Submission to OGTR Technical Review

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(This is a personal submission made under the consultation category "open to the public")[1]

As part of its Technical Review, OGTR has provided a Discussion paper, '"Options for regulating new technologies", that canvasses "four options for how new *(gene)* technologies could be regulated, which includes consultation questions." and also invites "Proposals for amendments to other technical or scientific aspects of the GT Regulations".

I. Comments on the Discussion paper and approach to consultation

1. The Discussion paper (DP) itself: I note that the format for submissions stated in the DP is very prescriptive. Although this may assist OGTR in more easily considering submissions it significantly restricts (discourages) submitters from expressing their views – while still being based on scientific arguments and examples – and weakens the consultation process.

The citations are unbalanced, many being too old to capture gene-editing advances of only the last 2-3 years while neglecting the comprehensive May 2016 US National Academies' Press report "Genetically Engineered Crops: Experiences and Prospects",[2] and reference to the ongoing (US) Whitehouse Review on Modernizing the Regulatory System for Biotechnology Products and its draft reports, [3] which is particularly relevant to the questions in the OGTR technical review. Several citations from non-independent sources (e.g. CropLife) is also concerning.

Multiple references to lengthy Australian Government documents without noting relevant sections or page numbers is not helpful to submitters, who are unlikely to have time to wade through them.

I note that one of these references – to "The Australian Government Guide to Regulation"[4] – to justify its approach on options[5] is misleading. Consulting the Guide indicates it does *not* provide guidance for regulatory authorities in conducting activities such as this technical review but rather it is provided *specifically* for policy makers. Ignoring this inconsistency and considering the guidance that is offered, its 5th principle is that "Policy makers should consult in a genuine and timely way with affected businesses, community organisations and individuals."[6] As a check list, the Guide also notes (p. 11) "Have you identified all of

[1] p.2, final para of Discussion paper

[2] "Genetically Engineered Crops: Experiences and Prospects", US National Academies Press, May 2016, 407 pp., http://www.nap.edu/23395

[3] Whitehouse Review on Modernizing the Regulatory System for Biotechnology Products https://www.whitehouse.gov/sites/default/files/microsites/ostp/biotech_national_strategy_final.pdf

[4] https://www.dpmc.gov.au/sites/default/files/publications/Australian_Government_Guide_to_Regulation.pdf

[5] p.2 of Discussion paper

[6] p.2 of Guide, footnote 6.

the viable policy options?" (*cf.* my comments below). The Guide also provides useful guidance on the requirements for open consultation (principle 5. above and pp. 39-45) and document presentation (p.14). I note that no public media announcement of the Technical Review appears to have been made (p.43). I am aware that OGTR informed institutional IBCs; they may variably have informed researchers and other interested individuals and stakeholders.

2. Options section: The DP "offers options to provide clarity in relation to new technologies. OGTR is seeking your submissions in support of your favoured option". However, these options do not include "none of these"; this would provide submitters with the formal opportunity to make suggestions within its general guidelines, i.e. "supported by a rationale and, where possible, a science-based argument".[7] I address this issue further under section **II.**

Also, it is confusing that the four options do not broadly address the problems of regulating new technologies that can be used for "modifying" genes or genomes, and the possible biological effects thereof, but rather is restricted to the rapidly developing field of gene-editing methods, particularly CRISPR-Cas9.

3. Assumptions of the technical review. While acknowledging that the definition of GMO in the 2000 GT Act was based on whether it could arise naturally – *"whereas techniques which mimic natural processes and work through natural mechanisms do not result in GMOs"*[8] – and that what is now considered possible naturally has changed (a stunning example for sweet potato is documented in section **III**), this recognition is not carried through in other parts of the DP, in particular the Options.

4. Restricting discussion of policy. The DP indicates in many places that "policy settings" should not be raised as "separation of policy and regulation is a standard governance arrangement in place for most regulatory agencies of the Australian Government".[9] It is indeed true that regulatory authorities should not seek to set policy but in undertaking a "technical review" it makes no sense to restrict discussion of the product *vs* process debate by simply stating that "central policy setting of the scheme is the process trigger built into the GT Act".[10] This ignores the fact that technology now allows products to be made by GM processes but without leaving a trace of the process by which they have been made (see examples in **IV**)! This important development needs to be brought out in the technical review as the process trigger is now widely agreed to be obsolete (section **III**).

