Environmental Protection Authority
Te Mana Rauhī Taiao

EPA staff supporting advice on applications APP201857, APP201858 and APP201859

To import into containment low-risk new organisms (unmodified and genetically modified), and to develop in containment low-risk genetically modified organisms for research and teaching purposes

December 2014

ADVICE TO THE DECISION MAKING COMMITTEE

New Zealand Government

Executive Summary

On 7 November 2014, the University of Otago lodged the following applications pursuant to section 40(1) of the Hazardous Substances and New Organisms (HSNO) Act:

- APP201857 to import into containment low-risk genetically modified organisms (GMOs) for research and teaching purposes;
- APP201858 to import into containment new unmodified low-risk organisms for research and teaching purposes; and
- APP201859 to develop in containment low-risk GMOs for research and teaching purposes.

The applications describe a broad range of unmodified and genetically modified microorganisms, cell lines, and animal and plant species because the University of Otago is seeking approval to replace all of the University's existing low-risk containment approvals, and to cover all future research and teaching containment work with one of these aforementioned applications. The use of the applications will be governed and administered by the University of Otago Institutional Biological Safety Committee (IBSC) – a Committee comprising people with expertise in various fields of bioscience, iwi representatives, and lay people.

Although broad in nature, the applications are not for novel or unusual new organisms or activities, and we consider that the adverse effects are negligible, taking into consideration the stringent staff proposed controls (see Appendix 1 of this report) and the University's good compliance record.

Amalgamating existing low-risk HSNO approvals and future anticipated containment work under three approvals with one project purpose, research and teaching, and one consistent set of containment controls will not only result in ongoing gains in scientific knowledge, but will also facilitate and streamline the University's auditing processes and provide for ease of training. Our assessment has identified beneficial effects from this streamlined approach, such as increased understanding and compliance with containment controls amongst the University's research faculty.

Therefore, we recommend that the HSNO Decision Making Committee approve the applications *with controls*.

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Background information and application process

The University of Otago and its history with the HSNO Act

1. The University of Otago is one of New Zealand's most research intensive universities, and currently holds over 400 HSNO approvals, including:
   - three approvals to import into containment low-risk unmodified new organisms;
   - 78 approvals to import into containment low-risk genetically modified organisms (GMOs); and
   - 350 approvals for the development in containment of low-risk GMOs.

2. The vast majority of the University's low-risk HSNO approvals fall under the criteria of 'low-risk' as the term is defined by the HSNO (Low-Risk Genetic Modification) Regulations 2003 or the superseded 1998 version of the Regulations, and as such, most of the approvals have been granted by the University's delegated Institutional Biological Safety Committee (IBSC). The approved organisms include a wide range of microorganisms, cell lines, plants and animals.

3. Many of the approvals held by the University of Otago describe a distinct project purpose, for example, *Escherichia coli* research work has been approved for the following projects:
   - To develop in containment genetically modified *Escherichia coli* and *Pseudomonas aeruginosa* in order to study genes that contribute to the ability of *Pseudomonas aeruginosa* to cause infection (ERMA200357);
   - To permit development of genetically modified *Escherichia coli* bacteria as part of a laboratory class for undergraduate science students (GMD02011); and
   - To express *Streptococcus pneumoniae* LytA and PsaA in *Escherichia coli* in order to improve currently available diagnostic tools for the detection of invasive pneumococcal disease (GMD05049).

4. Besides approving defined projects, many approvals have been amended by the University's IBSC or another HSNO decision-maker under section 67A of the HSNO Act when the University has needed to expand the scope of a particular approval, whether it be the range of genetic modification (i.e. vectors and donor DNA) or the host organism list. The amendment is approved if the proposed alteration(s) is "*minor in effect*" or "*corrects a minor or technical error*"; that being a comparatively insignificant change to the result or consequence of the approval.

5. The regulatory practice of approving (and then amending) defined low-risk research projects has created a situation where the same host organism is described in multiple low-risk HSNO approvals, each with slightly different research purposes under similar containment regimes - particularly non-pathogenic *Escherichia coli* in development in containment approvals (see paragraph 3).

6. Furthermore, managing compliance to the defined scope and differing controls of each of the University's HSNO approvals - of which there are more than 400 - is a significant administrative

burden in time and cost for the University's internal auditing processes and external MPI audits (section 2.3 of application APP201859).

The lodged containment applications

7. On 7 November 2014, the University of Otago (the applicant) lodged the following applications pursuant to section 40(1) of the HSNO Act:
   - APP201857 to import into containment low-risk GMOs for research and teaching purposes;
   - APP201858 to import into containment new unmodified low-risk organisms for research and teaching purposes; and
   - APP201859 to develop in containment low-risk GMOs for research and teaching purposes.

8. These applications share one set of outcome-based containment controls and one broad but familiar purpose; that being research and teaching. The University is seeking approval to amalgamate all of the University's existing low-risk HSNO containment approvals, and to cover future low-risk containment work with one of the aforementioned applications.

9. All subsequent legislative requirements were carried out following formal receipt of the applications. These requirements are explained in Appendix 2. Notable outcomes are described below:
   - The applications were not considered to meet the threshold of 'significant' public interest and were not publicly notified;
   - The Department of Conversation (DOC) and the Ministry for Primary Industries (MPI) were notified and provided with the opportunity to comment on the applications. Their salient comments have been incorporated throughout this report where relevant, and the full comments received from MPI are provided in Appendix 5;
   - The EPA staff risk assessment was performed in accordance with section 45 of the HSNO Act.

Organisms to be considered

Unmodified new organisms to be imported

10. Figure 1 is a graphical comparison of the unmodified new organisms described within import into containment approvals held and used by the applicant (Figure 1A), and the new unmodified organisms the applicant intends to import under APP201858 (Figure 1B). The specific organisms in application APP201858 are described in Appendix 3 of this report.

11. None of the unmodified organisms listed in APP201858 (Figure 1B; Appendix 3) are novel as they have previously been assessed by ERMA, the EPA or delegated IBSC. A summary of the organisms to be imported under APP201858 and prior assessments are provided below.

Figure 1A: Unmodified organisms within HSNO approvals held and used by the applicant

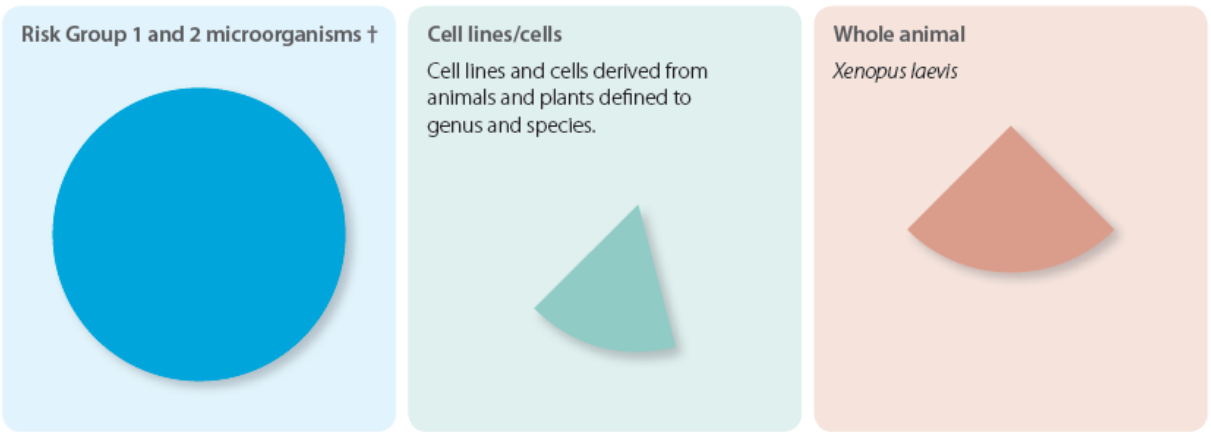
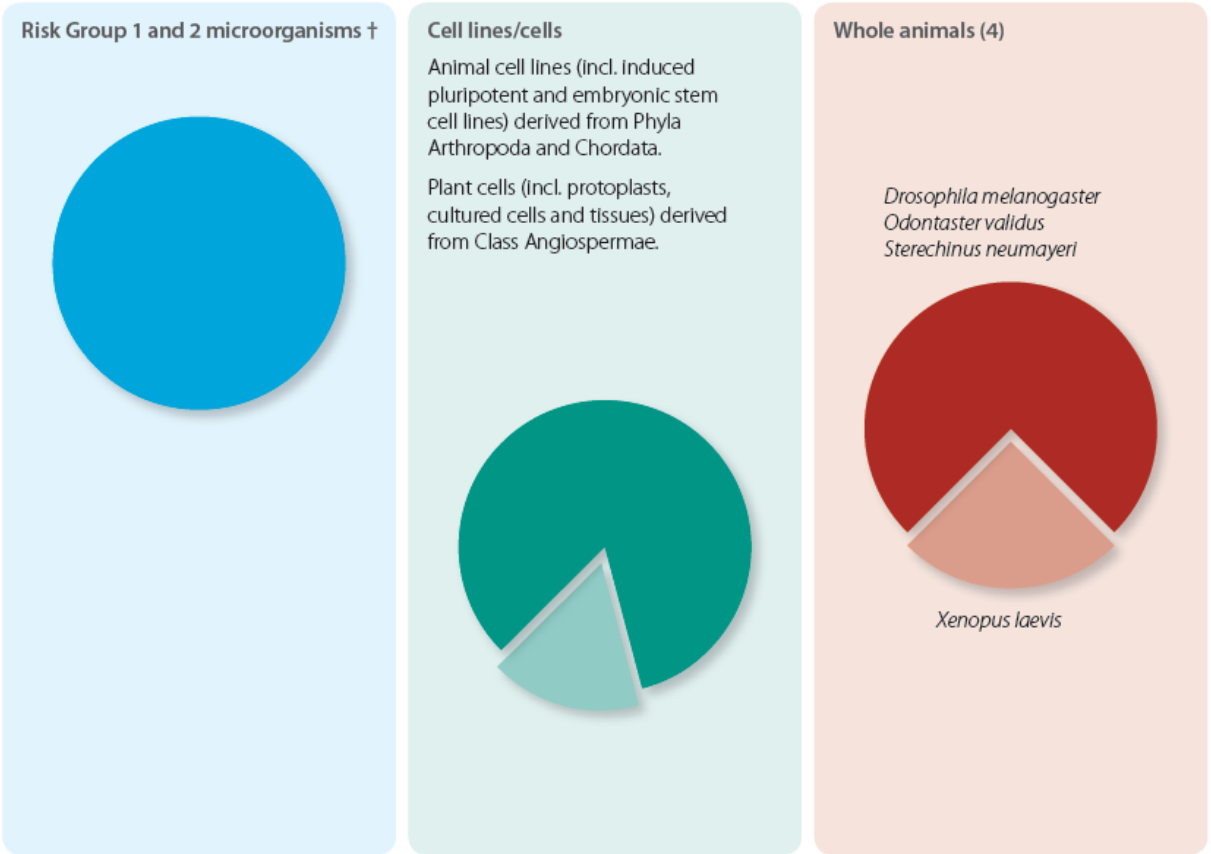


