Submission to 2017 Review of the National Gene Technology Regulatory Scheme, stage 1

from Professor Jill E. Gready, Australian National University
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(This is an individual submission)

Abstract: My submission is restricted to addressing the Terms of Reference (TORs) of the Background Paper (p.5) but has a major aim within TOR (1) of drawing attention to new, emerging or rediscovered techniques of genetic modification as well as novel ways of practicing them, increasingly by amateurs.

These matters have been neglected in relevant Australian reviews in 2016 (Productivity Commission Inquiry on the Regulation of Australian Agriculture and OGTR Technical Review) but will provide challenges in formulating clear legislation to cover regulation of these techniques, some describable as "grey", and expected new techniques.

Well-informed foresight ("horizon scanning") is necessary to "*accommodate continued technological development*" (TOR (1)), including the examples I draw attention to and undoubtedly others I am not aware of, so as to ensure the revised legislation is not quickly obsolete and meets Australia's needs over *at least* the next 5 years.

I have also addressed the implications of the technical matters I raise under TOR (1) with other comments and suggestions under TORs (2)-(4).

Preamble: My submission:

- Is focussed on technical issues in Terms of Reference (1), but also addresses some relevant parts of TORs (2) - (4) of the TORs (p.5) of the Background Paper for the Review.
- **Discusses technical examples focussed on current and emerging gene technology relevant to land plants** although many of these details will have relevance to other organisms.
- Recapitulates some material I have presented in recent submissions to the Productivity Commission 2016 report on the Regulation of Australian Agriculture[1] and the ongoing Technical Review of the Gene Technology Regulations 2001.[2] I understand from the Background Paper (p. 4) that the Review will take account of these publicly available submissions.
- References material, ideas and recommendations from the recent comprehensive US White House review "Modernizing the Regulatory System for Biotechnology Products". This review process and final Reports,[3,4] and associated Reports from the National

[1] Submission DR212 Jill Gready http://www.pc.gov.au/__data/assets/pdf_file/0008/207449/subdr212-agriculture.pdf
Transcript from Canberra Public Hearing–Jill Gready (pp. 449-464)
http://www.pc.gov.au/inquiries/completed/agriculture/public-hearings/20160822-canberra-agriculture.pdf

[2] Submission Jill Gready
http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/8884A10B0BA5CF42CA2580B10016087D/$File/Gready%20Jill.pdf

[3] National Strategy for Modernizing the Regulatory System for Biotechnology Products: Product of the Emerging Technologies Interagency Policy Coordination Committee's Biotechnology Working Group, September 2016 as updated and released 4 Jan 2017
https://obamawhitehouse.archives.gov/sites/default/files/microsites/ostp/biotech_national_strategy_final.pdf

[4] Modernizing the Regulatory System for Biotechnology Products: Final Version of the 2017 Update to the Coordinated Framework for the Regulation of Biotechnology, released 4 Jan 2017.

Academies of Sciences, Engineering and Medicine (NASEM),[5,6,7] had much greater resources for consultation and garnering independent scientific, ethical and other expert advice than the Australian reviews can command and it makes little sense that it was so little referenced and considered in the recent relevant Australian reviews, especially the OGTR Technical Review.

Scope of Submission: My comments are restricted to addressing the TORs of the Background Paper.

- **I note that these do not explicitly cover related critical issues such as innovation and Australia's competitiveness** considered by the Productivity Commission's Inquiry (and my submission to it), although the introductory sentence to the TORs on p.5. of the Background Paper alludes to innovation (*"The Review aims to improve and strengthen the Scheme's effectiveness whilst ensuring it is appropriately agile and supports innovation. "*). My expectation is that in this whole-of-government Review these other issues will be explicitly considered although the current descriptions of Phases 2 and 3 of the Review give no indication of this.

- Except for the generic developments in points 6. and 7., **my specific gene technology examples for TOR (1), are restricted to applications to land plants** but do not cover gene-drive applications. These are relevant to conventional applications for crop plants for food, forage, turf, materials and fibre, and plants used for other current applications such as in reparation of degraded land, including salinity, metal or man-made chemical toxicity, and as "factories" for vaccines and other high-value extractable products. However, these comments also anticipate possible future novel applications of plants, including novel applications for defence and military, and possibly dual-use civilian, use; some such applications are already under development but have little or no public profile.

- **Recent advances in gene technology are of particular relevance to plants** for several reasons. First, the lower cost, ease of use and shorter timeframe for development of a modified plant using new gene technology is enabling basic and strategic research and plant and agricultural R&D that was hitherto inaccessible to innovative researchers and small companies and startups; globally, plant and agricultural research is poorly (<5%) funded (public, private and philanthropic) compared with biomedical and associated animal research. Secondly, plants are genetically more "plastic" than animals and it is possible to modify plants more easily and to regenerate viable self-reproducing modified plant lines using a wider variety of genetic manipulation techniques, as illustrated by the presented examples.

Comments and Examples on TOR (1):

"1) current developments and techniques, as well as extensions and advancements in gene technology to ensure the Scheme can accommodate continued technological development."

Scope: My focus here is:

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https://www.epa.gov/sites/production/files/2017-01/documents/2017_coordinated_framework_update.pdf

[5] National Academies of Sciences, Engineering, and Medicine. 2016. *Genetically Engineered Crops: Experiences and Prospects.* Washington, DC: The National Academies Press. doi:10.17226/23395.

[6] National Academies of Sciences, Engineering, and Medicine. 2016. *Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values*. Washington, DC: The National Academies Press. doi: 10.17226/23405.

[7] National Academies of Sciences, Engineering, and Medicine. 2017. *Preparing for Future Products of Biotechnology*. Washington, DC: The National Academies Press. doi:10.17226/24605.