The DP's restrictions are also inconsistent as it itself raises issues outside OGTR's brief, which is "to protect the health and safety of people, and to protect the environment",[11] by introducing mention of commercialization and trade.[12]

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[7] OGTR web page "Technical Review of the Gene Technology Regulations 2001 - call for submissions" and Consultation questions 6.-8., p.4 of Discussion paper

[8] pp.6-7 of Discussion paper

[9] p.1, final para *ibid.*

[10] p.1, final para and numerous other pages *ibid.*

[11] p.5, para 1 *ibid.*

II. Regulatory options for new technologies

As noted above, and for reasons detailed in sections **III** and **IV** with arguments supported by scientific information, I do not consider any of the 4 options proposed in the DP for *"Regulatory options for new technologies"* is viable. Briefly, this position is summarised as:

1. The current legislation is inadequate and complete revision is required. The system is broken and can't just be "patched".
2. Persevering with complex Amendments that are likely to be obsolete even before enactment, judging from the 5-year time lag for the last amendments from the 2011 review,[13] will simply lead to continuing uncertainty for researchers and developers, especially of GM crops, of likely regulatory decisions, which is already impeding uptake of technologies and investment.
3. The ongoing commissioned (US) National Academies of Sciences study on "Future Biotechnology Products and Opportunities to Enhance Capabilities of the Biotechnology Regulatory System",[14] which is due to report by the end of 2016, is tasked with projecting developments in new technologies in the next decade and their implications for updating the regulatory framework, i.e. it is proactive. By comparison, OGTR's current schedule of reactive 5-yearly technical reviews is inadequate.

III Scientific arguments for why complete revision of the legislation is necessary

There has been a revolution in the scientific knowledge and technical capabilities that underpin the intent of the 2000 GT Act to regulate research activities and release of organisms with modified genes. Although in the initial years, development of new methods was incremental and their impact on needs for modification of the regulations may have been able to be accommodated by Amendments, this is no longer the case.

Arguments presented here for the need for a complete revision of the 2000 GT Act is based on the following relevant current status of scientific knowledge [15] and projected developments in the next decade (see **II** point 3.[16]).

1. Product *vs* process definition. For the purposes of satisfying the stated object of the 2000 GT Act, i.e. "to protect the health and safety of people, and to protect

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[12] pp. 9,10,11,15, 18 of cons for options 2-4 *ibid.*

[13] From web page "The Gene Technology Amendment Act 2015 & implements minor and technical recommendations of the 2011 Review as agreed by all governments in 2013….." "The Gene Technology Amendment Act 2015 received Royal Assent on 10 September 2015 commenced on 11 March 2016."

[14] http://nas-sites.org/biotech/2016/02/01/statement-of-task/

[15] A list of citations for major scientific advances is not provided here as these are standard knowledge and can easily be verified by googling

[16] http://nas-sites.org/biotech/2016/02/01/statement-of-task/

the environment",[17] the current process-based definition of GMO rather than a product-based definition is untenable. The potential safety risk is rooted in the product. The process to produce it is irrelevant unless the product cannot be adequately characterized to identify unwanted or unknown changes that pose separate risks (see 3. below).

2. Process-based definition can be circumvented. The failure to recognize that the risk is product-based not process-based is leading to reactionary behaviour of researchers who design their experiments to circumvent the regulations, with attendant waste of talent, time and money;[18] a compelling example is mentioned in section **IV**. The power and flexibility of NBTs provide opportunities for such creativity that will exploit loopholes to defeat OGTR's out-dated regulatory framework, and these opportunities will likely increase. As is generally acknowledged, regulations that cannot be enforced are worse than useless.

3. Inconsistency in treatment of unintended genetic effects. It is scientifically and logically inconsistent to raise concerns about off-target effects using gene-editing methods, notably CRISPR-Cas9, i.e. additional unintended genetic changes at unknown locations in the genome, without mention of analogous "collateral" changes (damage) from use of conventional breeding techniques using chemical- and radiation-induced mutation, which escaped regulation under the 2000 GT Act from "legacy" provisions. This exclusion was based on there being no evidence[19] from >50 years of such conventional breeding of adverse safety effects. If this argument still holds what is the scientific reason for suspecting off-target effects from application of CRISPR-Cas9 would have different-in-type adverse safety effects?

Also, it should be noted that since the 2000 GT Act there has been a revolution in understanding of the biological function of most of the genomic DNA that does not code for proteins and was considered "junk". It is now known that this DNA is widely transcribed into multiple families of RNAs with as-yet poorly understood functions. It is likely that a large (but unknown) proportion of unwanted changes from CRISPR-Cas9 or chemical- or radiation-induced damage are in these regions. Based on now-current understanding, it is unjustified scientifically to assume that none of such changes raise safety concerns or that only those due to use of CRISPR-Cas9 do. Rather it appears that the precise nature and consequences of such changes should be evaluated on a case-by-case basis – for all three mutational methods, i.e. including chemical- and radiation-induced mutation.