Figure 1B: Unmodified organisms to be imported under APP201858



† Imported as either cultures or within samples derived from apparently healthy animals and plants, and environments with no recent reports of plant and animal disease.

Risk Group 1 and 2 microorganisms to be imported

12. The EPA previously approved the import into containment of Risk Group 1 and 2 microorganisms[1] as cultures or within samples derived from animals, plants and the environment in 2013 (APP201737). This approval can be used by people or operators other than the original applicant, and the University of Otago is using this approval for the containment of some unmodified microbes (Figure 1A, blue circle). The HSNO Decision-Making Committee for application APP201737 considered that the risks associated with the microorganisms were limited by the biological characteristics of the organisms, and accordingly, did not identify any potentially significant adverse effects from importing the microorganisms into containment.

13. The applicant is applying for Risk Group 1 and 2 microorganisms under APP201858 for research and teaching purposes (Figure 1B), not simply "*laboratory based research*" as is imposed on the existing APP201737 approval.

Cell lines and cells to be imported

14. The applicant holds and uses approvals that allow import into containment of unmodified cell lines/cells derived from various named animal and plant species (Figure 1A), but intends to import a broader range of cell lines/cells derived from animal and plant species within Phylum Arthropoda[2], Phylum Chordata[3] and Class Angiospermae[4] under APP201858 (Figure 1B).

15. Cell lines, cultured cells and tissues are reliant on specific laboratory culture conditions for survival, and a large number of cell lines/cells derived from named animal and plant species have previously been assessed and defined as low-risk host organisms (i.e. category 1 as defined in the HSNO (Low-Risk Genetic Modification) Regulations 2003) in several HSNO approvals (see Appendix 4 of this report).

16. Although APP201858 proposes to import a broader range of cell lines/cells, the biological characteristics related to containment of these organisms are identical to those previously assessed and approved by the EPA, ERMA and the University's IBSC. No distinct risks have been identified for unmodified cell lines/cells derived from any particular species.

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[1] **Risk Group 1 microorganisms** are those organisms that require a microscope to observe, and are unlikely to cause disease in humans, plants or animals. **Risk Group 2 microorganisms** are those organisms that require a microscope to observe, and can cause disease in humans, plants or animals, but are unlikely to be a serious hazard to laboratory workers, the community, animals or the environment. Laboratory exposures may cause infection, but effective treatment and prevention measures are available and the risk of spread is limited (Australia/New Zealand Standard 2243.3).

[2] Arthropoda: a phylum of invertebrate animals that have a segmented body, an external skeleton and jointed limbs (including insects, spiders and crustaceans) (International Wildlife Encyclopedia 3rd ed).

[3] Chordata: a phylum of animals that possess a notochord at some stage during their development (including vertebrates, sea squirts and lancelets) (Stemple, 2005).

[4] Angiospermae: a class comprising flowering plants that produce seeds enclosed in an ovary (Hickey and King, 1997).

Whole animals to be imported

17. The applicant has previously obtained approval to import into containment the aquatic frog species *Xenopus laevis* (APP201982, Figure 1A), but intends to import *X. laevis* and three additional animal species under APP201858 (Figure 1B).

Drosophila melanogaster and Xenopus laevis

18. The invertebrate animal species *Drosophila melanogaster* (fruit fly) and vertebrate *Xenopus laevis* (aquatic frog) are common animal models for various fields of biological research. Both species have been previously defined as low-risk host organisms (i.e. category 2 as defined in the HSNO (Low-Risk Genetic Modification) Regulations 2003) in HSNO approvals that grant the import into, and/or development in containment of GM *Drosophila melanogaster* or GM *Xenopus laevis* for laboratory research purposes (see Appendix 4 of this report).

Odontaster validus and Sterechinus neumayeri

19. Aquatic animal species *Odontaster validus* (Red cushion starfish) and *Sterechinus neumayeri* (Antarctic sea urchin) are commonly used as animal models in evolutionary developmental biology, and were legally held in containment before 29 July 1998 under the Zoological Gardens Regulation 1977. Both species were subsequently 'deemed approved' upon the advent of the HSNO Act (deemed approvals PRE009016 and PRE009029, respectively).

20. In 2011, a HSNO Decision-Making Committee decided that there were grounds to reassess a variety of commonly held species, including *O. validus* and *S. neumayeri*, based on significant new information about the effects of the organisms and a significant change in use of the organisms in containment (ERMA200651). Of note, the ERMA200651 application form and decision document do not describe any specific adverse effects associated with holding *O. validus* or *S. neumayeri* in containment.

21. We consider the whole animals *O. validus* and *S. neumayeri* to be low-risk host organisms (i.e. category 2 as defined in the HSNO (Low-Risk Genetic Modification) Regulations 2003) based on the following biological characteristics that relate to containment:
    - Both animals are common crustaceans in the freezing sea waters that surround the polar Antarctic continent.
    - The life cycle of both animals comprise externally fertilised oocytes, larvae and adults that can grow up to 10 cm (*O. validus*) and 6 cm (*S. neumayeri*) in diameter (McClintock, 1988; Pearse, 1969; Brey, 1995).
    - No inseparable organisms were identified for either organism.

22. The following table provides a summary of paragraphs 12 – 21;

Unmodified organisms to be imported under APP201858	Novel	Previously assessed *
Risk Group 1 and 2 microorganisms	X	✓
Cell lines/cells derived from Phyla Arthropoda and Chordata, and Class Angiospermae	X	✓
Whole animals (4 named species)	X	✓

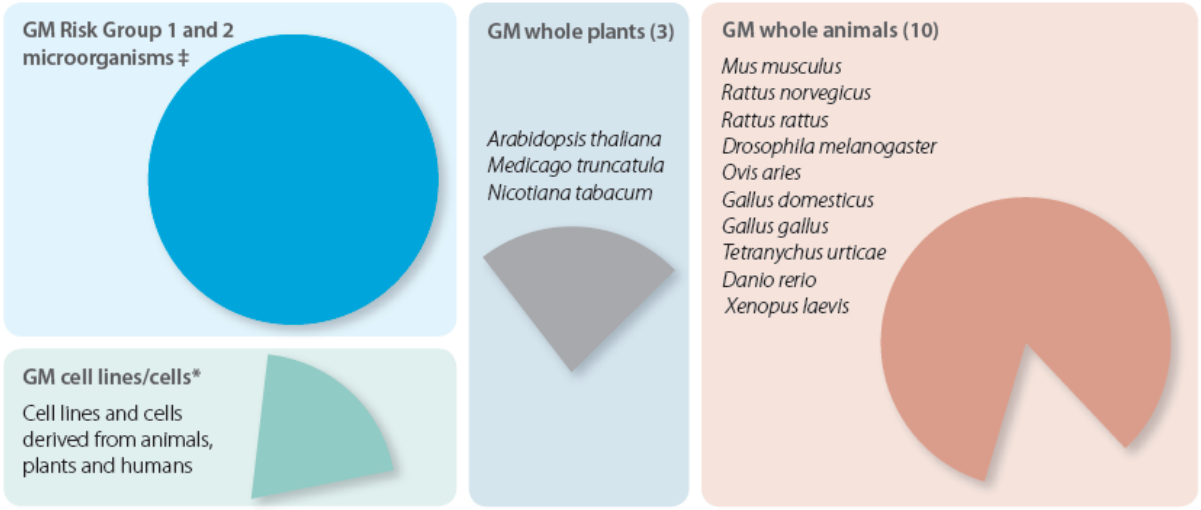
* See Appendix 4 (includes deemed approvals).

GMOs to be imported and/or developed

23. Figure 2 is a graphical comparison of the GM microorganisms, cell lines/cells, plant and animal species approved within low-risk import into, and/or development in containment approvals held by the applicant (Figure 2A); and the low-risk GMOs the applicant intends to import into containment under APP201857 and/or develop in containment under APP201859 (Figure 2B). The specific characteristics and modifications of the GMOs intended for import and/or development (Figure 2B) are described in detail in Appendix 3 of this report.