- **Presenting and discussing *some* recently reported research findings that illustrate both current and potential future difficulties in defining "GM methods" for the purposes of developing regulations.** Note that several of these findings and observations, especially grafting and their potential "GM" implications, are not new but as they don't require specialised laboratory or other equipment or specialised scientific expertise have not been regulated or if recognized at all have been classed as "legacy" methods. The material presented here shows that this position has changed.
- **Illustrating the emergence of "regulation avoidance methods", particularly for gene-editing applications, designed to escape regulation by circumventing process-based definitions.** It has been pointed out that this has disturbing implications for scientific practice and diverts researcher creativity and effort away from more productive innovations.[8,9] Although hitherto uncommon in science this behaviour has obvious analogies with avoidance in other areas of human activity.
- **Illustrating technology "grey areas" that will increasingly confound regulation** and may require revision to procedures and standards used to assess the safety of their products.
- Noting some recent reports which confound what genetic changes are possible by "natural" mechanisms, e.g. Kyndt *et al.* (2015).[10]
- Where possible both the original scientific papers or reviews as well as short commentaries more accessible to non-scientific readers are cited, as well as reference to the two NASEM Reports[11] as relevant.

This section recapitulates some material presented in my OGTR Technical Review submission[12] – but in a different format –, and adds further examples.

Note that the main classes and regulatory issues of gene-editing methods in general, particularly, CRISPR-Cas9 and its so-for reported variants, are not covered here. This topic has been well rehearsed elsewhere. Rather my treatment of other techniques and resultant genetic changes may serve to highlight the futility of reactive attempts to dissect the known types of possible changes from current gene-editing methods, i.e. process-based definitions as in the OGTR Technical Review's options, and move the emphasis of the legislative review to proactive considerations focussed on safety (and, hopefully, innovation) implications of genetic modification methods in totality.

It is also pertinent to point out that major drivers in the innovation sector for novel developments in CRISPR gene editing, including Cas9 orthologues, have arisen from patent-ownership uncertainty playing out in the US courts between the Broad Institute (issued patent) and the University of California (patent pending).[13] Although research-only applications globally have been accommodated as necessary by licensing from (mainly) the Broad Institute, the recent analysis of Gray and Spruill[14] suggests that the dynamic US biotech start-up sector is actively developing its own methods. Such methods may differ

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8 Nick Staropoli, "CRISPR may redefine what it means to be GMO", 23/10/15. http://acsh.org/news/2015/10/23/crispr-may-redefine-what-it-means-to-be-gmo

9 Noah Feldman, "This is no way to regulate GMOs", Bloomberg View 21/10/15. https://www.bloomberg.com/view/articles/2015-10-21/this-is-no-way-to-regulate-genetic-modification

10 Kyndt et al. (2015), The genome of cultivated sweet potato contains Agrobacterium T-DNAs with expressed genes: An example of a naturally transgenic food crop", PNAS 112, 5844–5849.

11 NASEM Reports, footnotes 5 and 7.

12 J. Gready *ibid.* footnote 2.

13 Gray and Spruill (2017), CRISPR-Cas9 claim sets and the potential to stifle innovation, Nature Biotech. 35, 630-633. doi:10.1038/nbt.3913

14 *ibid.*

significantly in mechanism (i.e. process/mode of action), which may have implications for regulatory definitions.

1. CRISPR-Cas9 application that circumvents regulation. This method was first reported by Woo *et al.* in 2015[15] and attracted wide coverage in scientific commentaries, e.g.[16],[17] . The method used a pre-assembled Cas9 and gRNA complex (RNP – ribonucleoprotein) which is introduced into plant protoplasts using solvents, rather than introducing a plasmid encoding these components that might insert recombinant DNA into the nuclear genome. The topic has recently been reviewed.[18]

Comment. In this case a "GMO" is produced but the means by which the change has been made is undetectable; neither Cas9 DNA nor gRNA is incorporated into the nuclear DNA nor is the Cas9 DNA even transiently present in the cell. However, as for the standard CRISPR-Cas9 method, unwanted, off-target gene-editing mutations are still possible, so the safety of the RNP-produced GMO may be similar although there is a report that off-target mutations in wheat cells are less.[19] This topic is not covered in the NASEM Reports.

2. Adventitious and targeted modification of epigenome regulating gene expression. Epigenetic changes can occur at two main levels: the DNA level by DNA methylation of cytosine residues; or at the histone level by affecting accessibility of the DNA to transcriptional activation. This topic is not covered by the NASEM reports except for a comment in the 2016 NASEM report (p.242). "*Construction of GE plants commonly relies on in vitro plant tissue culture that can result in unintended, somaclonally induced genetic change*."

One example is identification by Sally Mackenzie and co-workers of high-yielding offspring of a transgenic sorghum grass plant that had lost the engineered gene. It was suspected that the transgene triggered an epigenetic change, i.e. altered gene expression in the plant,[20] leading to the improved trait. USDA deemed the sorghum variety as not needing regulation; the same decision was made for non-transgenic offspring of other crops with improved features (faster breeding).[21] The mechanisms and stability of these changes over generations are highly variable; examples of published papers from Sally Mackenzie's group detailing molecular modes of action are given on the web pages of Epicorp Technologies, the start-up company she founded to develop commercial applications.[22]

Comment. The reported case of apparent, unintended, modification of the epigenome concurrent with targeted genetic modification and, thus, modification of expression of non-targeted gene(s) and properties of the product plants raises the issue of whether such effects are also common adjuncts to characterized gene changes from legacy methods such as radiation and chemical mutagenesis. Changes to properties might include increase in expression of toxic compounds or reduction in expression of compounds of, for example, nutritional value. The long-term persistence (stability) of epigenome modifications is

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15 Woo et al. (2105), DNA-free genome editing in plants with preassembled CRISPR-Cas9 ribonucleoproteins, Nature Biotechnol. 33, 1162–1164. doi.org/10.1038/nbt.3389

16 N. Staropoli *ibid.*; N. Feldman *ibid.*

17 D. Cyranoski (2015), CRISPR tweak may help gene-edited crops bypass biosafety regulation, Nature News doi:10.1038/nature. 18590

18 Kanchiswamy (2016), DNA-free genome editing methods for targeted crop improvement, Plant Cell Reports, 35, 1469–1474. doi 10.1007/s00299-016-1982-2

19 Liang *et al.* (2017), Efficient DNA-free genome editing of bread wheat using CRISPR/Cas9 ribonucleoprotein complexes, Nature Commun., 8:4261. doi: 10.1038/ncomms14261

20 Heidi Ledford (2013), US regulation misses some GM crops, Nature News 500, 389–390. doi:10.1038/500389a

21 Ledford *ibid.*

22 Epicorp Technologies Inc. http://www.epicrop.com/relevant-publications.html

variable; the sorghum example suggests it may decay over generations. For the purposes of regulation, this class of unintended changes has unusual safety implications, taking into account that unlike unintended mutations to the DNA, epigenetic changes may vary over generations (as the sorghum example seems to show).