4. Technology to identify unintended or unknown genetic changes. Fortunately, technology to identify genotypes and phenotypes from unintended or unknown genetic changes (often termed "adventitious presence") in a GMO produced by any process, and to assess its metabolic consequences, are now available, or under active development that can be expected to provide robust automatable low-cost testing systems within a few years. This technology is

[17] p.5, para 1 of Discussion paper

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

[19] Would the same decision be made in 2016 using characterization tools now available?

broadly called "-omics testing";[20] the main components of relevance to OGTR's brief being genomics and metabolomics, but there are increasing examples where epigenomcs testing may also be desirable (see examples in **IV**).

5. What should be the "unit" for regulation? Taking account of points 1.-4., it is clear that the definition of "gene" as the unit for modification in GMO (genetically modified organism) under the 2000 GT Act is itself scientifically out dated. Rather the unit should be the "genome" as it is now recognised that changes to specific nucleotides can produce wider genome effects by mechanisms as-yet uncharacterised; some examples are given in section **IV**. Such a change would be consistent with the now common replacement of "genetic" by "genomic" in many contexts. Thus, it is submitted that revision of the 2000 GT Act should change the wording and meaning of GMO to "genomically modified organism". However, see also points 7. and 8.

6. What genetic changes are possible by "natural" mechanisms?. 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). Of note, several "surprising" instances of horizontal gene transfer - exchange of genes between different species, i.e. transgenes - have been identified. 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.[21] Furthermore, the fact that these T-DNA sequences were shown to be active in sweet potato – but only rarely in wild species – suggest 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."

7. Is GMO a "scientific" term? It has been argued that "GMO is really not a science term, it is a regulatory definition, a legal distinction. As science literate readers know, all organisms have had their *(DNA)* genetically modified in some fashion, for as long as we have existed and had agriculture. Legacy techniques like artificial selection (i.e. breeding) and mutagenesis do this very randomly and at the whole genome level." [22]

It is sobering to conclude from this statement that much of the controversy and public concern about GMOs has arisen simply by their definition as having been produced by unnatural mechanisms – i.e. the process-based definition – rather

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[20] "Genetically Engineered Crops: Experiences and Prospects", US National Academies Press, May 2016, pp.15, 252-262 , http://www.nap.edu/23395

[21] 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.

[22] N. Staropoli *ibid.*

than focussing simply on the safety of the product, as is done for regulation of other product classes. For example, for drugs based on a natural compound, regulatory authorities such as the TGA do not consider whether it has been produced by direct extraction and purification from natural sources, from amplification by GMOs (!) or by direct organic synthesis. For safety purposes of the compound itself (product) all that counts is its purity.

Summary: As the (current) purpose of the 2000 GT Act is to assess risk and regulate modified organisms (i.e. products) as necessary for the "health and safety of people, and to protect the environment", perseverance and refinement (*via* Amendments) of legally-constructed terms which do not accord with contemporary scientific understanding, and indeed do not anticipate likely scientific developments over a realistic future timeframe [23] commensurate with the slowness of government processes to respond to GT developments is poor government practice. Failure to recognize that the regulatory system based on the 2000 GT Act "is broken" and needs complete revision – as has been recognized and acted on by the US government[24] - will only lead to further regulatory uncertainty that discourages researchers and product developers from pursuing preferred directions and hamper investment. Rather, it will encourage researchers and developers into wasteful directions that seek to exploit regulatory loopholes, as is already happening, as noted.[25]

IV. Some recent research findings that illustrate difficulties in regulating "GMOs"

1. CRISPR-Cas9 application that circumvents regulation. Korean researchers have reported a CRISPR-cas9 method using a pre-assembled Cas9 and gRNA complex which is introduced into plant protoplasts using solvents.[26] 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 in the nuclear DNA nor is it transiently present in the cell.[27]

What is the difference between this method of inducing mutations compared with radiation or chemical mutagenesis? Indeed it has been noted that "…if the fully assembled CRISPR-Cas9 system is introduced into the cell without using the target cell's genome or machinery the crop would fall into a regulatory gray area. This is a

[23] http://nas-sites.org/biotech/2016/02/01/statement-of-task/

[24] Whitehouse Review on Modernizing the Regulatory System for Biotechnology Products https://www.whitehouse.gov/sites/default/files/microsites/ostp/biotech_national_strategy_final.pdf