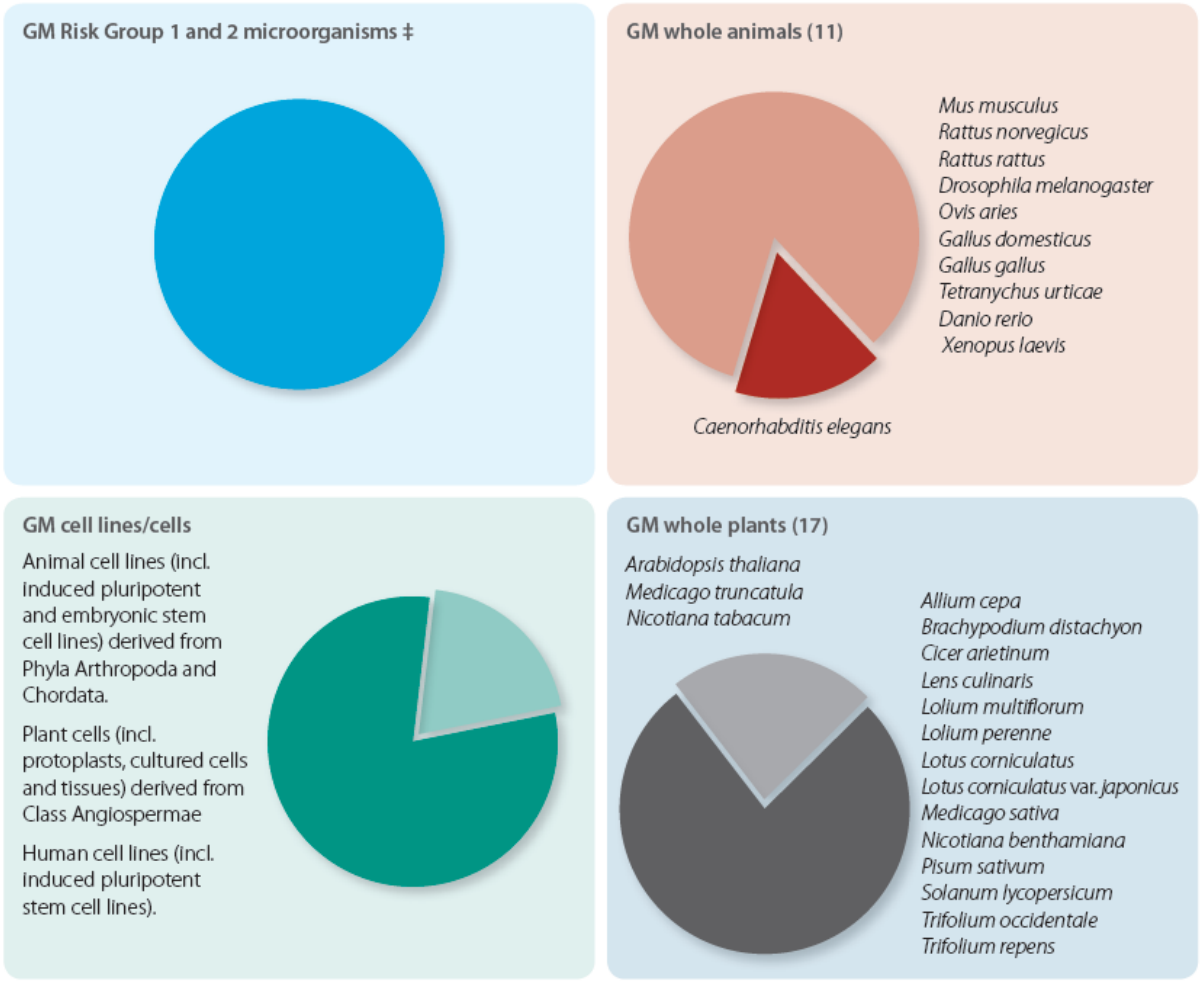
24. Although the applicant intends to import into, or develop in containment a broader range of GMOs under APP201857 or APP201859, respectively (Figure 2B, darker circles), many of the wildtype host organisms and genetic modifications have previously been assessed as low-risk under the HSNO (Low-Risk Genetic Modification) Regulations 2003 (or 1998 version) by the EPA, ERMA, or a delegated IBSC. A summary of the GMOs described in APP201857 and/or APP201859, and prior assessments are provided below.

Figure 2A: GMOs within low-risk HSNO approvals held by the applicant



* Derived from organisms defined to genus, species and strain if appropriate

Figure 2B: GMOs to be imported and/or developed under APP201857 and APP201859



‡ Defined to genus and species; and family, class, order and division taxonomic categories as appropriate

GM Risk Group 1 and 2 microorganisms to be imported and/or developed

25. The applicant has previously obtained approval to develop in containment GM Risk Group 1 and 2 microorganisms in 2011 (APP201030; Figure 2A). The HSNO Decision-Making Committee concluded, taking into account the containment controls imposed, that the adverse effects of developing these GM microorganisms in containment were negligible.

26. Since approval APP201030 expired on 20 October 2013, the applicant is now applying for ongoing approval to develop in containment GM Risk Group 1 and 2 microorganisms under APP201859 - as well as approval to import GM Risk Group 1 and 2 microorganisms into containment under APP201857. Although the applicant requests approval to import and/or develop a broad range of GM microorganisms based on risk profile, in all cases, the imported and developed GM microbes will be defined to the "*Latin binomial*"[5], and family, class, order and division taxonomic categories (as appropriate).

27. The applicant intends to import into, and/or develop in containment GM Risk Group 1 and 2 microorganisms that contain a broad range of modifications involving different types (e.g. purification tags, promoters, terminators etc.) and sources (e.g. human, plant, synthetic etc.) of genetic material, and which utilise different molecular technologies (e.g. vectors, genome editing technologies). The specific genetic modifications are described in detail in Appendix 3 of this report. The applicant has also specified a number of important exclusions for the modification of these microorganisms, which are summarised below.

Exclusions - GM Risk Group 1 microorganisms

28. The applicant does not expressly limit the genetic modification of Risk Group 1 microorganisms to developments that only involve known genetic sequences (section 3.1 of applications APP201857 and APP201859), but does specify a number of important exclusions. For example, genetic modifications that render Risk Group 1 microorganisms more pathogenic, virulent, or infectious than a Risk Group 2 microorganism are not permitted. Furthermore, genetic modifications that increase the pathogenicity, virulence, or infectivity of the Risk Group 1 microorganism to laboratory personnel, the community or the environment, or increase the ability to escape from containment are also excluded. The full breadth of proscribed genetic modifications is provided in Appendix 3, and is consistent with the HSNO (Low-Risk Genetic Modification) Regulations 2003.

29. The modification of Risk Group 1 microorganisms with fragments of uncharacterised genetic material enables the construction of gene libraries (a collection of bacteria which have been genetically modified to hold the entire genome of another organism). Gene libraries have played a crucial role in the whole genome sequencing of several organisms – including the human genome (International Human Genome Sequencing Consortium, 2001).

[5] i.e. *Genus species* taxonomic classification

Exclusions - GM Risk Group 2 microorganisms

30. Genetic modifications for Risk Group 2 microorganisms will be limited to using donor genetic material sourced from Risk Group 1 microorganisms or characterised donor genetic material. Additionally, genetic modifications that increase the pathogenicity, virulence, or infectivity of a Risk Group 2 microorganism to laboratory personnel, the community or the environment, or enhance the ability to escape containment are excluded. The full breadth of proscribed genetic modifications is described in Appendix 3, and is consistent with the HSNO (Low-Risk Genetic Modification) Regulations 2003.

GM cell lines and cells to be imported and/or developed

31. The applicant holds several approvals that allow import into containment of GM cell lines/cells derived from various named animal and plant species (Figure 2A), but intends to import and/or develop a wider range of GM cell lines/cells derived from animal and plant species within Phylum Arthropoda, Phylum Chordata and Class Angiospermae under APP201857 and APP20185 (Figure 2B).

32. As described in paragraph 15; cell lines, cultured cells and tissues are reliant on specific laboratory culture conditions for survival, and many GM cell lines/cells derived from named animal and plant species have been previously assessed and defined as low-risk host organisms (i.e category 1 as defined in the HSNO (Low-Risk Genetic Modification) Regulations 2003) in several HSNO approvals (see Appendix 4 of this report).

33. The applicant intends to import into, and/or develop in containment GM cell lines/cells that may contain a broad range of genetic modifications (see Appendix 3 of this report), but in all cases, the modifications will be limited to those that involve characterised genetic material. Furthermore, genetic modifications that increase the pathogenicity, virulence, or infectivity of the cell line/cells to laboratory personnel, the community or the environment, or enhance the ability to escape containment are not permitted. The full breadth of proscribed genetic modifications for GM cell lines/cells is described in Appendix 3, and is consistent with the HSNO (Low Risk Genetic Modification) Regulations 2003.

GM whole animals to be imported and/or developed

34. The animal species listed in Figure 2B are common animal models for various fields of biological research, and have all previously been defined as low-risk host organisms (i.e. category 2 as defined in the HSNO (Low-Risk Genetic Modification) Regulations 2003) in HSNO containment approvals (see Appendix 4 of this report).

35. The applicant intends to import into, and/or develop in containment GM animals that contain a broad range of genetic modifications involving characterised donor genetic material, but also specifies a number of important exclusions that are consistent with the HSNO (Low-Risk Genetic Modification) Regulations 2003 (see Appendix 3 of this report). For example, genetic modifications

that increase the pathogenicity, virulence, or infectivity of the animal to laboratory personnel, the community or the environment, or enhance the ability to escape containment are excluded.

GM plants to be imported and/or developed

36. All but two of the GM plant species listed in Figure 2B, *Cicer arietinum* (chickpea) and *Lens culinaris* (lentil), have previously been assessed as low-risk host organisms (i.e. category 2 under the HSNO (Low-Risk Genetic Modification) Regulations 2003 or superseded 1998 version) by the EPA, ERMA, or a delegated IBSC (see Appendix 4 for a list of prior approvals). We consider *C. arietinum* and *L. culinaris* to also be low-risk host organisms (i.e. category 2 under the HSNO (Low-Risk Genetic Modification) Regulations 2003) based on the biological characteristics described below.