3. Transgenic RNAi (interference) and spray-on or oral RNA to achieve RNAi down-regulation of protein expression. RNAi is an established technique for down regulating gene expression at the level of interfering with mRNA translation into protein. Nuclear genetic modification of plants to effect RNAi has a long history, including recent commercial release of varieties of Simplot Innate™ potatoes (multiple features) and Okanagan Specialty Fruits Arctic® non-browning apples. These products have been deemed not needing to be regulated by USDA under their "relaxed" conditions for within-species transgenes, and have also been deemed safe for growth (potatoes) and consumption by the US EPA and FDA, as well as in Canada (recently for potatoes).[23] It is unclear how the OGTR would assess such RNAi-based GM varieties for growth in Australia although (selected) processed Innate™ potato varieties were cleared for consumption by FSANZ in 2016.

An alternative RNAi technique under development that does not require integration of DNA into nuclear genomes is supply of dsRNA (double stranded) for pest control to plants (spray on), being investigated by several large agbiotechs including Monsanto[24] and academic researchers, [25] or, recently, directly (orally) to insects.[26,27] University of Queensland researchers have recently published a refined spray-on plant method in an application for virus protection in which dsRNA is loaded onto clay nanosheets to slow RNA degradation and wash-off and for slow release.[28,29]

Comment. These topical-application methods have become feasible due to the plummeting cost of synthetic RNA, thus enabling the practical possibility of achieving RNAi in the plant or insect cell without permanent incorporation of transgenic DNA. Although this method may have drivers for regulatory avoidance, as for RNPs in 1., its active component (just dsRNA) differs significantly from 1. and the mode of administration is similar to conventional agents of pest control. However, as the dsRNA is taken up (and processed) by cells there is a theoretical risk of it being converted to DNA by reverse transcriptases and permanently incorporated in the nuclear genome; there appears to be no literature on this.

4. Genetic changes by "natural" mechanisms. Of particular relevance to issues of definition and regulation of plant GMOs is the recent finding that one or more T-DNA sequences of the plant pathogen *Agrobacterium* ssp. was found in all 291 tested accessions of cultivated sweet potato suggesting that an *Agrobacterium* infection occurred in evolutionary times.[30] Furthermore, the fact that these T-DNA sequences were shown to be

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23 Keith Ridler, Canada OKs Idaho company's genetically engineered potatoes, Star Tribune 3/8/17. http://www.startribune.com/canada-oks-idaho-company-s-genetically-engineered-potatoes/438367613/

24 Anthony Regalado, The next great GMO debate, MIT Review 11/8/15. https://www.technologyreview.com/s/540136/the-next-great-gmo-debate/

25 San Miguel and Scott (2016), The next generation of insecticides: dsRNA is stable as a foliar-applied insecticide. Pest Management Science 72, 801–809. doi: 10.1002/ps.4056

26 Killiny *et al.* (2014), Double-stranded RNA uptake through topical application, mediates silencing of five CYP4 genes and suppresses insecticide resistance in *Diaphorina citri*, PLoS ONE 9: e110536. doi.org/10.1371/journal.pone.0110536

27 Ghosh *et al.* (2017), Double strand RNA delivery system for plant-sap-feeding insects, PLoS ONE 12: e017186. doi:10.1371/journal.pone.0171861

28 Jamie Condliffe,_Spray-on RNA protects plants from viruses for weeks, MIT Review 9/1/17. https://www.technologyreview.com/s/603330/spray-on-rna-protects-plants-from-viruses-for-weeks/

29 Mitter *et al.* (2017), Clay nanosheets for topical delivery of RNAi for sustained protection against plant viruses, Nature Plants 3:16207. doi: 10.1038/nplants.2016.207

30 Kyndt et al. (2015), The genome of cultivated sweet potato contains Agrobacterium T-DNAs with expressed genes: An example of a naturally transgenic food crop", PNAS 112, 5844–5849.

active in sweet potato – but only rarely in wild species – suggests they provide advantages that were selected by farmers in traditional breeding during domestication. As adaptations of this naturally occurring mechanism using *Agrobacterium rhizogenes* and *A. tumefaciens* is the method used for incorporating functional genes in most of the GM crops grown globally today, the authors comment that "*given that this crop has been eaten for millennia, (this finding) may change the paradigm governing the "unnatural" status of transgenic crops.*"

While the example above is of transfer of a bacterial gene to a plant, a recent Australian study[31,32] is the first example of a horizontal gene transfer of a fungal gene to plants, in this case of a β-1,6-glucanase gene from an ancestral fungal endophyte to ryegrass.

Comment. The current legislation excludes genetic changes that can occur by natural mechanisms. However, understanding of the scope of genetic changes that can occur naturally has developed greatly since the 2000 GT Act and has, particularly, been expanded by results exploiting the power of high throughput genome analyses (NGS; next generation sequencing). The above examples of instances of horizontal gene transfer - exchange of genes between different species, i.e. transgenes – almost certainly represent only the tip of the iceberg. Although the above examples are ancient in origin it is arguable that the incidence of such events with advantage to humans being "fixed" in crops by plant domestication over the last ~10,000 years and by more recent intensive breeding and selection methods has increased greatly.