[25] N. Staropoli *ibid.*

[26] Woo et al. Nature Biotechnol. 33, 1162–1164, 2015 http://dx.doi.org/10.1038/nbt.3389

[27] D. Cyranoski, Nature News 19/10/15 doi:10.1038/nature. 18590 "Kim and his colleagues avoid gene shuttling altogether. They report a recipe to assemble the Cas9 enzyme together with its guide RNA sequences (which the enzyme requires to find its target) outside the plant, and use solvents to get the resulting protein complex into the plant. The technique works efficiently to knock out selected genes in tobacco plants, rice, lettuce and thale cress, they say, reporting their results in Nature Biotechnology"

legal loophole but since the definition of GMO is legal and not scientific it makes sense."[28]

2. Gene modification produced by gene gun not regulated. In 2011 USDA ruled that a herbicide-tolerant Kentucky bluegrass didn't need to be regulated because the gene modification was produced using a gene gun to fire DNA-coated gold particles into plant cells rather than using the usual *Agrobacterium*-based (plant pathogen) method to introduce the gene.[29] The same decision has been made for gene-gun modifications of grapes and switchgrass.[30]

3. Non-transgenic offspring of GM plants with improved features not regulated. High-yielding offspring of a transgenic sorghum grass plant were identified that had lost the engineered gene. It was suspected that the transgene triggered an epigenetic change, i.e. altered gene expression in the plant,[31] leading to the improved trait. USDA deemed this variety as not needing regulation; the same decision was made for non-transgenic offspring of other crops with improved features (faster breeding).[32]

The question in all these cases is the mechanism behind the improved features, that is, what is the nature of the "residual" change, which in these cases was only linked to an original gene modification process by knowing the GM history of their parents. Are these examples the "tip of the iceberg" of mechanisms that occur commonly naturally? These examples were favourable traits that were "noticed". But the examples illustrate that whole new classes of modified plants (or other organisms) could be engineered that do not fall within current definitions of GMOs but nonetheless could pose risks, for example the epigenetic changes might result in dangerous organisms, such as more robust pests, diseases or weeds. The underlying genetic mechanism behind these examples could be in common with those produced by conventional chemical- or radiation-induced mutation.

In summary, they illustrate that the focus of regulation should be the safety of the "product" that is to be released, not the process by which it has been produced.

4. Modifications involving PPO gene for non-browning of fruit and vegetables. Engineering non-browning features involving down-regulation (using RNAi) or deletion (using CRISPR-Cas9) of the polyphenol oxidase (PPO) gene, in potato and apple, and mushroom, respectively, have all been deemed not needed to be regulated by the USDA but in the CRISPR-Cas9 case also deemed as non-GMO as no gene was introduced – simply deleted.[33,34] These examples are simply a hint of engineered crops with the same or similar features likely to be produced in the future by an expanding repertoire of "GM" methods and their variations, but with

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[28] N. Staropoli *ibid.*

[29] N. Staropoli *ibid.*

[30] H. Ledford "US regulation misses some GM crops", Nature 500, 389–390, 2013.

[31] H. Ledford *ibid.*

[32] H. Ledford *ibid.*

[33] E. Waltz, "Gene-edited CRISPR mushroom escapes US regulation", Nature Nature 532, 293, 2016.

[34] C. VanLong, "CRISPR-modified mushrooms escaped GMO regulations, and here's what it means for the future", Forbes Magazine Quora 9/11/16 http://www.forbes.com/sites/quora/2016/11/09/crispr-modified-mushrooms-escaped-gmo-regulations-and-heres-what-it-means-for-the-future/

safety risks that will likely be indistinguishable. Yet another reason for moving to the product as the subject for regulatory consideration.

V. Gene drive and dual-purpose research

My response to the question of "whether containment requirements for gene drive research should be increased"[35], particularly for NLRDs, is that identification of basic and applied research that might be used for gene-drive applications may not always be straightforward, either because it is not declared by researcher-applicants or because researchers do not recognise that their research may have dual purposes, one being (unrecognised) gene drive.

I consider that in carrying out its regulatory responsibilities OGTR should be considering all categories of "GMO research" that may have dual purposes, including, as one example, biowarfare, as is being done by the ongoing (US) National Academies of Sciences study on "Future Biotechnology Products and Opportunities to Enhance Capabilities of the Biotechnology Regulatory System", [36] noted previously. Note that potential biowarfare applications are wider than those commonly supposed; for example, they include those using plants modified to disrupt food supplies.

35 p.19 of Discussion paper

36 http://nas-sites.org/biotech/2016/02/01/statement-of-task/