Cicer arietinum

37. *Cicer arietinum*, the chickpea, is a legume 'pulse' crop species that has been cultivated as a food source since antiquity (van der Maesen, 1972), and is present in New Zealand (MPI Plant Biosecurity Index). *C. arietinum* is a self-pollinated diploid annual (Winter et al. 2000) with white flowers, grows to approximately 0.6 m in height and requires full sunlight for optimal growth.

Lens culinaris

38. *Lens culinaris*, the lentil, is another edible legume 'pulse' crop species that is cultivated in many countries (Sarker and Erskine, 2006), and is present in New Zealand (MPI Plant Biosecurity Index).

39. The applicant intends to import into, and/or develop in containment GM plants that may contain a broad range of genetic modifications involving characterised donor genetic material, but has also specified a number of important exclusions that are consistent with the HSNO (Low-Risk Genetic Modification) Regulations 2003 (see Appendix 3 of this report). For example, genetic modifications that increase the pathogenicity, virulence, or infectivity of the plant to laboratory personnel, the community or the environment, or enhance the ability to escape containment are excluded.

Summary of the GM host organisms and proposed genetic modifications

40. The following table provides a summary of the GM host organisms

GMOs to be imported and/or developed	Novel	Previously assessed *
GM Risk Group 1 and 2 microorganisms	**X**	✓
GM cell lines/cells	**X**	✓
GM whole animals (derived from 11 named species)	**X**	✓
GM whole plants (derived from 17 named species)	**X**	✓

* See Appendix 4.

41. The following table provides a summary of the proscribed genetic modifications

GMOs to be imported and/or developed	Uncharacterised genetic material	Increased pathogenicity [1]	Increased virulence [1]	Increased infectivity [1]	Greater ability to escape
GM Risk Group 1 microorganisms	✓	X [2]	X	X	X
GM Risk Group 2 microorganisms	✓ [3]	X	X	X	X
GM cell lines/cells	X	X	X	X	X
GM whole animals	X	X	X	X	X
GM whole plants	X	X	X	X	X

[1] Increased pathogenicity, virulence or infectivity to laboratory personnel, the community or the environment.

[2] In addition, greater pathogenicity, virulence or infectivity than a Risk Group 2 microorganism is excluded.

[3] Only when sourced from Risk Group 1 microorganisms.

Potential research covered by the applications

42. The applicant proposes to, among other things, perform the following activities with the described organisms:

- Plant pathogenicity test Risk Group 1 and 2 microorganisms on whole plant species (flowering and non-flowering);
- Expose animals to Risk Group 1 and 2 microorganisms;
- Grow Risk Group 1 and 2 microorganisms using large-scale fermentation (i.e. culture volumes greater than 10 L)[6];
- Administer animal cell lines to vertebrate animals;
- Regenerate tissues or organs from human and animal cell lines; and
- Regenerate whole plants from GM plant cells (only those named plant species in APP201857 and APP201859).

[6] Under applications APP201857-859, the applicant will require all large-scale fermentation work to meet the relevant requirements described in the University of Otago Containment and Quarantine Manual (including subject to inspection by the IBSC prior to commencing work).

The organisms can be adequately contained

Background

43. As noted, many of the organisms to be considered have already been approved by the EPA, ERMA, or an IBSC. Most of the containment controls imposed on the organisms held by the applicant are either prescriptive PC1 (Physical Containment Level 1) or PC2 containment controls[7] because the majority of these organisms met the HSNO (Low-Risk Genetic Modification) Regulations (1998 or 2003 versions) and were approved under section 42, 42A and 42B of the HSNO Act (by rapid assessment).

44. However, prescriptive containment controls do not allow HSNO approval holders to review and update their containment systems to incorporate current best practice in the containment of organisms – which has the potential to put laboratory personnel and the environment at risk. To address this issue, the EPA, since 2012, has implemented a new framework for enacting controls on containment approvals. These new containment approvals have outcome-based, or results-based, containment controls imposed rather than prescriptive controls. This means that instead of prescribing specific measures that must be adhered to, the controls direct that secure containment is required. The onus is on the approval user to demonstrate that they can meet that control outcome.

45. The EPA has imposed outcome-based controls on several new organisms approved for import into, and development in containment, including the import into containment of the aquatic frog species *Xenopus laevis* (APP201982), the import of Risk Group 1 and 2 microorganisms into containment (APP201737) and the development and import of genetically modified *Arabidopsis thaliana* in containment (ERMA200706 and ERMA200792).

Applicant proposed containment regime

Containment controls

46. The applicant intends to develop and work with the proposed new organisms within MPI-approved containment facilities, and has proposed a set of 24 outcome-based containment controls (see Appendix 2 of the applications).

47. These outcome-based controls describe a series of requirements that, among other things, relate to accountability for compliance with the controls, access to the containment facility that house the organisms, and the removal of any waste that may harbour the organisms. These proposed outcome-based controls are very similar to those already imposed on a number of HSNO approvals (see paragraph 45).

[7] PC1 and PC2 containment controls as prescribed by the Australia/New Zealand Standard 2242:3.

Management plan

48. As the outcome-based controls are only specific directives, the onus is then on the applicant to demonstrate that they can meet that control outcome.

49. The management plan (Appendix 3 of the applications) starts to delineate how each outcome-based control will be met by the University, and who specifically within the University will be responsible for meeting a particular control.

50. The University of Otago Containment and Quarantine Manual, or CQM (Confidential Appendix to the applications), is often referred to in the management plan – which indicates many of the containment procedures that the applicant will implement to contain the organisms are outlined in this one crucial reference document.

Containment and Quarantine Manual

51. The CQM is a *risk based* operational manual comprising seven sections that document the general procedures that members of the University of Otago must follow to ensure compliance with the outcome-based containment controls. These sections specifically address the management structure, design, construction, and maintenance of the containment facilities that house new organisms; access to those containment facilities; training of facility users; record keeping; transport of organisms; internal auditing procedures; specific operational requirements for the different types of organisms i.e. microbes, cell lines, plants, invertebrate animals and vertebrate animals and different types of activities (includes best practice from PC1, PC2 and other information sources); transport and destruction of organisms; regular review of containment protocols; contingency plans in case of an emergency (e.g. power failure, fire, theft or sabotage) and for the retrieval or eradication of different types of escaped organisms (including any organism-specific contingency plans, if appropriate); and vermin control.

52. The EPA notes that because the proposed outcome-based controls direct the approval holder to incorporate any improvements to best practice, the CQM will be continually improved over time.

MPI comments on the applicant's Quality Management System

53. The applicant has described that the management plan and CQM (i.e. the documents that constitute the Quality Management System (QMS)) outline the steps that members of the University of Otago must follow to ensure compliance with the outcome-based containment controls. However, MPI has reservations about the adequacy of this QMS.

54. MPI believes a substantive amount of work is still needed before the applicant has a robust QMS that meets the requirements of the outcome-based controls. However, despite this, MPI is complementary of the applicant's systems and is confident that further work on the QMS will eventually "*bring it all together*".

Stewardship of APP201857-859

55. If approved, the use of applications APP201857-859 will be governed and administered by the University of Otago IBSC – a committee comprising people with expertise in various fields of bioscience, iwi representatives, and lay people. Briefly, University of Otago staff and students will apply to this IBSC for approval to use APP201857-859 for their research activities, providing sufficient information about the organisms they propose to import and/or develop in containment. The IBSC will grant permission to use APP201857-859 if the project meets the approved low-risk criteria and approved organism description, and if they are satisfied that there are no other associated risk factors.

EPA staff proposed containment regime

56. We propose a similar set of outcome-based controls for these applications. A full list of these proposed controls can be found in Appendix 1 of this report, and proposed controls 1-24 provide for each of the matters specified in Schedule 3 in accordance with section 45(2) of the HSNO Act.

Potential pathways of escape

57. The following potential pathways of escape have been identified and are addressed by the proposed controls;
    - Escape during transport to/between containment facilities;
    - Escape via unauthorised persons being present within the containment facility;
    - Escape in waste or on contaminated equipment;
    - Escape due to the presence of undesirable organisms (e.g. vermin);
    - Escape via laboratory personnel;
    - Escape via failure of the containment regime through inadequate maintenance/upkeep; and
    - Escape via failure of containment regime following fire or natural disaster.

Escape during transport to/between containment facilities

58. Escape during transport to or between containment facilities has been identified as a potential pathway for escape. Proposed **controls 12-13** address the requirements for moving the approved organisms to or between containment facilities (i.e. formal receipt of consignments upon arrival), including maintaining containment and accompanying documentation (i.e. appropriately detailed transfer forms).

Escape via unauthorised persons being present within the containment facility

59. Unauthorised persons have been identified as providing a potential pathway of escape, as they may deliberately or accidentally remove the approved organisms from the containment facility. Proposed **controls 14-16** address requirements around access to the facility, including the requirements to exclude unauthorised persons (i.e. by lock and key or swipe card), and the identification of entrances (including entrances that are primarily used as exits).

Escape in waste or on contaminated equipment

60. The removal of waste and contaminated equipment from the facility has been identified as a potential pathway of escape. Proposed **controls 17** and **18** specify requirements for removing equipment (including personal protective equipment) and waste from a containment facility to prevent the escape of the approved organisms. It is noted that waste can be treated off-site to kill any approved organism or heritable material) using heat (i.e. autoclave or incineration) or chemicals (i.e. sodium hydroxide), and the approved organisms must be contained during transport to the treatment location.

Escape due to the presence of undesirable organisms in the facility

61. The presence of undesirable organisms, such as vermin, has been identified as a possible pathway of escape. Proposed **control 19** requires the facility be secured and monitored to ensure the exclusion of undesirable organisms that might compromise the containment of the approved organisms. For example, various sites surrounding the containment facility might be serviced for pest control on a regular six weekly basis.