5. Transfer of DNA and whole organelles, chromosome doubling and epigenome editing across plant grafts. This topic is not covered in either of the NASEM Reports although the 2016 Report notes (p. 242) "*It is well known that if a plant is grafted, RNAs and proteins can move between the rootstock and the scion; thus, in a grafted plant with a transgenic rootstock or a transgenic scion there is the potential for GE-derived molecules to be transported to non-GE portions of the plant.*"[33]

In ground-breaking work in 2009 and 2012, Bock and co-workers transferred whole chloroplasts and their genomes or fragments of chloroplast DNA across graft junctions of different plant species.[34,35,36] In a further study in 2014[37] they showed that entire nuclear genomes could be transferred between plant cells at graft junctions creating a new allopolyploid species from the chromosome doubling. The organelle-transfer trifecta was completed by the study of Maliga and co-workers in 2016[38,39] showing plant cells can also exchange mitochondria. Further exploring the potential of transferring genetic changes

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31 Agriculture Victoria media release "Trail of 13 million year old gene transfer uncovered". http://agriculture.vic.gov.au/about-us/media-releases/trail-of-13-million-year-old-gene-transfer-uncovered

32 Shinozuka *et al.* (2017), Horizontal transfer of a β-1,6-glucanase gene from an ancestral species of fungal endophyte to a cool-season grass host, Scientific Reports 7: 9024. doi:10.1038/s41598-017-07886-2

33 Haroldsen *et al.* (2012), Mobility of transgenic nucleic acids and proteins within grafted rootstocks for agricultural improvement, Frontiers in Plant Science 3:39. doi: 10.3389/fpls.2012.00039

34 Michael LePage, Farmers may have been accidentally making GMOs for millennia, New Scientist 7/3/16. https://www.newscientist.com/article/2079813-farmers-may-have-been-accidentally-making-gmos-for-millennia/

35 Stegemann and Bock (2009), Exchange of genetic material between cells in plant tissue grafts, Science 349, 649-651. doi:10.1126/science.1170397

36 Stegemann *et al.* (2012), Horizontal transfer of chloroplast genomes between plant species, PNAS 109, 2434-2438. doi: 10.1073/pnas.1114076109

37 Fuentes *et al.* (2014), Horizontal genome transfer as an asexual path to the formation of new species, Nature 511, 232-235. doi:10.1038/nature13291

38 Michael LePage *ibid.*

39 Gurdon *et al.* (2016), Cell-to-cell movement of mitochondria in plants, PNAS 113, 3395-3400. doi:10.1073/pnas.1518644113

across plant grafts, Kasai *et al.*[40] have recently shown editing of the epigenome of potato across a graft using transgenic tobacco as siRNA donor to induce heritable transcriptional gene silencing via RNA-directed DNA methylation.

In the case of chloroplast and mitochondria, these studies experimentally manipulated the rare natural phenomenon of "organelle capture" and characterized the optimum conditions to facilitate this horizontal genome transfer between plant species.

In contrast to the nuclear and plastid genomes, there are no methods for genetic engineering of the mitochondrial genome in plants. Thus, the possibility for whole mitochondrial genome transfer offers a means for introducing mitochondrial trait genes into plants, for example for male sterility an attractive trait in breeding of hybrids.

Comment. Plant grafting, both human-aided and from widespread natural plant-plant interaction, particularly of roots,[41] with co-mingling of plant tissue from different species provides favourable conditions for unintended genetic engineering with exchanges of DNA and RNA and, in the cited examples, whole organelles and their genomes or fragments of them. These provide support for the contention that "*We have been accidentally genetically engineering plants – and eating GMOs – for millennia*."[42] Grafting has a long human history with experience gained from trial and observation. Although the theoretical concept of "graft-hybridization" first originated from Darwin it became linked to Lysenko[43] and the concept is still dogged by unresolved controversy.[44]

The new work of the Bock, Maliga and Kasai groups using mainstream plant-biology protocols, characterization and explanations provides the impetus and starting methodologies to explore the opportunities of introducing new genes by grafting for crop improvement. For reasons noted above, use of the refined grafting techniques may be particularly attractive in the future for plant breeders to introduce mitochondrial-genome encoded traits. From the regulatory viewpoint an interesting aspect is how to treat a "scion" that might already have undergone a genetic modification and, under current regulations, would be classified as "GM".

6. Digital to Biological Converter for on-demand production of biologics.

Boles *et al.* [45] have recently reported "*development of a digital-to-biological converter for fully automated, versatile and demand-based production of functional biologics starting from DNA sequence information. Specifically, DNA templates, RNA molecules, proteins and viral particles were produced in an automated fashion from digitally transmitted DNA sequences without human intervention*". The authors are located at Synthetic Genomics Inc.[46] founded by Craig Ventor, one of the co-authors. The technologies reported are not new *("The device is actually a hodgepodge of smaller devices that contribute to the whole"*[47]) but represent an innovative conceptual and practical integration of component technologies for product delivery that the authors describe as "distributed manufacturing". Local synthesis at point-of-need has advantages in rapid response, reduced transport costs, easily scalable

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40 Kasai *et al.* (2016), Epigenome editing of potato by grafting using transgenic tobacco as siRNA donor, PLoS ONE 11:e0161729. doi:10.1371/journal.pone.0161729

41 Goldschmidt (2014), Plant grafting: new mechanisms, evolutionary implications, Frontiers Plant Science 5:727. doi.org/10.3389/fpls.2014.00727

42 Michael LePage *ibid.*

43 Liu *et al.* (2010), New insights into plant graft hybridization, Heredity 104, 1-2. doi:10.1038/hdy.2009.115

44 Goldschmidt *ibid.*

45 Boles *et al.* (2017), Digital-to-biological converter for on-demand production of biologics, Nature Biotech. 35, 672-675. doi: 10.1038/nbt.3859

46 https://www.syntheticgenomics.com/digital-to-biological-converter-for-on-demand-production-of-biologics-developed-by-synthetic-genomics-inc/

