The University of Melbourne

Comments on Options for regulating new technologies: Technical Review of the Gene Technology Regulations 2001

Consultation Question	Comment
1. Which option/s do you support, and why?	Option 4 would be the ultimate aim and is perhaps the most sensible option in terms of how to appropriately deal with site-directed nuclease (SDN) techniques, but it is difficult to see how this could be implemented without a corresponding review of the scheme and without potentially increasing the burden for Institutional Biosafety Committees (IBC). Therefore, at this point in time we support option 2. Option 2 would provide clarity to what technologies are subject to regulation and it will not alter the way our IBC works, nor will it increase the current regulatory burden for our IBC, which is already assessing dealings involving the use of new gene technologies. Should amendments be introduced so oligo-directed mutagenesis (ODM) and SDN techniques are subject to regulation, the language used to explain why is key for stakeholders. Our opinion is that ODM and SDN techniques enable a specific modification while techniques such as chemical or radiation induced mutagenesis result in non-targeted modifications. Although regulating these technologies may not be commensurate with the risk posed by the technologies and may have potential commercial implications, we support a cautious approach to regulating new technologies because there are still unknowns and off-target concerns that require consideration. For our IBC, one of the key benefits of the current regulatory scheme is that it prompts our stakeholders to stop and think through the work they have planned and the risks associated with it. It becomes challenging for both the IBC and our stakeholders when there is uncertainty, use of language that enables varying interpretations, and no supporting explanation as to why a technology or organism is or is not subject to regulation.
2. Are there other risks and benefits of each option that are not	No

identified in this document?	
3. Is there any scientific evidence that any of options 2-4 would result in a level of regulation not commensurate with risks posed by gene technology?	While we support option 2, we do acknowledge that regulating new technologies may not be commensurate with the risk posed by the technologies. There is potential for organisms to be produced using new techniques that may not be distinguishable from organisms resulting from non-regulated techniques and which have a long history of not posing a risk to the health and safety of people and the environment. In the event two organisms are indistinguishable and one is subject to regulations and the other is not purely due to the technique used to generate it, the absence of reason could challenge stakeholders.
4. How might options 2-4 change the regulatory burden on you from the gene technology regulatory scheme?	We would continue to operate in the same manner and at present we require all research involving the use of gene technology or genetically modified organisms, unless the dealings meet the Exempt Dealing criteria, to be submitted to the IBC for formal review and assessment. Consequently, options 2-4 would not increase our regulatory burden. Unless the use of specific technologies and the resulting mutant organism were to be excluded from the regulatory scheme, or were to be regulated but considered to meet the Exempt Dealing criteria, our approach will be to continue to review and assess the research.
5. How do you use item 1 of Schedule 1, and would it impact you if this item was changed?	The impact would depend on the change made. If a researcher uses any technique to modify genes or other genetic material, other than those few techniques currently listed in Schedule 1A, the work is assessed regardless of whether the mutational event did or did not involve the introduction of foreign nucleic acid. Given this technical review must maintain the current policy settings of the gene technology regulatory scheme, for item 1 of Schedule 1 to become of greater use to us it would need to be clarified to include what gene technology techniques could be used to introduce the mutational event so that the use of the technique/s and the resulting mutant organism were both excluded from the current regulatory scheme.
6. Might contained laboratory research on GM gene drive organisms pose different risks to other contained research with GMOs, and how could these risks be managed?	Research involving GM gene drive need to be assessed and considered on a case by case basis. If the GM gene drive organism posed an increased risk then additional containment requirements may be applicable, but if the risk was assessed to be the same or similar to that of other contained research with GMOs, then the containment requirements should be the same. As with all dealings with GMOs, the type of facility and containment level is directed by the level of risk associated with the GMO and this should be the same approach for research on GM gene drive organisms. Perhaps GM organisms permitted to be contained in lower levels of containment, such as PC1 facilities, when carrying gene-drive constructs should be required to be

