MONASH University

SUBMISSION TO THE Third Review of the National Gene Technology Scheme 2017

Summary:

Monash University would like to thank the OGTR for the opportunity to provide comment on the Third Review of the National Gene Technology Scheme. Monash University continues to appreciate the OGTR's commitment to receiving stakeholder feedback and focus on ensuring that the impact the Regulations have on the research community is commensurate with the level of risk posed by recombinant DNA technologies to both the environment and people. Monash University welcomes the opportunity to contribute to ensuring that a workable and robust framework continues to support research within the Australian jurisdiction.

Monash University has operated under the Gene Technology Act 2000 since commencement, and although reviews of the regulations continue to improve the existing framework we have always found the applications of the Regulations by the OGTR to be practical and commend the OGTR for their supporting role in research involving genetic modification within Australia.

Monash University would like to offer the following points where we believe the regulatory framework could be improved to better support research activities in Australia while addressing the risks associated with recombinant DNA technology.

1. Dealing classifications of GM *Drosophila melanogaster* strains

The current technical review of the Gene Technology Regulations 2001 states that amendments to the regulations could be considered if our scientific understanding of the risks posed has changed.

The proposal here, is that the requirement for PC2-level Arthropod facility for all GM Drosophila melanogaster research be removed, unless the nature of the genetic elements is such that a higher level of containment is warranted.

This suggested amendment is based on an improved understanding of the very low level risks associated with most GM Drosophila melanogaster strains. During the past 35 years, and in particular the 15 years since the 2001 Gene Technology Regulations were put in place, to 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 Drosophila melanogaster. This is in spite of the fact that Drosophila research has burgeoned in recent years (currently ~4000 papers/year on Drosophila) with thousands of scientists around the world routinely using GM flies.

The PC2 containment levels in Australia, are also now out of step with other modern countries conducting research with GM flies (e.g. US, UK, Spain), where work is conducted at a PC1 level, unless the nature of the genetic modifications has an inherent higher risk and warrants PC2 (see below).

Reducing the classification of standard Drosophila research to Exempt would reduce administrative costs and increase research productivity. Precedent for this proposal can be found in the classification of the nematode worm Caenorhabditis elegans as Exempt unless an advantage is conferred by the genetic modification or the animal is made capable of producing an infectious agent.

1.1. Drosophila melanogaster is a harmless species

Drosophila melanogaster (also known as the fruit fly, vinegar fly, 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 environment, crops, and human health with this species because:

- 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, tse-tse, etc.
- it does not bite or sting.
- it is not a crop pest. Although D. melanogaster is often called 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.

1.2. Genetic modifications commonly used in GM fly research do not pose risks to health or the environment.

The vast majority of transgenic fly 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 other marine species
- lacZ – found in common bacteria (E. coli)

These sorts of genes pose no hazards to humans (i.e. no pathogenicity or toxicity), nor the environment since they do not confer a selective advantage and are not able to cause genetic modification of non-GM flies that they might come in contact with.

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 Facility such as PC2 or higher would still be appropriate.

1.3. Laboratory-kept GM flies are unlikely to be successful in the wild

Studies have shown that when wild Drosophila are brought into 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 (~50 generations), the descendants of wild flies rapidly lost their ability to tolerate environmental stresses of the type normally encountered in the wild (heat, cold, 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. We deal with Drosophila that has 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 GM Drosophila escape containment.

1.4. Royal Society report that GM D. melanogaster is harmless and no adverse consequences recorded

In May 2001 a report on the use of genetically modified animals was prepared by the Royal Society, London. The section on *Drosophila melanogaster* from 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. ... The use of GM flies to analyze gene function has been a key part of these studies for nearly 20 years, during*

which time the precision and power of these genetic tools have made their use ubiquitous. ... Modern Drosophila research is completely dependent on the use of genetic modification for the generation and analysis of mutants, and for the insertion and expression of genes either from Drosophila or from other sources."