Escape via laboratory personnel

62. Accidental/unintentional removal of approved organisms by laboratory personnel has been identified as a potential pathway of escape. Proposed **control 7** requires that persons entering and exiting the containment facility do so in a way that does not compromise containment. Proposed **control 20** requires that any person entering the containment facility has sufficient training on the containment regime that they are able to meet their responsibilities. Training could be performed in person and/or via online courses, and include competency tests and annual refresher courses.

Escape via inadequate maintenance or failure of containment measures

63. Escape as a result of failure of the containment regime through inadequate maintenance of the regime has been identified as a potential pathway of escape. Proposed **control 6** requires that the containment facility where the approved organisms are held be designed, constructed and maintained to prevent the approved organisms from escaping (i.e. constructed to an appropriate New Zealand building standard). Proposed **control 23** specifies that containment measures must be inspected, monitored and reviewed to ensure that containment is being achieved, and this could be realised by performing regular internal audits. **Control 23** also requires that containment measures be inspected as soon as possible after any event that could compromise containment.

Escape via failure of containment regime following fire or natural disaster

64. Escape as a result of failure of the containment regime following fire or natural disaster has also been identified as a potential pathway of escape. Proposed **control 23** requires that containment measures be inspected as soon as possible after any event that could compromise containment – including fire, Acts of God (such flood, earthquake, tornado), or attempts to break into the facility.

Conclusion on adequacy of containment

65. Escape from containment via the pathways identified is **highly improbable** taking into account the staff proposed containment regime. After considering the biological characteristics of the organisms under consideration, the potential pathways of escape and the proposed containment regime, we concluded that the organisms under consideration can be adequately contained.

Limited potential for undesirable self-sustaining populations

66. The potential for these organisms to escape from containment and form undesirable self-sustaining populations is limited by the stringent containment regime.

67. The applicant states that many of the microorganisms to be considered are laboratory-adapted strains, and, in addition, GM microbes that have a greater ability to escape and survive in the environment than the wildtype host organism will not be imported or developed under the applications. However, in the event that an undesirable self-sustaining population of microorganisms did establish, it may be difficult to eradicate such a microbial population.

68. If the cell lines/cells to be considered escaped containment, they are highly unlikely to survive and establish self-sustaining populations because of their reliance on specific laboratory culture conditions for survival.

69. In the event of unmodified aquatic animal species *Odontaster validus*, *Sterechinus neumayeri* and *Xenopus laevis* breaching containment, the organisms are unlikely to encounter a suitable aquatic environment that would support self-sustaining populations because *O. validus* and *S. neumayeri* are native to polar areas, and the natural aquatic environment of *X. laevis* ranges between 16 – 26°C. Low elevation streams and rivers in New Zealand typically fluctuate within a 10 – 20°C temperature range (APP201982). Unmodified invertebrate *Drosophila melanogaster* may be able to survive and replicate outside of containment, but is predicted to have little impact on New Zealand ecosystems (section 6 of application APP201858).

70. Many of the GM animals to be considered (Figure 2B) are highly inbred strains and are poorly adapted to survival without human intervention. Accordingly, escaped GM animal strains are unlikely to survive outside of a containment facility, and even less likely to establish a self-sustaining population in the New Zealand environment. However, in the unlikely event that a GM animal did escape and subsequently form a self-sustaining population, the animals could be identified and eradicated using focused searches, insecticides, baits, or traps.

71. In the event that a self-sustaining population of GM plants did establish, the GM plants could be easily identified using molecular diagnostic techniques, and eradicated using herbicides or manual destruction.

Potential beneficial effects of having the organisms in containment are medium

72. The applicant states that the new organisms to be considered in the applications "*will underpin the University's research and teaching in many areas of biology, including but limited to genetics and molecular biology, microbiology, biochemistry, cancer research, human disease research, physiology, immunology, medicine, dentistry, and plant and animal science*", and research using these new organisms "*will have beneficial implications for the health and well-being of New Zealanders, and will have economic and social benefits for the country through, for example, improved agricultural practices and through gains in scientific knowledge*".

73. Furthermore, the applicant states that the applications are "*designed to consolidate the use of almost all low-risk new organisms at the University of Otago's Dunedin, Christchurch and Wellington campuses under a single set of outcome-based controls, so will have the benefit of facilitating and simplifying regulatory compliance assurance*".

74. The EPA and DOC concur that conducting low risk fundamental research under three applications with one project purpose (research and teaching) and one consistent set of containment controls is a pragmatic approach to simplifying the internal and external auditing processes that ensure compliance. Streamlining these processes will provide ease of training and encourage compliance. Furthermore, simplifying administrative burdens will provide the University of Otago with more time to raise awareness of biosafety issues and containment controls within the research faculty, which will strengthen the University's biosafety culture and compliance with containment controls. Increased compliance with containment controls begets significant environmental benefits due to reduced risk of unintentional non-compliance/escape from containment.

75. MPI agrees there will be a degree of facilitation and simplification afforded by the applications, however, MPI has "*reservations about how much of a degree that will be*". As described in paragraph 54, MPI considers a substantive amount of work is still needed before the applicant has a robust QMS that meets the requirements of the outcome-based controls.

Conclusion on beneficial effects

76. We consider that on-going gains in scientific knowledge and the strengthening of biosafety culture and compliance with containment controls will be of **moderate** benefit to New Zealand, and it is **highly likely** that these benefits will eventuate if the applications are approved. Therefore, the potential beneficial effects of having the organisms in containment are **medium**.

Potential adverse effects of having the organisms in containment are negligible

77. In considering the adverse effects of having the organisms in containment, it is noted that the organisms will be developed and maintained in containment.

Potential adverse effects on the environment

78. The organisms to be considered do not pose a serious risk to the environment if they escaped because of their low risk classification or because of their limited potential to survival outside of a laboratory.

79. Inadvertently importing higher risk group 3 and 4 microorganisms[8] does introduce additional risk to the environment, should the organisms subsequently escape containment. However, to limit the likelihood of this occurring, the applicant will restrict importation to samples derived from apparently healthy animals and plants, and environments with no recent reports of plant and animal disease. If the applicant receives notification of a disease outbreak where received samples were recently collected, the applicant will destroy the received samples and the EPA and MPI will be notified.

80. Furthermore, the applicant will also cease working with microorganisms upon their registration on the MPI Unwanted Organism register. The microbial sample will be stored while an application is made for CTO approval.

Potential adverse effects on human health

81. Laboratory personnel have the potential to be exposed to the organisms under consideration; however, these organisms do not under normal circumstances infect or cause disease in humans, and therefore are unlikely to be a serious risk to laboratory personnel, or the wider community.

82. Unintended exposure to microorganisms of a higher risk grouping (i.e. zoonotic diseases) does introduce additional risk to laboratory personnel, however, the applicant intends to limit the likelihood of this occurring by restricting importation to samples from apparently healthy animals (as described in paragraph 79) and by performing all open container manipulations of animal, plant or environmental samples that contain unidentified mixed cultures or microorganisms within a Class II Biological Safety Cabinet, sealed glove box or anaerobic hood. Cultured microorganisms will be destroyed if they do not meet Risk Group 1 or 2 classification.

83. Risk of allergic or toxic reactions to the organisms, or injuries caused by the organisms (i.e. bites, cuts from claws) will be limited as personnel are trained to safely handle these organisms, and direct exposure will be limited by personal protective equipment (PPE)[9] and good laboratory practices. Furthermore, all manipulations of Risk group 2 microorganisms that are likely to form

[8] **Risk Group 3 microorganisms** are those organisms that usually cause serious human or animal disease and may present a significant risk to laboratory workers. It could present a limited to moderate risk if spread in the community or the environment, but there are usually effective preventive measures or treatment available.
Risk Group 4 microorganisms are those organisms that usually produce life-threatening human or animal disease, represents a significant risk to laboratory workers and may be readily transmissible from one individual to another. Effective treatment and preventive measures are not usually available (Australia/New Zealand Standard 2243.3).

[9] Personal protective equipment (PPE) is clothing and equipment worn by employees, students, contractors or visitors to protect or shield their bodies from exposure to hazards (i.e. chemicals); such as, gloves, laboratory coats, safety glasses and face masks (Australia/New Zealand Standard 2243.3).

aerosols, or Risk Group 1 and 2 microorganisms that form spores will be performed in Biological Safety Cabinets.

84. Inadvertently importing cell lines that contain increased risk factors (i.e. infectious particles) introduces additional risk to laboratory personnel. However, to limit the likelihood of this occurring, the applicant states that only established animal and human cell lines obtained from commercial sources or from reputable scientific laboratories will be imported.

Potential adverse effects on Māori and their culture and traditions

85. The University of Otago consulted with the Ngāi Tahu iwi representative on their delegated IBSC with regard to using these applications. No concerns about the use of the applications on the University's Dunedin and Christchurch campuses were raised, and the University was informed that wider consultation with Māori was not required.

86. The applicant states that dialogue with Ngāi Tahu will continue throughout the life of the applications as a Ngāi Tahu iwi representative will form part of the IBSC Committee that will govern and administer the APP201857-859 approvals. The Ngāi Tahu representative will play a pivotal role in deciding whether to grant approval to researchers that apply to use the applications and genetic material derived from New Zealand native and taonga flora and fauna, with or without wider Māori consultation.

87. Before the applications are used on the University's Wellington campus, the applicant has declared to undertake Maori consultation with the Tenths Trust.