47 Bob Yirka, Synthetic Genomics unveils digital-to-biological converter using digital DNA to print biologics, 7/8/17. https://phys.org/news/2017-08-synthetic-genomics-unveils-digital-to-biological-digital.html

manufacture and viability of biologistic products under non-ideal storage conditions. The inventors are moving to doing the same with a so-called minimal cell.[48]

Comment. Although this report is very recent and extrapolation to what might be achievable in the future may still be in the realms of scifi, it is noted as an example of the directions that scientific imagination is moving to exploit the huge opportunities opened up by modern genetic technology and, in this case, coupling it to advances in automation and computation "*for remotely printing material for creating living organisms*". Although beneficial uses could be as a "biological teleporter" to transmit DNA, viruses and vaccines by email to produce rapidly synthesized weapons against pandemics it could also "produce a virus at a given location that could be released as a biological weapon". [49,50] How could revised Australian legislation and an OGTR-like regulatory enforcement authority deal with such technology?

7. Biohacking, DIY Genetic Engineering ("DIYbio"), Community Science. This is a new, non-mainstream, topic not documented in the formal peer-reviewed literature; hence, the presentation here cites informal or commentary sources. The NASEM 2017 report has given it substantial attention as an emerging topic they expect will become increasingly important in the GM-regulatory space; some of its comments are reproduced here.

In addition to an explosion of activity in the institutional biological community, the increased ease, low cost and ability to undertake experiments in genetic engineering without expensive equipment or other infrastructure, especially with the advent of CRISPR-Cas9, has led to a large community of amateur scientists – or highly trained independent scientists working outside conventional laboratories – to undertake such experiments, mostly in the US. As summarised by the NASEM 2017 report in "Box 2-2 New Actors and Market Niches" (p. 32) and text on pp. 33-34. "*In 2013, a survey of the DIYbio community,*[51] *estimated to be between 3,000 and 4,000 people worldwide, found that the majority of the 359 respondents (82%) were in the United States*" with 10% from Europe, 4% from Canada, 1% from China and 2% elsewhere. "*The community respondents were mostly adult males (75%), and few of them (less than 10%) work solitarily, that is, outside of community laboratory spaces where technical expertise and equipment are concentrated*." Clearly these data are now outdated. The current level and distribution of activity is unclear; the author has found no report for Australia. A recent report indicates a hostile attitude to the movement from German authorities.[52]

Mostly such activity is undertaken by science enthusiasts as a hobby – not for commercial gain – and the opportunity to interact with like-minded individuals in clubs or online blogs. This development and possible problems have been recorded in several commentaries in the international scientific press, mostly from ~2015.[53] It has been suggested by ex-NASA scientist Josiah Zayner, who left NASA to found ODIN selling the do-it-yourself CRISPR kit online,[54] that this movement democratizes science and to confine it to scientific institutions

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48 Bob Yirka *ibid.*

49 Bob Yirka *ibid.*

50 Tom Whipple, 'Machine enables vaccines, viruses and DNA to be digitally conveyed",The Australian & London Times, 6/9/17 http://www.theaustralian.com.au/higher-education/machine-enables-vaccines-viruses-and-dna-to-be-digitally-conveyed/news-story/d00d63af852d4900d686545c1cc20a9e

51 Daniel Grushkin *et al.* (2014), Seven Myths & Realities about Do-It-Yourself Biology. Washington, DC: Woodrow Wilson Center for International Scholars. https://www.wilsoncenter.org/sites/default/files/7_myths_final.pdf

52 Kristen Brown, Germany is threatening biohackers with prison, Gizmodo 11/2/17. https://www.gizmodo.com.au/2017/02/germany-is-threatening-biohackers-with-prison/

53 Heidi Ledford (2015), Biohackers gear up for genome editing, Nature News, 524, 398-399. Todd Kuiken (2016), Learn from DIY biologists, Nature News 531, 167-168.

54 ODIN, Gene Engineering Kits. http://www.the-odin.com/gene-engineering-kits/

would stonewall scientific progress.[55] Indeed, it has been suggested that this sector could be an incubator of significant innovation. The interest has generated a substantial market for low-cost kits, including from ODIN.[56]

In the US, the developments have been open and not officially regulated but, with assistance from professional scientists, responsible codes of practice have been widely discussed and evolved.[57] This includes community biology labs receiving advice and oversight from professional scientists, that may be sufficient for them to be accredited by regulatory authorities if required, or undertaking experiments at formally licensed premises in universities and other institutions. NASEM 2017, p. 32 states "*Finally, it is important to note that regulation is not the only means of governance and oversight. Codes of conduct, such as those developed in the DIYbio community (Kuiken, 2016), can also play an important role.*" Opinions of four experts from different perspectives are in Skerrett[58] including by Dr Henk Greely, Director of the Center for Law and the Biosciences at Standford University who comments "*Finding and regulating do-it-yourself users is much harder and, under our current system, impossible. We urgently need to find a balanced regulatory approach that allows responsible do-it-yourself use while protecting health and the environment. There is no time to lose!* "

Nonetheless, issues of possible use of the technology in bio-terrorism and other hostile applications have been raised and it is not clear whether clandestine activity for malevolent purposes exists or may develop. Worries have been expressed about "*inadvertent side effects of well-intentioned uses*"[59] but this concern also applies for research using these techniques in universities and other institutions. Box 3-2 in the NASEM 2017 Report (p.72) states "*For example, the safety and biosecurity of do-it-yourself biology (DIYbio) products may be determined by the skill or the intent of the user." "The Federal Bureau of Investigation's Biological Countermeasures Unit is active in identifying and responding to threats related to DIYbio with a focus on the potential for bioterrorism (You, 2016). These programs, however, are neither focused nor scaled to address the risks of diverse biotechnology consumer products expected in coming years, and existing consumer safety regulators like FDA, CPSC, and EPA lack statutory tools to take on this responsibility*." The US FBI has a unit with a named Special Agent, Edward You, who circulates widely within the US DIYbio community attending meetings etc.[60,61] This seems to represent a "friendly policing and intelligence-gathering" approach in contrast to the German approach[62] which is likely to merely drive questionable activities or unwitting poor practices underground.