Royal Society Report (May 2001) The use of genetically modified animals – section 40 https://royalsociety.org/~/media/Royal_Society_Content/policy/publications/2001/10026.pdf

1.5. The United States Department of Agriculture regards most GMO Drosophila as a non-regulated organism

The following statement is made on their website:
https://www.aphis.usda.gov/aphis/ourfocus/biotechnology/SA_Permits_Notifications_And_Petitions/SA_Permits/CT_Permits_drosophila

"Biotechnology Regulatory Services (BRS) issues courtesy permits for non-regulated organisms upon request in order to facilitate their movement, which might otherwise be impeded because of the similarity of the organism to other regulated organisms. A genetically engineered organism is considered a "regulated article" if the donor organism, recipient organism, vector or vector agent used in engineering the organism belongs to one of the taxonomic groups listed in 7 CFR part 340 and is also a plant pest, or if there is a reason to believe it is a plant pest. ***Since most transgenic Drosophila developed for research purposes do not contain genetic sequences from plant pests and are themselves not considered plant pests, most transgenic Drosophila do not require permits from BRS for their movement.*** *However, shipments manifested as "fruit flies" have recently raised agricultural and environmental concerns because this common name also refers to plant pests like the Mediterranean and oriental fruit flies…."*

Other countries do not use PC2-level insectaries for standard GM Drosophila melanogaster work.

In the United States, almost all transgenic *Drosophila* research is considered Biosafety Level 1, the least restrictive containment level under the NIH Guidelines (see Section III-D-4-a):
https://osp.od.nih.gov/wp-content/uploads/NIH_Guidelines.html

However, when the nature of the Genetic Modifications DOES actually constitute a real risk then a higher level of containment is used. Examples would include:
• flies containing pathogenic microbes
• flies expressing prion sequences
• flies expressing gene-drive constructs
For example the opening paragraph from a recent article about gene drive states:

*"…****Even though D. melanogaster ordinarily poses no threat to human health or agriculture****, the accidental release of flies carrying gene drive constructs from the laboratory could have unpredictable ecological consequences. This study therefore used institutionally approved stringent barrier methods. Only one experimenter handled the flies, inside an Arthropod Containment Level 2 insectary suitable for work with mosquitoes carrying human pathogens."*
Akbari et al. (2015) Safeguarding gene drive experiments in the laboratory. Science (2015) vol. 349 (6251) pp. 927-929

Thus the containment is matched to the real risks. A similar situation exists in the UK. For large GMOs such as insects, a risk assessment in the form of an environmental impact statement is required. If that risk assessment concludes that the risk to the environment is minimal it does not require Biosafety Level 2 containment.

1.6. The requirement for PC2-level insectaries for standard GM *Drosophila melanogaster* work hinders undergraduate education opportunities

The status of Drosophila melanogaster as one the key model organisms used in molecular genetics research worldwide, combined with the ease of culture and experimentation, make it an ideal organism for teaching undergraduate students critical research skills. However

undergraduate education using Drosophila is currently limited to traditional genetics using naturally-occurring fly strains due to logistical barriers to making teaching laboratories compliant as PC2-level insectaries. Demotion of GM Drosophila melanogaster to Exempt would greatly enhance undergraduate education opportunities by allowing students to engage with cutting edge genetic technologies

1.7. Summary

The current requirement for GM *Drosophila melanogaster* to be maintained in PC2-level insectaries necessitates the construction and maintenance of costly laboratory infrastructure that is ultimately paid for by Australian taxpayers. This diverts funds that would otherwise be devoted to research, putting Australian researchers at a competitive disadvantage compared to their colleagues in leading research nations such as the USA, UK, Germany, France, Spain, China, Singapore and Japan. We argue that the negligible environmental and health risks posed by GM *Drosophila melanogaster* do not warrant such stringent containment requirements and that demotion of standard GM *Drosophila* research to Exempt will bring Australia into line with the majority of countries hosting *Drosophila* research, freeing up funds for greater research productivity and improving educational outcomes for Australian University students.

2. **Certification Processing timeframes**.

The time provisions made under Section 14 of the Gene Technology Regulations 2001 continue to have a significant impact on facility operations within the University, and broader research sector. This has been an ongoing issue for many and we have heard of various creative ways to work through the challenges.