Potential adverse effects on the market economy, society and communities

88. No potential adverse effects on the market economy, society or communities were identified.

Conclusion on potential adverse effects

89. We consider it **highly improbable** that any potential adverse effects on the environment, human health, Māori and their culture and traditions, the market economy, society or communities will occur if our recommended controls are adopted and the applicant's importation restrictions and good laboratory practices are enforced. Therefore, the potential adverse effects of having the organisms in containment are **negligible**.

Impact on international obligations

90. We are not aware of any international obligations that may be impacted by the approval of these applications.

Conclusion and Recommendations

91. Based on the information available, and taking into account the biological characteristics of the new organisms (unmodified and GMO), the potential pathways of escape and the proposed containment regime, we consider that the organisms can be adequately contained.

92. The adverse effects of having the new organisms (unmodified and GMO) in containment are **negligible**, while the potential beneficial effects of having the new organisms (unmodified and GMO) in containment are **medium**. Therefore the beneficial effects outweigh the adverse effects.

93. Given this, we recommended that the applications be approved (approved organisms as described in Appendix 3 of this report) subject to the controls listed in Appendix 1 of this report.

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Appendix 1: Staff proposed containment regime[10]

Any person importing or developing the approved organisms under the approval granted by this decision must ensure compliance with the controls set out below in respect of any activity they carry out under this approval in a facility under their control.

Requirement for the containment of approved organisms

1. The approved organism(s) must be contained.

Requirements for accountability for compliance with controls

2. The organisation, entity or person(s) responsible for the ownership, control and management of the containment facility where the approved organisms are held (including Board members and/or directors) must ensure compliance with the controls of this approval.

Requirement to specify how controls will be met

3. Procedures that specify how the controls will be implemented must be documented, and these procedures must be reviewed at least annually to ensure they:
   a) are effective in maintaining containment and achieving their purpose,
   b) reflect any relevant changes in the facility and its operation, and
   c) incorporate any improvements to best practice.
4. The containment facility must be operated in compliance with the documentation specified in control 3.

Requirements for the containment regime

5. The containment facility where the approved organisms may be held must be clearly defined, described, and documented, including the location and boundaries.
6. The containment facility must be designed, constructed, managed, and maintained to prevent the approved organism(s) from escaping.
7. Persons entering and exiting the containment facility must do so in a way that does not adversely affect containment of the approved organism(s).
8. The approved organism(s) must be identifiable as a new organism and be able to be linked to the relevant HSNO Act approval.

Requirements for notification to the EPA and/or MPI

9. Notification must be given to MPI of any movement of approved organisms outside of the facility, or any proposed modification to the containment regime which may affect the integrity of containment of the approved organism(s), before the modifications are undertaken.

[10] Compliance with the controls imposed in this decision does not affect the requirements of the Biosecurity Act 1993 including any authorisations or approvals that may be required under that Act (such as approvals of containment facilities by MPI).

10. The EPA and MPI must be notified in writing before this HSNO Act approval is used for the first time.
11. MPI must be notified as soon as possible, and within 24 hours, of any escape and/or breach of containment and the actions taken in response to that incident.

Requirements for moving approved organisms

12. The approved organism(s) must be contained during movement within, to, or from the containment facility.
13. When being moved outside of a containment facility, within New Zealand, the approved organism(s) must be accompanied by documentation stating the:
    a) Identity of the approved organism(s);
    b) Containment requirements;
    c) Details of the sender; and
    d) Details of the receiving facility.

Requirements to limit access to the containment facility

14. Unauthorised persons must be excluded from the containment facility.
15. All containment facility entrances must be clearly identified including specifying who has the right of access.
16. The number and location of entrances to the containment facility where the approved organism(s) are held must be identified and documented.

Requirements for removing equipment and waste from the containment facility

17. Any waste (including biological material) that may harbour the approved organism(s), or heritable material from the approved organism, must be treated to ensure that the approved organism or any heritable material is killed prior to disposal.
18. Any equipment, that may harbour the approved organism(s) or heritable material from the approved organism, must be treated to ensure that the approved organism or any heritable material is killed prior to the equipment being used for another purpose or being removed from the containment facility.

Requirement for dealing with undesirable organisms

19. The containment facility must be secured and monitored to ensure the exclusion of undesirable organisms that might compromise the containment of the approved organism(s).

Requirements for instruction and training

20. Any person (including contractors, staff, students, visitors, and volunteers) entering the containment facility must have received sufficient instruction on the containment regime to enable the person to meet their responsibilities in relation to containment.

Requirements for contingency plans

21. There must be a documented contingency plan for each approved organism held in the containment facility.
22. The contingency plan must be implemented immediately if there is any reason to believe that an approved organism has escaped or been released from the containment facility, or any other breach of containment has occurred.

Requirements for internal inspections and monitoring

23. To ensure containment is being achieved, containment measures must be:
    a) Inspected, monitored and reviewed as appropriate
    b) Inspected as soon as possible after any event that could compromise the containment regime, such as an Act of God (such as flood, earthquake) or any unauthorised attempt to enter the containment facility.
24. Any remedial requirements identified under control 23, or by any other means, must be actioned as soon as possible.

Interpretation

In these controls, unless otherwise specified below, a word has the same meaning as it is defined in the HSNO Act (if any).

Unless the context otherwise requires:

Term	Definition
approved organism	New organisms approved under applications APP201857, APP201858 and APP201859 (as described in Appendix 3 of this report) for import into, and/or development in containment for research and teaching purposes.
audit	A systematic documented review or examination and evaluation of evidence to determine the extent to which specific criteria are fulfilled.
authorised person	Authorised persons are those identified in the containment facility documentation as being allowed to be in the containment facility or any part thereof.
breach	Escape of organism(s), unauthorised entry to the facility and/or the structural integrity of the facility being compromised.
containment	Restricting an organism to a secure location or facility to prevent escape (section 2 of the HSNO Act).
containment facility	A place approved by MPI in accordance with section 39 of the Biosecurity Act 1993, for holding approved organisms.
contingency plan	A plan devised for a specific situation where things could go wrong, for example escape of an approved organism. It contains information, tasks and procedures that are necessary for timely decision-making and response to an unexpected event, or situation where the preferred plan fails.

controls	Any obligations or restrictions imposed on any approved organism, or on any person in relation to any approved organism, by the HSNO Act, or any regulations, rules, codes, or other documents made in accordance with the provisions of this or any other Act for the purposes of controlling the adverse effects of that organism on people or the environment (section 2 of the HSNO Act).
disposal	The action or process of discarding or getting rid of something, including but not limited to burial, incineration, or placing in the general waste. [Excludes the act of transferring to another containment facility under section 29 of the Biosecurity Act].
decontaminate	Kill or remove all approved organisms and heritable material.
documentation	Written or electronic records (including manuals, lists, diagrams, maps, policies, procedures, plans and protocols, records of training, access).
EPA	The Environmental Protection Authority.
heritable material	(In relation to an approved organism) viable biological material, including gametes and spores, arising from that organism that can, without human intervention, regenerate the organism or reproduce a new generation of the same species of the organism (section 2, HSNO Act).
HSNO Act	Hazardous Substances and New Organisms Act 1996.
MPI	Ministry for Primary Industries.
MPI Inspector	A person appointed under the Biosecurity Act to undertake administering and enforcing the provisions of the Biosecurity Act.
maintenance	The process of maintaining (preserving or providing for the preservation of) or continuing a state of good repair.
new organism	Defined by section 2A of the HSNO Act (a) an organisms belonging to a species that was not present in New Zealand immediately before 29 July 1998 (b) an organism belonging to a species, subspecies, infra-subspecies, variety, strain, or cultivar prescribed as a risk species, where that organism was not present in New Zealand at the time of promulgation of the relevant regulation (c) an organism for which a containment approval has been given (ca) an organism for which a conditional release approval has been given under the HSNO Act (cb) a qualifying organism approved for release with controls (d) a genetically modified organism (e) an organism that belongs to a species, subspecies, infra-subspecies, variety, strain, or cultivar that has been eradicated from New Zealand.
organism	Defined in section 2 of the HSNO Act: (a) Does not include a human being (ab) Includes a human cell (b) Includes a micro-organism (c) Includes a genetic structure, other than a human cell, that is capable of replicating itself, whether that structure comprises all or only part of an entity, and whether it comprises all or only part of the total genetic structure of an entity (d) Includes an entity (other than a human being) declare to be an organism for the

	purposes of the Biosecurity Act 1993 (e) Includes a reproductive cell or developmental stage of an organism.
treat (with reference to waste)	Kill all approved organisms and make heritable material non-viable.
undesirable organism	Organisms such as rodents, insects, and birds within the containment facility that could compromise containment (dependent on what organism is being contained).
waste	Unusable or unwanted substances or materials (including water, liquids, solids or air).

Appendix 2: Legislative requirements

Public notification

94. Under section 53(2) of the HSNO Act, the EPA has discretion to publicly notify an application to import into containment or develop in containment any new organism if it is considered that there is likely to be significant public interest in the application.

95. The Chief Executive has delegation to decide whether to publicly notify an application to import into containment or develop in containment any new organism under section 19(1) of the HSNO Act.

96. Applications APP201857, APP201858 and APP201859 were not publicly notified because the Chief Executive did not identify any exceptional circumstances warranting public notification, and significant public interest in these applications was not anticipated.

Application risk assessment

97. Applications APP201857, APP201858 and APP201859 were lodged pursuant to section 40(1) of the Act. The applications must be determined in accordance with section 45, taking into account the matters specified in sections 37, 39, 43 and 44 and other matters relevant to the purpose of the Act, as specified in Part 2 of the Act, and relevant provisions of the HSNO (Methodology) Order 1998 (the Methodology).

98. Section 45(1)(a)(i) of the Act requires that the applications be for one of the purposes specified in section 39(1) in order to be approved. The purpose of applications APP201857, APP201858 and APP201859 fits within section 39(1)(h) *such other purposes as the Authority thinks fit*, that being research and teaching.