Supporting information and science-based arguments should be provided where possible.	contained in a higher level of containment, such as PC2 facilities or higher. There is support for this approach in relation to GM *Drosophila melanogaster,* which in a number of countries overseas can be contained in PC1 equivalent facilities, but when carrying gene-drive constructs have been contained in PC2 facilities because of unpredictable ecological consequences in the event of an accidental release of flies carrying gene-drive constructs (Akbari et al. 2015, Safeguarding gene drive experiments in the laboratory, Science vol. 349 (6251): 927-929).
7. What RNA interference techniques are you using, and are there RNA interference techniques that you believe have unclear regulatory status? Please provide details of the techniques and science-based arguments for whether these techniques pose risks to human health or the environment?	Our researchers use a variety of RNA interference techniques including expression vectors and viral vectors containing siRNA or shRNA. As it is becoming increasingly clear that regulatory non-coding RNAs are key players in host pathogen interactions, and that a wide range of eukaryotic pathogens and parasites export RNAs to their hosts, with the exported RNAs thought to interfere with host gene expression (Chaloner, T., van Kan, J.A.L, Grant-Downton, T. (2016) *RNA 'RNA Information Warfare' in Pathogenic and Mutualistic Interactions*, Trends in Plant Science, Vol. 21, No. 9, p738-748 http://dx.doi.org/10.1016/j.tplants.2016.05.008), we argue that the application of naked RNA to plant or animal cells should be included as a technique that is not gene technology because the process mimics a natural process. Furthermore, the organisms have not had genes inserted or deleted by virtue of gene technology and the process gives rise to organisms that can occur in nature, and as such do not pose a particular biosafety risk to the environment or human health and safety. Therefore, we propose the following amendments (highlighted red) to the *Gene Technology Regulations 2001*: Schedule 1A, Techniques that are not gene technology (regulation 4) Item 10: A natural process, if the process does not involve genetically modified material. Examples Examples of natural processes include conjugation, transduction, transformation, transposon mutagenesis and RNA silencing involving the application of naked DNA or RNA. Schedule 1, Organisms that are not genetically modified organisms (regulation 5) Item 3: Naked plasmid DNA or RNA that is incapable of giving rise to infectious agents when introduced into a host cell.
8. Do you have proposals for amendments to any	Yes, we propose an amendment to the requirement to contain all genetically modified *Drosophila melanogaster* in at least a PC2 Invertebrate facility. The proposal is to lower the requirement so that dealings with GM *Drosophila melanogaster*, where

other technical or scientific aspects of the GT Regulations? All proposals should be supported by a rationale and a science-based argument.	the modification does not confer an advantage on the fly or, the fly is not capable of secreting or producing an infectious agent as a result of the modification, be suitable for containment in at least a Physical Containment Level 1 facility. The rationale for the proposal is that the containment requirements are not commensurate with the risk and nor with standard requirements by collaborators internationally, and we do acknowledge that this would require a corresponding amendment to the Guidelines for Certification of Physical Containment Level 1 Facility. This proposal is based on an improved understanding of the very low risks associated with most GM *Drosophila melanogaster* strains. During the past 35 years, and in particular the 15 years since the regulatory scheme came into effect in Australia, to the best of our knowledge there have been no reports of incidents with adverse effects on human health or the environment associated with the use of common genetic modifications in *D. melanogaster*. This is in spite of the fact that Drosophila research has burgeoned in recent years (currently there are approximately 4000 papers per year on *Drosophila* species) with thousands of scientists around the world routinely using GM *D. melanogaster*. The physical containment level 2 requirements in Australia no longer align with other modern countries conducting research with GM *D. melanogaster* (such as the US, UK and Spain). Internationally work involving GM *D. melanogaster* can be undertaken within physical containment level 1 facilities or equivalent, but when the modification has an inherent higher risk a higher level of containment is still required. *D. melanogaster*, also known as the fruit fly, vinegar fly or pomace fly, is an experimental species that has been used for genetic research since 1909, when it was first utilized in the laboratory of T.H. Morgan. There is a very low level of inherent risk to the environment, crops, and human health with this species for the following reasons: • It is already an established species in Australia; it evolved in central Africa but is now a cosmopolitan species found associated with human populations throughout the world, • It is not a disease vector like mosquitoes or tse-tse, • It does not bite or sting, and • It is not a crop pest. Although *D. melanogaster* is often referred to as the common fruit fly it is not a true fruit fly such as the family Tephritidae, which is indeed a pest. It should also be distinguished from the spotted winged Drosophila species, *Drosophila suzukii*, which is also a fruit pest species. The genetic modifications commonly used in GM Drosophila research do not pose risks to the health and safety of people, or the environment. The vast majority of transgenic Drosophila stocks involve innocuous genetic

elements commonly found in non-pathogenic species. These include:

- FLP, GAL4, GAL80 found in common baker's yeast,
- GFP and other fluorescent proteins found in jellyfish, coral and a variety of marine species, or
- lacZ found in common bacteria (*E.coli*).

These sorts of genes pose no risk to humans, the genes are not pathogenic or toxic, nor do the genes pose a risk to the environment. These modifications do not confer a selective advantage and would not result in a genetic modification to wild type populations in the event the GM Drosophila were unintentionally released. There will of course always be cases in which the genetic elements are inherently at a higher risk, and in these cases a higher level of containment, such as PC2 or higher, would remain appropriate.

Studies have shown that when wild Drosophila are brought into the laboratory and cultured under standard laboratory conditions they rapidly adapt to laboratory life. A study performed by Hoffmann, Hallas, Sinclair & Partridge (Evolution, 55(2): 436-438), showed that within three years of laboratory culture (approximately 55 generations), the descendants of wild flies rapidly lost their ability to tolerate environmental stresses of the type normally encountered in the wild (for example, heat, cold or desiccation). This study, as well as those described by Sgro & Partridge (Laboratory adaptation of life history in Drosophila, American Naturalist. 158(6): 657-658) suggest that Drosophila grown under standard laboratory conditions for prolonged periods no longer display the traits required to survive and successfully reproduce in the wild. Our researchers may work with Drosophila that have been bred in laboratory conditions for over 70 years (over 1000 generations), consequently, genetic manipulation of this species poses minimal risk to the environment in the unlikely event that the GM *D. melanogaster* were to escape containment.

In May 2001, a report on the use of genetically modified animals was prepared by The Royal Society, London (https://royalsociety.org/~/media/Royal_Society_Content/policy/publications/2001/10026.pdf). Within the report, a section on *D. melanogaster* (page 11) states "methods for reproducibly creating stable, heritable GM insects were developed almost 20 years ago, using the well-known genetic model insect Drosophila melanogaster. It is generally considered harmless as it is neither a significant agricultural pest nor a disease vector and no adverse consequences to human health or the environment of this large-scale genetic engineering have been reported. Many thousands of different GM strains of Drosophila have subsequently been produced in laboratories around the world, and there are far more GM strains of Drosophila than there are of all other GM insects combined. It has become the paramount model organism for studying animal development and

	genetics…..Modern Drosophila research is completely depended on the use of genetic modifications for the generation and analysis of mutants, and for the insertion of expression of genes either from Drosophila or from other sources." In the United States GM Drosophila is not regulated (https://www.aphis.usda.gov/aphis/ourfocus/biotechnology/permits-notifications-petitions/sa_permits/ct_permits_drosophila) and many other countries do not require PC2 invertebrate facilities for the containment of standard GM *D. melanogaster* work. In the US, almost all transgenic Drosophila research is undertaken within BSL1, which is equivalent to our PC1 facilities. However, when the nature of the genetic modification(s) constitutes a real risk, then a higher level of containment is required. Examples of such modifications would include flies containing pathogenic microbes or flies expressing prion sequences or flies expressing gene-drive constructs. Thus the containment should correspond with the real risks. It is understood that in the UK a risk assessment in the form of an environmental impact statement is required for GMOs such as insects. If the risk assessment concludes that the risk to the environment is minimal it does not require the equivalent of PC2 containment. Given the low risk and precedent overseas, we propose the requirement for GM *D. melanogaster* dealings to be contained in at least a PC2 invertebrate facility be reviewed and amended so that low risk dealings can be undertaken within a suitably certified PC1 facility.