act* do not require the broad multi-party consultation that is required for GMOs regulated under the *GT Act*.

One final issue relates to the interpretation of the *AgCode Act*, which, as the *Wolbachia* case showed, allows anything modifying pest physiology, to be regulated. Arguably, this would allow the APVMA to regulate a very broad range of biotechnologies without oversight of the OTGR.

B *Civil Regulation*

Are there other pathways toward achieving the goal of ensuring that new technologies do not pose a threat to the environment or to human health and safety? One possibility is the use of actions for damages arising out of negligence or common law nuisance. The option of bringing an action for damages is available in most jurisdictions and persons developing or using new technologies must always be alert to the financial consequences of their causing environmental damage or economic harm to others. In this way, the civil system provides a general incentive to ensure that new technologies are as safe as possible, and should be seen as a supplement to existing regulatory arrangements.

However, in relation to GMOs, the only specific example of a civil action to date is the case of *Marsh v Baxter*[58], which relates to GMO cultivation. This case, decided by the Western Australian Court of Appeal,[59] was an action for negligence and nuisance brought by Mr and Mrs Marsh, who were organic farmers, against a neighbour, Baxter, who farmed GMO crops. 'Swathes' (seed-pods) from Baxter's GMO canola were found on the Marsh property and, as a result, the National Association of Sustainable Agriculture (Australia) Ltd (NASAA) and its wholly owned subsidiary NASAA Certified Organic Pty Ltd (NCO) removed certification for areas of the Baxter farm. Both the negligence and nuisance actions failed in the trial at first instance and also on appeal. Interestingly, in the trial at first instance, some of the most scathing assessments were of NASAA/NCO for what was viewed as an unnecessarily harsh

[57] Ibid ss 36-37.
[58] (2015) 49 WAR 169.
[59] (2014) 46 WAR 377.

reaction to the presence of GMO canola on the Marsh property.[60] This view was contested by McLure P[61] and the application of the Standard by NASAA was held to be 'difficult to assess' by the majority.[62] As the action failed, the case has limited influence on GMO regulation at present, but as biological technologies develop and become more prevalent, it is increasingly likely that similar cases will arise and continue to add urgency to the case for regulatory reform.

There are important differences between civil actions and conventional regulation. Regulation is an expression of public law and in the GM field, its primary focus is on the community as a whole and specifically the protection of health and safety from new and potentially damaging technologies. It is less concerned with losses suffered by individuals. Civil actions, on the other hand, are brought to enforce private rights and to seek compensation for damages suffered because of a breach of those rights and are less concerned with the wider social impacts of the harms in question. Consequently, they can be opportunistic and expensive, and they require proof of actual loss or damage, instead of focusing on prevention. Nevertheless, private remedies, in the form of compensation or injunctions that flow from successful civil actions, can be a salutary warning to a whole industry and a powerful message to change current practices lest more cases be brought.

IV How Should We Respond?

A *New Legislation: A Way Forward*

The regulatory regime for new and emerging GM technologies is inadequate and needs to change. It needs flexibility and agility rather than focusing on the 'known knowns' of established science. This problem has long been recognised: nearly 50 years ago, Windeyer J noted that 'Law, march[es] with medicine but in the rear and limping a little'.[63] The law can ill afford to continue to limp. Given the speed and spread of technological development, considerable damage to the environment and public health can be wrought in the blink of an eye by wayward technology.

The current regulatory framework for biological developments in Australia is, as shown above, complex and very uncertain. The current approach relies on cooperation between several Government departments that coordinate numerous pieces of legislation. Moreover, responsive or pre-emptive solutions tend to come in the form of legislative amendments that can add further complexity by modifying existing definitions. Rather than attempting to future-proof laws by deploying either deliberately vague or overly detailed and ever-expanding definitions, Australia needs to ensure that its regulatory responses focus on a desired *outcome*.

Ideally, legislation should offer a system that can be clearly navigated by a proponent of new technologies, and it should ensure that risk is negated or minimized, so as to maintain public confidence in the whole process.

We propose a single consolidated piece of legislation — a *Bio-Regulation Act*, to ensure stricter adherence to the Precautionary Principle ('the Principle') for all biotechnology deployments in Australia. This proposed Act would specifically ask, 'Will the use of the technology in question cause environmental harm?' In addition to mitigating risk, this

[60] Ibid [733]-[739].
[61] *Marsh v Baxter* (2015) 49 WAR 169, [211].
[62] Ibid [733]-[734].
[63] *Mount Isa Mines v Pusey* (1970) 125 CLR 383, 395.

broad regulatory approach might also improve dissemination of information about emerging technologies, increasing public confidence in the regulatory process. It would also provide a streamlined single-department process and a clearly defined regulatory procedure. A broadly based Act would also prevent a proponent of new technology from shopping around to find the regulatory body of 'best fit'.

Although outcome-based biological regulation is a somewhat novel approach, it is far from unprecedented. In public health for example, a harm-based approach to regulation has been suggested and implemented. An outcome-based regime should focus on issues of permanence or likely spread of a technology. For *Wolbachia*-infected mosquitos, where permanence and spread are the objective, the risk assessment process could set a higher bar. It could focus on the likelihood of a particular risk occurring and mediate accordingly. Finally, in accordance with the operation of the Principle, potential benefits can be assessed and weighed against potentially adverse impacts as the primary consideration, rather than focusing on the *type* of technology involved.