Comments from Department of Conservation and the Ministry for Primary Industries

99. In accordance with section 58(1)(c) of the Act, and clauses 2(2)(e) and 5 of the Methodology, the Department of Conservation (DOC) and the Ministry for Primary Industries (MPI) were notified and provided with the opportunity to comment on applications APP201857-859.

100. DOC did not raise any concerns about the applications.

101. MPI comments are provided in Appendix 5, and the agency's salient comments are incorporated throughout the staff advice report where relevant.

Appendix 3: Organism Description

Unmodified organisms to be imported under APP201858:

Risk Group 1 organisms	**Risk Group 1 micro-organisms** (including Bacteria, Archaea, Viruses, Bacteriophages, Micro-eukaryotes, Algae, Fungi, Yeasts, phytoplankton, zooplankton, protozoa and micro-invertebrates) that are unlikely to cause disease in humans, plants, or animals. Microorganisms will imported as either axenic or mixed cultures, or within samples[11] derived from animals, plants and the environment. **Plant cells**, including protoplasts, cultured cells, and tissue. Taxonomic level: Angiospermae
Organism description	These organisms are low risk organisms because; • they are clearly identifiable and classifiable; • they are characterised to the extent that their main biological characteristics are known; • they are not normally able to (or contain inseparable infectious agents normally able to) cause disease in humans, animals, plants or fungi; • they do not normally infect, colonise or establish in humans; and • they do not produce desiccation-resistant structures such as spores or cysts that can be normally disseminated in the air. Plant cells and tissues will not have reproductive structures, will not be used to regenerate whole plants and will be kept in closed containers.
Risk Group 2 organisms	**Risk Group 2 micro-organisms** (including Bacteria, Archaea, Viruses, Bacteriophages, Micro-eukaryotes, Algae, Fungi, Yeasts, phytoplankton, zooplankton, protozoa and micro-invertebrates) that may cause disease in humans, plants, or animals, but are unlikely to be a serious hazard to laboratory workers, the community, animals, or the environment; for which there are effective treatment and preventative measures with respect to any infections that may be caused, and which present a limited risk of the spread of infection. Microorganisms will imported as either axenic or mixed cultures, or within samples[12] derived from animals, plants and the environment. **Animal cell lines** (including immortalized and primary cell lines) from organisms within the Kingdom Animalia, Phylum Arthropoda, or Phylum Chordata. **Whole animals** *Drosophila melanogaster* Macquart 1843 – Fruit fly, vinegar fly (syn.

[11-12] Samples derived from animals, plants and the environment includes: dung, guano, saliva, blood, serum, gastro-intestinal tract and contents, tissue, hair, feathers, bone, soil, sediment, water, non-viable plant material.

	Sophophora melanogaster) *Xenopus laevis* Daudin 1802 – African clawed frog *Odontaster validus* Koehler, 1906 – Red cushion starfish *Sterechinus neumayeri* (Meissner, 1900) – Antarctic sea urchin There are no inseparable organisms.
Organism description	These risk group 2 organisms; • are clearly identifiable and classifiable according to genus, species, strain or other subspecific category; • may be an infectious agent or contain an infectious agent that is pathogenic to humans/animals/plants/fungi; • may produce desiccation-resistant structures such as spores or cysts that can be normally disseminated in the air; • may not be characterised to the extent that their main biological characteristics are known; • may normally infect, colonise or establish in humans; • may be mammalian cell lines containing active viruses or infectious agents normally able to cause disease in humans; • may be whole animals, vertebrate or invertebrate including oocytes, zygotes, early embryos and other cells able to grow without human intervention into a whole animal; and • may be whole plants with reproductive structures, and may or may not be kept in closed containers.

GMOs to be imported and/or developed under APP201857 and APP201859:

Category 1 host organisms	**Risk Group 1 micro-organisms** (including Bacteria, Archaea, Viruses, Bacteriophages, Micro-eukaryotes, Algae, Fungi, Yeasts, Phytoplankton, Zooplankton, Protozoa and Micro-invertebrates) that are unlikely to cause disease in humans, plants, or animals. **Plant cells**, including protoplasts, cultured cells, and tissue. Taxonomic level: Angiospermae There are no inseparable organisms.
Organism description	These organisms is are considered low-risk risk group 1 host organisms because; • they are clearly identifiable and classifiable; • they are characterised to the extent that their main biological characteristics are known; • they are not normally able to (or contain infectious agents normally able to) cause disease in humans, animals, plants or fungi; • they do not normally infect, colonise or establish in humans; and

	• they do not produce desiccation-resistant structures such as spores or cysts that can be normally disseminated in the air. Plant cells and tissues will not have reproductive structures and will be kept in closed containers
Modifications	Modifications may include: • the introduction, deletion or modification of nucleic acids (DNA or RNA); • deletions and point mutations with or without the addition of genetic material; • the introduction of wild-type genes and mutants thereof (including deletion, substitution, and chimaeric mutant genes); and • the expression of multiple transgenes. Modifications may be made using: • plasmid or bacteriophage-based cloning, binary, and protein expression vectors; • genome editing technologies; • purified nucleic acids with or without an origin of replication that functions in the host organism • viral or transposon-based vectors, including replication-defective viral vectors such as lentiviral vectors, adenoviral vectors, and adeno-associated viral (AAV) vectors; and • replicative viral vectors (including baculovirus-based vectors). Vectors may contain regulatory elements including promoters, regulatory element binding sites, transcriptional activators, enhancers, terminators, multiple cloning sites, site directed recombination sequences, T-DNA border sequences; silencing elements (short interfering RNA, short hairpin RNA); and origins of replication. The vectors may also contain selectable marker genes; reporter genes; antibiotic resistance genes; transposons, recombination sequences and recombinases; retrotransposons or other transposable elements; protein targeting, localisation and secretory signals; solubility enhancement tags; protein purification tags, and affinity tags including epitope tags. Donor genetic material may consist of non-coding nucleic acids and/or nucleic acids that code for genes; gene regulatory elements; transposons, retrotransposons or other transposable elements; reporters or selectable markers. Donor genetic material may be sourced from plant, animal (including protozoa, zooplankton and phytoplankton), human, insect, bacterial, archael, fungal (including yeasts), viral, or synthetic sources. The modifications will not include; • the production of infectious particles normally able to cause disease in humans, animals, plants, or fungi; • genes that encode for vertebrate toxins with an LD_{50} < 100 µg/kg; • genetic material derived from Māori; • genetic material derived from New Zealand native or taonga flora and fauna, unless consultation has been conducted with Ngāi Tahu representatives and, if appropriate, other iwi;

	• genetic material from species listed by the Convention on International Trade in Endangered Species (CITES) unless appropriate permission has been gained; • uncharacterised sequences from pathogenic microorganisms (**import only**) • modifications that result in a genetically modified organism that is more pathogenic, virulent, or infectious than a Risk Group 2 host organism; or • modifications that result in the GMO having a greater ability to escape from containment than the unmodified host organism. Genetically modified cultured plant cells may be used to generate whole plants, if the tissue cultures are derived from the named plant species approved for genetic modification in this application.
Category 2 host organisms	**Risk Group 2 microorganisms** (including Bacteria, Archaea, Viruses, Bacteriophages, Micro-eukaryotes, Algae, Fungi, Yeasts, Phytoplankton, Zooplankton, Protozoa and Micro-invertebrates) that may cause disease in humans, plants, or animals, but are unlikely to be a serious hazard to laboratory workers, the community, animals, or the environment; for which there are effective treatment and preventative measures with respect to any infections that may be caused, and which present a limited risk of the spread of infection. ***Terrestrial laboratory animals*** *Mus musculus* Linnaeus 1758 – Mouse *Rattus norvegicus* Berkenhout 1759 – Brown rat, Norway rat, laboratory rat *Rattus rattus* Linnaeus 1758 – Black rat *Drosophila melanogaster* Macquart 1843 – fruit fly, vinegar fly (syn. *Sophophora melanogaster*) *Caenorhabditis elegans* Maupas 1900 – roundworm *Ovis aries* Linnaeus 1758 – sheep (**for development only**) *Gallus domesticus* Linnaeus 1758 – chicken (**for development only**) *Gallus gallus* – Red junglefowl (**for development only**) *Tetranychus urticae* Koch 1836 – red spider mite (**for development only**) ***Aquatic laboratory animals*** *Danio rerio* Hamilton-Buchanan 1822. Common name: zebrafish *Xenopus laevis* Daudin 1802. Common name: African clawed frog ***Cell lines*** Animal cell lines (including immortalized and primary cell lines) from organisms within the Kingdom Animalia, Phylum Arthropoda, and Phylum Chordata. Animal cell lines may include induced pluripotent stem cell lines and embryonic stem cell lines. Human cell lines (including immortalized and primary cell lines). Human cell lines may include induced pluripotent stem cells, but not human embryonic stem cell lines.