Comments. As noted, the author is not aware of the extent of any DIY-bio activity in Australia or regulatory discussions. It is likely that the Australian police and security agencies are monitoring any such activities as part of wider surveillance of potential criminal activity or bio-terrorism threats. Henk Greely's comments above demonstrate the regulatory challenges and the urgency to deal with them.

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55 Dyllan Furness,_What happens when anyone can edit genes at home? Digital Trends 15/8/16. https://www.digitaltrends.com/cool-tech/the-odin-diy-crispr-kit/

56 ODIN *ibid.*

57 Todd Kuiken (2016), Our Collective Biology: Enabling Public Science to Build an Ecosystem of Makers in Biology. Presentation to the NASEM Committee on Future Biotechnology Products and Opportunities to Enhance Capabilities of the Biotechnology Regulatory System, June 1, Washington, DC.

58 Patrick Skerrett, Is do-it-yourself CRISPR as scary as it sounds? STAT News 14/3/16. https://www.statnews.com/2016/03/14/crispr-do-it-yourself/

59 Furness (2016) *ibid.*

60 Anthony Regalado, On patrol with America's top bioterror cop, MIT Tech Review 20/10/16. https://www.technologyreview.com/s/602643/on-patrol-with-americas-top-bioterror-cop/

61 Alexandra Ossola, Why is the FBI reaching out to student bioengineers, Motherboard 28/11/16. https://motherboard.vice.com/en_us/article/yp3knm/igem-fbi

62 Kristen Brown *ibid.*

Comments on TOR (2)

"2) existing and potential mechanisms to facilitate an agile and effective Scheme which ensures continued protection of health and safety of people and the environment."

My comments on TOR (2) also include relevant recommendations from the US White House review and their final Reports.[63,64]

(i) **The operation and effectiveness of existing structures to manage and "facilitate an agile" Scheme as shown on the organizational chart (Figure 1.) on p. 9 of the Background Paper are unclear.** Specifically:

- Figure 1 shows a link between GTTAC (Gene Technology Technical Advisory Committee) and GTECCC (Gene Technology Ethics and Community Consultative Committee) and the LTFGT but it is not clear if and how these advisory committees are used by the LTFGT, particularly between 5-yearly Reviews.
- Figure 1 also shows a link between GTTAC and GTECC and GTR/OGTR. However, it is the author's understanding that the advisory committees are used primarily in advising OGTR on individual applications for GMOs release under DNIR and DIR dealings and other specific matters in administering the 2000 GT Act.
- As advisory committees, the GTTAC and GTECC presumably do not have proactive roles. There does not appear to be any ongoing formal mechanism for relevant technical or ethical developments for GMOs to be brought to the attention of LTFGT between 5-yearly Reviews except indirectly by press or other coverage that penetrates the intergovernmental radar.
- The role and history of activity of the Gene Technology Standing Committee linked to LTFGT in Figure 1 is unclear.

(ii) **Following from (i), there does not appear to be any publicly advertised mechanism (e.g. through the LTFGT website[65]) for researchers, members of the community or other interested parties to contact the LGFGT between Reviews** to alert it to relevant developments. Figure 1 does not show any ongoing mechanism for *input* from the public or regulated community to either the GTR/OGTR or LGFGT on new developments or general comments on perceived problems with the current regulations.

The author suggests that a new independent committee (for technical developments administered, for example, by the Australian scientific academies, ATSE and AAS) be constituted under LGFGT (or its Standing Committee) to receive ongoing input from the public, regulated community or other interested parties and proactively to advise the LGFGT. This could include early information on new developments (as exemplified under TOR (1)), including concerns on safety, adequacy of existing legislation or impediments to innovation. Ideally the public portal to this new committee would be *via* an easily accessible link on the LTFGT website.

(iii) **The following cites *selected* recommendations from the US White House Review. Because of the different agency structure regulating GMOs in the US** (i.e. mainly USDA, FDA and EPA) compared with Australia (mainly OGTR, APVMA (Australian Pesticides and Veterinary Medicines Authority) and FSANZ (Food Standards Australia New Zealand) **these recommendations will not be directly translatable to the Australian Scheme but the objectives will be clear**. These recommendations also

63 Footnote 3.

64 Footnote 4.

65 http://www.health.gov.au/internet/main/publishing.nsf/Content/gene-gtmc.htm

don't partition cleanly among the Review's TORs! The US National Strategy for Modernizing the Regulatory System for Biotechnology Products[66] has divided their recommendations into several themes:

- ***Increasing Transparency*** *(p. 8, p. 9)*
- *Coordinate the development of tools and mechanisms for assisting small businesses developing biotechnology products to navigate the regulatory system.*
- *Engage with the public to discuss how the Federal Government uses a risk-based, scientifically sound approach to regulating the products of biotechnology, and clearly communicating to the public which types of products are regulated, which types of products are not regulated, and why.*
- *Product developers who are uncertain regarding the relevant regulatory requirements, particularly small businesses, are encouraged to contact the agencies early in the product development process to obtain information from the agencies on potential safety and regulatory requirements that may be associated with their intended products.*
- ***Increasing Predictability and Efficiency*** *(pp. 8-9, pp. 13-14)*
- *Develop a plan for periodic, formal horizon-scanning assessments of new biotechnology products to ensure that regulatory agencies are prepared for future products well before they reach the regulatory system.*
- *Identify changes to authorities, regulations, and policies that could improve agencies' abilities to assess expeditiously the potential impacts and risks arising from future products of biotechnology and to ensure the transparency, predictability, and efficiency of regulatory oversight for such products.*
- *EPA, FDA, and USDA rely on horizon scanning techniques to detect early signs of important developments in biotechnology. The three regulatory agencies maintain staffs of experts, trained in a variety of scientific disciplines, who keep up with knowledge in the various sciences important to understanding and evaluating biotechnology products. These agencies learn about new technologies and new products in development through a combination of activities……On occasion, EPA, FDA, and USDA have also sought advice on cutting-edge issues from groups of independent technical experts including, for example, NASEM.*
- *USDA's encouragement of product development through its Am I Regulated process and its permit and notification system. USDA developed the Am I Regulated process by which developers, including small private- and public-sector entities, will ask whether a proposed product would be subject to USDA regulations prior to requesting an authorization for a regulated activity. This allows USDA to have some early notification of products that may be about to enter the regulatory system and provides an additional window into emerging technologies.*

These citations indicate a US system that is proactive, forward looking, encourages innovation and assists small businesses, and has both its own high-level up-to-date in-house expertise and established mechanisms for seeking further expert advice. The current Australian Scheme does not have these characteristics.