Development of research facilities comes at significant cost and the construction or refurbishment of a such spaces is often part of a larger plan. In the past many organizations submitted applications for certification prior to all the defects being rectified. The aim being that the OGTR would have completed their desktop review of the paperwork submitted and issues the certification instrument and stickers by the time defects have been completed and those responsible for performing the certification inspections could perform their final walkthrough and if satisfied, could affix the stickers to the facility door.

This practice has been openly discussed at previous IBC forums and at the recent forum it was made clear that the OGTR wanted to ensure applications were not made for certification until the facility was complete and met all the certification requirements.

In practical terms, this means that after spending, in many cases, millions of dollars to construct or refurbish a certifiable space that the investment must sit empty for 90 working days (approximately 126 calendar days or just over 4 months) before it can be used for its intended purpose. This often has flow on effect to building projects where relocating research team to new facilities enables work to commence in space they vacate. The current time lag between completion and certification has profound effects.

Given that the OGTR delegate the responsibility to individuals the institutional IBC believes to be competent to inspect these facilities and ensure they meet the certification criteria the role of the OGTR becomes and desktop audit and registration of the facility, with the final responsibility of affixing the stickers and then the ongoing responsibility of ensuring the facilities continue to meet the certification criteria being passed back to those individuals considered competent by the IBC.

Although Monash University's experience is likely only a small sample of the applications for certification processed by the OGTR, in the last 16 years of operation of the currently regulatory framework and several hundred applications for certifications over a broad range of facility types we have never had an application for certification denied, nor had any substantive questions or issues to be addressed by the OGTR. The most common request for clarification has related to room numbering or naming of facilities.

Acknowledging that the above may not be the typical experience for the OGTR, we would hope that part of the current review of the regulations and the regulatory framework could explore mechanisms to meet the OGTRs requirements while reducing the downtime of completed facilities, thus facilitating research within Australia.

Research is a global endeavor and very competitive. A 4-month hiatus while waiting for certification to be finalized has a negative impact on research programs moving forward and publishing outcomes before international competitors.

We acknowledge that the OGTR must operate under constrained resourcing which contributes to the ability to reduce timeframes and manage the workload. However, the OGTR may like to consider alternate approaches such as providing provisional approval for certification on receipt of a complete applications with ratification. Given the OGTR conduct a desktop audit and delegate the responsibility to ensuring the facility is operational and managing the risks associated with research involving genetically modified organisms to the institute, the risks associated with this alternate approach are no greater that current practices.

Furthermore, if the OGTR have any concerns about the competency levels of individuals conducting certification inspections they could explore a process of accrediting and registering individuals who could perform certification inspections and submit applications for certification. Such applications could be treated under a provisional approval process. Such accreditation could be a fee for qualification type training with registration of individuals deemed competent and meeting the OGTR's standards.

This could allow a two-tier approach, the existing process whereby an application is submitted once a facility has been completed and the OGTR process the applications as is the current practice, and a process whereby an OGTR accredited person can inspect a facility, lodge the application and the facility be issued provisional approval while the OGTR process and ratify the approval.

Institutes with large numbers of certifications and regularly updating, certifying or repurposing and recertifying spaces would welcome the option to explore ways to reduce the lag time between completing facility construction and having the facility operational.

3. Funding arrangements to support the Scheme

The topic of funding arrangements or cost recovery have been raised many times. Monash's position has been raised in opposition to cost recovery at each instance, for the following reasons.

Research conducted at Monash University, as is similar throughout the university sector, is predominately funding by Government grants which come from the tax payer. Any additional costs imposed on the University research sector will need to be sourced either from the Government through the funders or the Department of Education block funding support of universities. Research in Australia is not fully costed or funded and therefore universities have to source alternate funding to support research. The costs to support regulatory frameworks that impact university research activities is already high and further increases are becoming unsustainable. Monash University has a long history of ensuring internal frameworks the manage compliant are well resourced.

From a philosophical perspective, the concept of cost recovery is unethical. Introducing another process to administer a cost recovery process is a poor use of tax payers money. Essentially funds would be collected from tax payers, which the government allocate for research, which is awarded to the universities, who pay it back to support a government regulatory framework. All at an additional cost to the tax payer. Funds to support research in Australia are not increasing. Monash would support any means to reduce the introduction of an additional layer of administration to manage the scheme and reduce existing ones to liberate funds to directly support societies endeavors.