There are several existing pieces of legislation that provide examples of how the Principle can be central to the operation of a regulatory Act. The New Zealand *Hazardous Substances and New Organisms Act 1996* (NZ) establishes a regulatory system for GMOs and hazardous chemicals. Section 7 of that Act states that any action taken in accordance with the provisions therein 'shall take into account the need for caution in managing adverse effects where there is scientific and technical uncertainty about those effects'. This ensures that rather than a more procedural approach, the New Zealand Act places a strong focus on the impact and benefits of a particular organism or chemical. However, it still relies on a 'technology' definition when considering outcomes; therefore, similar gaps can arise as they have in Australia. In fact, the New Zealand legislation holds that any organism modified with *in vitro* techniques is a GMO, establishing a considerably wider reach than the Australian GT Act. As *'in vitro* techniques' is not further defined, there is considerable ambiguity in determining if a particular technology falls under the Act. Prima facie, it may be argued that both *Wolbachia* and CRISPR based technologies constitute *in vitro* techniques, but if protocols were modified so as not to employ laboratory-based manipulation, how would this affect regulation?[64]

An additional example of legislation with a specific focus on both the Principle and an outcome-based approach, where the regulatory response is decided by the potential harm to human health associated with the activity, is the *South Australian Public Health Act 2011* (SA) (*'the SA Act'*). With respect to application of this Act, s 6 establishes the scientific consensus aspect of the Principle as 'full scientific certainty'. This threshold, as mentioned previously, can be difficult to obtain within a scientific field, but this Act also introduces several other principles to be considered in its application. Section 7 of the *SA Act* requires that any regulation be proportionate and minimise its impact on business interests. Perhaps of greater relevance to a potential new regulatory Act is that this piece of legislation operates with broad definitions, encompassing any number of health risks, with a clear focus on improving the health of the South Australian population. It also imposes a general duty to avoid causing harm to public health, which

[64] As an interesting aside, s 35(2)(d) of the New Zealand Act mentions inseparable organisms when considering organisms for release. This is highly relevant for organism associations like the *Wolbachia*-infected mosquitos, but it is also important as our understanding of microbiomes (all of the micro-organisms associated with a particular host) and their influence on the biology of their host grows. An 'inseparable organism' clause in any bio-regulation is an important consideration that is often overlooked.

is determined by the outcome, rather than by attempting to regulate an ever-changing range of potential actions that might, or might not cause harm.[65]

If public confidence in the regulatory process is to be maintained, any regulatory system must take account of new or controversial technology, regardless of how small the risk. However, an outcome-based examination of a particular technology application would potentially allow simplified regulation. This can feature a risk assessment process that allows for a tailored regulatory approach determined by the level of potential risk in question. For example, in traditional GMOs the development of a plant species that is herbicide-resistant has a greater risk of spreading beyond the release zone, due to a selective advantage, than a plant GMO that is modified to improve a downstream application, such as a higher vitamin yield. Another example might be the introduction of GMO mosquitoes. A mosquito designed to transform a whole population arguably should have a more substantial regulatory pathway than one in which offspring are engineered to die.

This approach would allow biotechnology to be regulated in a more subjective case-by-case manner. While devising and deploying the new approach might involve a greater amount of work initially, the increased efficiency would be considerable in the long term, as outcomes and their risks would previously have been fully explored and 'lessons learned' applied to future work.

This application of the Principle aims to change the regulation from focusing on how a technology is used, to examining the potential impact and outcomes of technology use and to err on the side of caution. In the examples of CRISPR and *Wolbachia,* the same Government body that was established to determine potential environmental risks would assess the deployment. Although the World Mosquito Program demonstrated an exemplary consultation and risk assessment approach, this process was managed by a government body dedicated primarily to act as the 'Australian Government regulator of agricultural and veterinary chemical products'.[66]

An outcome-based regime could focus on issues of permanence or the likely spread of a technology. The legislation could direct regulation down a pathway based on the type of change and risks that it poses. This could be streamlined by questions like, 'Will the organism persist in the environment? Will non-target organisms be affected? Can it breed with existing populations?' It could require regulators to consider, for example, whether the release of a new species and the collateral environment damage it might cause (and here the cane toad release provides a salutary warning) is a riskier proposition than, for example, a GM mosquito engineered to die. For *Wolbachia*-infected mosquitos, where the permanence and spread are the objective, risk assessment could be altered accordingly. In addition, it could focus on the likelihood of a particular risk occurring and mediate accordingly. Finally, as with operation of the Principle, potential benefits could be factored into the regulation without immediately focusing on the technology involved.

[65] *Public Health Act 2011* (SA) s 56.

[66] Australian Pesticides and Veterinary Medicines Authority, '*APVMA Basics'* 14 August 2015 <https://apvma.gov.au/node/15866> (accessed 16 March 2018).

V Conclusion

Legislative change tends to be an erratic process, characterised by ad hoc responses to specific problems as they arise. Even with bipartisan support it is laborious to work up a fresh approach designed from first principles. This is especially true for biotechnology, given its controversial nature and the need to ensure that the views and interests of the many stakeholders are taken into account. But it is worth pursuing and the development of a single regulatory framework that encompasses all biotechnology products, with the Precautionary Principle as its guiding value, would rectify much of the current confusion. Although the Principle is not without its complexities and shortcomings, it can, as a central focus in a body of legislation, drive a system that is not rigidly bound to definitions. It would allow lifesaving, or at least life-improving technology to develop, while keeping a clear focus on protecting the environment and maintaining public health. Hopefully, future conversations regarding GMO regulation will consider the advantages of an outcome-focused system.

Acknowledgements

Jai Denton was funded by the Okinawa Institute of Science & Technology. The authors would like to thank Dr Steven D Aird for editing the manuscript.

Conflicts of Interest

The authors have no financial, personal, academic, or other conflicts of interest in the subject matter discussed in this manuscript.