As an example of USDA's proactive approach, it has been reported[67] that the developer of the anti-browning mushroom produced using CRISPR-Cas9 was directly contacted by USDA regulators who had learnt of the development on the "grapevine" and invited him to present his findings to them after which he "*followed up with an official letter of inquiry to the agency*".

(iii) **Criminal and terrorism oversight.** My comments are covered in general under

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[66] Footnote 3.

[67] Emily Waltz (2016), Gene-edited CRISPR mushroom escapes US regulation, Nature News 532, 293. doi:10.1038/nature.2016.19754

point 7. of TOR (1). This oversight would need to deal with both local activity as well as with illegal import of products derived from international activity.

Comments on TOR (3):

"3) the appropriate legislative arrangements to meet the needs of the Scheme now and into the future, including the Gene Technology Agreement. "

I focus my comments here on the purpose of the legislation which, as captured in TOR (2), is still "*protection of health and safety of people and the environment*".

- Under TOR (2) I have offered comments on how new developments and perceived problems with the legislative arrangements could be more effectively brought to the attention of the intergovernmental authorities with responsibility to monitor the working of the legislative arrangements.
- Given the increasing complexity and rapidity of new biotechnological developments with potential GMO implications, as exemplified under TOR (1), there are clearly major challenges in drafting appropriate and clear revised regulatory legislation that can encompass now-current and so-far-anticipated technologies. Moving the primary definition of GMO from process-based to product-based will greatly simplify framing the regulations and allow the focus to be, rightly, on the primary purpose of the 2000 GT Act (i.e. health and safety), and also, hopefully, provide scope for encouraging innovation. Ensuring standards of product safety by assessment centred on product-based definitions provides a path to the desired, achievable target whereas convoluted theoretical process-based definitions do not.

  To emphasize this point I quote from the Background Paper (p.4) that "*(This) is important to provide clarity about whether organisms developed using a range of new technologies are subject to regulation as genetically modified organisms, and to ensure that new technologies are regulated in a manner commensurate with the risks they pose."*
- However, beyond the revised legislative regulations themselves their administration through the GTR/OGTR (as shown in Figure 1 of the Background Paper) will increasingly require significant technical expertise in interpreting them in particular cases, as shown by numerous decisions by USDA in recent years. The relevant recommendations from the US Review cited under TOR (2) highlight that high-level up-to-date in-house expertise and established mechanisms for seeking further expert advice are necessary and that the US has plans to further strengthen them (covered also in TOR (4) under the US Review's "Supporting the Science that Underpins the Regulatory System" theme). As noted under TOR (2), the current Australian Scheme does not have this expertise. In the author's opinion the OGTR in general lacks the required level of expertise to interpret the regulations in the changing GMO landscape. It is not known to the author whether the GTTAC is adequate for advising the GTR/OGTR on interpretation of the regulations in particular cases.
- The 2016 NASEM Report (p. xviii) notes that "*National regulatory processes for GE crops vary greatly because they mirror the broader social, political, legal, and cultural differences among countries*". One can add historical development to this list. As noted under TOR (2), the major US agencies (USDA, FDA, EPA) administering the US regulations have quite different mandates that do not map well to the main Australian agencies (OGTR, APVMA. FSANZ). Thus, translating the US findings and recommendations to the Australian Scheme – or evaluating their value for the Australian context - may not be transparent, but would be easiest for plants and agricultural crops. However, as noted in the Preamble (dot point 4), it makes sense for the LGFGT Review to capitalise as much as possible on all the new material assembled by the US White House Review and the 2016

and 2017 NASEM Reports. **This might be helped by inviting members of the US Review or NASEM Report committees to assist on the LGFGT Review**.

- It is unclear how the LGFGT Review will take into account other GMO issues that were considered by the Productivity Commission Inquiry[68] to promote Australian innovation and competitiveness by timely uptake of new genetic technology, although, as already noted, "innovation" does get a mention in the prefatory paragraph to the TORs on p.5 of the Background Paper. This appears to be a case of government policy and legislation "falling between the stools". TOR (2) addresses an "*agile and effective Scheme which ensures continued protection of health and safety of people and the environment*" but this agility and effectiveness does not explicitly extend to other desired outcomes of exploiting the opportunities of new genetic technology in advancing the well being of Australian citizens, both socioeconomically and in development of new beneficial products, some of which may have specific value in the Australian context. Failure to deal with these aspects of genetic technology developments will almost certainly jeopardise Australia's competitiveness. It is noteworthy that the Indian government has already recognized this in a recent Policy Commission report.[69]
- The author also questions whether the Ministry of Health is the appropriate Department to "house" the GTR/OGTR, a placement with historical origins. It is arguable that this placement is not ideal either for agriculture or the environment.

Comments on TOR (4)

"4) funding arrangements to ensure sustainable funding levels and mechanisms are aligned with the level and depth of activity to support the Scheme."

My comments here pick up on relevant recommendations from the US White House Review and the 2016 NASEM Report and then follow up with some suggestions specific to Australia that might meet these identified needs. The dot points under the US Review themes of *Increasing Transparency* and *Increasing Predictability and Efficiency* cited under TOR (2) all point to areas where increased funding to support new or extended support mechanisms are required in the US regulatory system. In summary these are:

- Co-ordination of tools and mechanisms to assist small businesses in navigating the regulatory system. Specific suggestions for Australia are offered below.
- Engagement with the public to discuss the risk-based, scientifically sound approach to regulating products of biotechnology. Effective communication with the public to re-assure them of the safety of GM products and overcome entrenched opposition is a vexed question. Many proposals have been advanced, including as part of the US Review, in the 2016 NASEM Report and the Productivity Commission Inquiry. There is general recognition that this issue is a major impediment to uptake of biotechnology products and the opposition, i.e. public opinion, has impact on parliamentary processes. An appropriately funded initiative – or set of initiatives - needs to be established but no specific suggestions are offered here.
- Mechanisms to provide early advice to product developers, particularly small businesses, to provide them with more certainty on potential safety and regulatory requirements that may be associated with their intended products. This is necessary to assess market viability and costs-to-market and for obtaining finance. Australia has no such mechanisms.

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68 Productivity Commission 2016, *Regulation of Australian Agriculture,* Report no. 79, Canberra.

69 Nidhi Verma et al., India government think-tank backs local GM crop policy: document, Reuters 26/4/17. http://www.reuters.com/article/us-india-gmo-idUSKBN17S1SW

- Proactive horizon-scanning assessments of new biotechnology products well before they reach the regulatory system. I have already noted that the Australian system lacks this foresight capability.
- Capacity "*to assess expeditiously the potential impacts and risks arising from future products of biotechnology*" and identify required changes to authorities, regulations and policies. Australia lacks the foresight capacity to assess risk in the Australian context.
- In another tool, encouragement of product development by the USDA's "Am I Regulated" process. This type of initiative synchs with the aspirations of the government's National Innovation and Science Agenda but again the Australian system falls short in straightforward, accessible enabling mechanisms.
- The third theme of the US Review Strategy, [70] *Supporting the Science that Underpins the Regulatory System,* mentions leveraging the FDA's and USDA's intermural and extramural research portfolios and research agencies to support regulatory science (pp.18-19). Australia does not have this capacity.
- In discussion of the potential of new technologies to expedite assessment of safety of biotechnology products, the 2016 NASEM Report (p. 262) finds that *"Application of -omics technologies has the potential to reveal the extent of modifications of the genome, the transcriptome, the epigenome, the proteome, and the metabolome that are attributable to conventional breeding, somaclonal variation, and genetic engineering"* and recommends "To realize the potential of -omics technologies to assess intended and unintended effects of new crop varieties on human health and the environment and to improve the production and quality of crop plants, a more comprehensive knowledge base of plant biology at the systems level (DNA, RNA, protein, and metabolites) should be constructed for the range of variation inherent in both conventionally bred and genetically engineered crop species." This suggests synchs with dot point 1. How this might be implemented in Australia is noted below.

- Some suggestions in the Australian context that could fill some of the support gaps identified above and might be relatively quickly implemented by providing additional funding to existing facilities are briefly noted below.
  1. Additional funding of existing -omics capacity in NCRIS and other centres, for example, the new ANU-CSIRO Centre for Genomics, Metabolomics and Bioinformatics (CGMB) targeted to plant and agricultural-crop sciences, could be a cost effective way to support specialized services for GMO developers to characterize their products to a level required for OGTR regulatory submission. The existence and expected rapid developments in the power and diminishing cost of such new technical capabilities require a re-think of how GMOs should be characterized for applications to OGTR for restricted field trials (DNIR) or general release (DIR).
  2. Such a service would also provide the data in a standard electronic format suitable for submission to OGTR and, thus, minimise the time and cost of preparation of the submission paperwork, a major inhibitory factor for small companies and startups. An independent standardised service might also provide increased reliability and reproducibility of results and inspire greater public confidence. A standard data format may also assist OGTR's assessment procedures.
  3. The WA Department of Primary Industries and Regional Development (DPIRD) have recently established field-research containment facilities for R&D purposes (New Genes for New Environments (NGNE)).[71] These are suitable for field-trial evaluation of GM crops with OGTR DNIR approval. Supplementary federal government funding may be justified as part of the National Innovation and Science Agenda to encourage development of new agbiotech products by small Australian companies and startups.

[70] Footnote 3.

[71] https://www.agric.wa.gov.au/genetic-modification/grains-research-facilities-new-genes-new-environments

4. I have noted concerns in the last dot point of TOR (3) that agricultural and environmental regulation under the 2000 GT Act is not well served by the location of the GT/OGTR within the Department of Health. Specific funding for plant-based GM regulation of GM products additional to that in points 1. and 3. may be warranted.
5. Currently a large proportion of the cost of regulation of the 2000 GT Act is borne by IBCs (institutional biosafety committees) in universities, CSIRO, research institutes and other bodies which handle exempt and NLRDs (notifiable low risk dealings) on behalf of the GT/OGTR. Given the increased workload of IBCs in administering the regulations (training and accreditation of researchers, approving NLRD applications, undertaking annual safety inspections of labs and reporting to the OGTR) and the increasing complexity of technological developments, it seems reasonable that IBCs be provided with direct funding.

Summary: Clarity, safety and commensurate risk, scientific sense and a forward-looking approach to gene-technology innovations and their potential applications should be the over-riding principles in drafting the long overdue legislative revisions to the Gene Technology Regulations. Although gene-editing techniques, especially nuclease-based such as CRISPR-Cas9, have provided the impetus to major revision of the legislation it should be kept in mind that these methods may (and probably likely will!) be superseded in the future by even cheaper, easier-to-use, safer and versatile general methods. Also, some of the other types of methods as discussed under TOR (1), especially new developments in RNAi and grafting, may be more suitable for some applications and become more widely applied.

Continuing opposition from anti-GM adherents based on process-based definitions need to be addressed by appropriate public communication and education efforts; suggestions for "*Effective communication and public engagement by government agencies…*" are made in the Productivity Commission Report[72] (p.261, pp.282-5.) and in the US government and NASEM reports cited in the Preamble.

[72] Footnote 68.