	Plants *Allium cepa* L. 1753. Common name: Onion; Taxonomic family: Amaryllidaceae *Arabidopsis thaliana* (L.) Heynh. Common names: Mouse-ear cress, thale cress, Arabidopsis. Taxonomic family: Brassicaceae *Brachypodium distachyon* L. Common name: purple false brome. Taxonomic family: Poaceae *Cicer arietinum* L. Common name: Chickpea; taxonomic family: Fabaceae *Lens culinaris* Medik. Common name: Lentil; taxonomic family: Fabaceae *Lolium multiflorum* Lam. Common names: Italian ryegrass, annual ryegrass. Taxonomic family: Poaceae. *Lolium perenne* L. Common names: perennial ryegrass or English ryegrass or winter ryegrass. Taxonomic family: Poaceae. *Lotus corniculatus* L. 1753 Common name: birdsfoot trefoil. Taxonomic family: Fabaceae *Lotus corniculatus* var. *japonicus* Regel 1864 Common name: Lotus japonicus Taxonomic family: Fabaceae *Medicago sativa* L. 1753. Common names: lucerne, alfalfa. Taxonomic family: Fabaceae *Medicago truncatula* Gaertn. 1791. Common name: Barrel medic. Taxonomic family: Fabaceae *Nicotiana benthamiana* Domin. 1929. Taxonomic family: Solanaceae *Nicotiana tabacum* L. 1753. Common name: Tobacco. Taxonomic family: Solanaceae *Pisum sativum* L. Common name: Garden pea, Taxonomic family: Fabaceae *Solanum lycopersicum* L. 1753. Common name: Tomato; taxonomic family: Solanacae *Trifolium occidentale* D. E. Coombe 1961. Common name: Western Clover, Taxonomic family: Fabaceae *Trifolium repens* L. Common name: White Clover: Taxonomic family: Fabaceae
Organism description	These risk group 2 organisms; • are clearly identifiable and classifiable according to genus, species, strain or other subspecific category; and • may be or may contain an infectious agent that is pathogenic to humans, animals, plants, or fungi; • may produce desiccation-resistant structures such as spores or cysts that can be normally disseminated in the air; • may not be characterised to the extent that its/their main biological characteristics are known; • may normally infect, colonise or establish in humans; • may be a mammalian cell line that contains active viruses or infectious agents normally able to cause disease in humans; • may be a whole animal, vertebrate or invertebrate including oocytes, zygotes, early embryos and other cells able to grow without human intervention into a whole animal; • may be a whole plant with reproductive structures; or • may be a whole plant without reproductive structures that will not be kept in

	closed containers.
Modifications	Modifications may include: • the introduction, deletion or modification of nucleic acids (DNA or RNA); • deletions and point mutations with or without the addition of genetic material; • the introduction of wild-type genes and mutants thereof (including deletion, substitution, and chimaeric mutant genes); and • the expression of multiple transgenes. Modifications may be made using: • plasmid or bacteriophage-based cloning, binary, and protein expression vectors; • genome editing technologies; • purified nucleic acids with or without an origin of replication that functions in the host organism • viral or transposon-based vectors, including replication-defective viral vectors such as lentiviral vectors, adenoviral vectors, and adeno-associated viral (AAV) vectors • replicative viral vectors (including baculovirus-based vectors. Vectors may contain regulatory elements including promoters, regulatory element binding sites, transcriptional activators, enhancers, terminators, multiple cloning sites, site directed recombination sequences, T-DNA border sequences; silencing elements (short interfering RNA, short hairpin RNA); and origins of replication. The vectors may also contain selectable marker genes; reporter genes; antibiotic resistance genes; transposons, recombination sequences and recombinases; retrotransposons or other transposable elements; protein targeting, localisation and secretory signals; internal ribosomal entry sites (IRES) solubility enhancement tags; protein purification tags, and affinity tags including epitope tags. Donor genetic material may consist of non-coding nucleic acids and/or nucleic acids that code for genes; gene regulatory elements; transposons, retrotransposons or other transposable elements; reporters or selectable markers. Donor genetic material may be sourced from plant, animal (including protozoa, zooplankton and phytoplankton), human, insect, bacterial, archaeal, fungal (including yeasts), viral, or synthetic sources. Modifications of Risk Group 2 organisms will only include nucleic acid that is sourced from Risk Group 1 microorganisms, or that is characterised to the extent that: (i) its sequence is known; and (ii) its gene function is understood; and (iii) its potential gene products are understood; and The modifications will not include; • the production of infectious particles normally able to cause disease in humans, animals, plants, or fungi;

- genes that encode for vertebrate toxins with an LD_{50} < 100 µg/kg;
- genetic material derived from Māori;
- genetic material derived from New Zealand native or taonga flora and fauna, unless consultation has been conducted with Ngāi Tahu representatives and, if appropriate, other iwi;
- genetic material from species listed by the Convention on International Trade in Endangered Species (CITES) unless appropriate permission has been gained;
- uncharacterised sequences from pathogenic microorganisms;
- modifications that increase the pathogenicity, virulence, or infectivity of the host organism to laboratory personnel, the community, or the environment;
- modifications that result in the GMO having a greater ability to escape from containment than the unmodified host organism;
- developments involving viral vectors whose host range includes human cells and that contain one or more inserted nucleic acid sequences coding for a product that can lead to uncontrolled mammalian cell proliferation or be toxic to mammalian cells, or both; or
- a pathogenic microorganism where the genetic modification results in resistance to antibiotics used for clinical, veterinary, agricultural, or horticultural treatment of infections caused by that microorganism.

In addition:

Modified microorganisms: may be grown by large-scale fermentation (i.e. culture volumes greater than 10 L) subject to the relevant requirements detailed in the University of Otago Containment and Quarantine Manual and inspection by the IBSC prior to commencing work.

Modifications to animals: may include the creation of genetically modified animals with new genotypes by the crossing of two genetically modified animals of different genotypes including different genetic modifications. In all cases, animals to be crossed will belong to the same species. Interspecific crosses will not be carried out under this approval.

Modifications to plants: may include the insertion of sequences derived from microorganisms capable of causing disease in plants; including promoters from Cauliflower Mosaic Virus, and border and regulatory sequences from *Agrobacterium tumefaciens* or *Agrobacterium rhizogenes* (i.e. left and right border sequences required for the transfer of DNA into plant cells; promoters and three-prime non-coding sequences derived from Ti or Ri plasmid genes). In each case the genetic material will be well characterized and is not expected to increase the pathogenicity of the modified organism.
Propagation of genetically modified whole plants by cloning or by generation from cultured plant cells or tissue culture is permitted only if the plant species are named as whole plants approved for genetic modification in this application.

Modifications to plants will not include:

- those that lead to the shedding of virus, virions, viroids, or prions.
- those that confer improved survival characteristics outside of the laboratory compared to the unmodified host organism

Modified animal and human cell lines to be imported or developed will be established cell lines obtained from commercial sources or from reputable scientific laboratories, or will be primary cell lines developed with appropriate ethical approval in the country of origin. Cell

	lines may include embryonic stem cell and induced pluripotent stem cell lines of animal species and induced pluripotent stem cell lines derived from humans, but will not include embryonic stem cell lines derived from humans. Modified human or animal cell lines may be used to regenerate tissues or organs but will not be used for the regeneration of whole animals.

Appendix 4: Organisms previously assessed by the EPA, ERMA or delegated IBSC

Organism to be considered	Existing HSNO approvals *
Risk Group 1 and 2 microorganisms as cultures or within samples derived from animals, plants and the environment	APP201737
Cell lines and cells derived from the animal Phylum Arthropoda	**Insect cell lines:** GMD04047, GMD08039, GMD05040, GMD05121, GMD05073, APP201411, GMD06012, APP201588, GMD05053, GMD04064, GMD04054
Cell lines and cells derived from the animal Phylum Chordata	**Mammalian, fish cell lines:** GMD05040, GMD08039, GMD05073, APP201411, GMD06012, APP201588, GMD05053, GMD04054
Cell lines and cells derived from the plant Class Angiospermae	**Plant cells/tissue:** GMD05053, GMD09017, GMD08047, ERMA200074
Odontaster validus	Deemed approval PRE009016
Sterechinus neumayeri	Deemed approval PRE09029
Drosophila melanogaster	GMD08071, ERMA200409, GMC05011
Xenopus laevis	GMD08040, GMD04002
GM Risk Group 1 and 2 microorganisms assessed on risk profile (as opposed to specifically named microorganisms)	APP201030, GMC04015
Mus musculus	APP202359, GMD04045, GMC01003,
Rattus norvegicus	ERMA200912, APP201238, ERMA200623
Rattus rattus	GMD08057, ERMA200504,
Ovis aries	APP202241
Gallus domesticus	GMD00151
Gallus gallus	GMD02044
Tetranychus urticae	GMD04065
Danio rerio	ERMA200880, GMD01083, GMC08014

Organism to be considered	Existing HSNO approvals *
Caenorhabditis elegans	GMD06019, ERMA200868, APP201122
Arabidopsis thaliana	GMD04046, GMC05006, GMD05103, ERMA200074, GMD02063
Medicago truncatula	ERMA200915, GMC08012, APP201575, GMD09017, GMD08047
Nicotiana tabacum	GMD00069, GMD01239, GMD05023, GMD09017
Allium cepa	GMD08056, ERMA200021, APP201459
Brachypodium distachyon	GMD08073, ERMA200127, ERMA200074
Cicer arietinum	No existing approval
Lens culinaris	No existing approval
Lolium mutiflorum	GMD08073, ERMA200127, ERMA200074
Lolium perenne	GMD09017, GMD08073, ERMA200127, ERMA200074, GMD08047
Lotus corniculatus	GMD09017, GMD08047,
Lotus corniculatus var. *japonicus*	GMD09017, GMD08047, GMC07005,
Medicago sativa	GMD08047, GMD02063, GMD09017
Nicotiana benthamiana	ERMA200074, GMD09017, APP201575
Pisum sativum	GMD08047, APP201459, APP201149
Solanum lycopersicum	GMD09017, APP201459, APP201149
Trifolium occidentale	GMD08047, GMD09017
Trifolium repens	GMD08056, GMD09017, GMD08047, GMD02063

* Not an exhaustive list of approvals for each organism, organism type (i.e. cell lines)

Appendix 5: MPI comments

General	▪ The applicant holds a large number of HSNO approvals to (a) import into containment low-risk new organisms, including genetically modified and unmodified organisms, and (b) develop low-risk GMOs in containment. Many of these are IBSC approvals, some of which have been amended over time, for various reasons (e.g., expand scope). ▪ Because of the large number of approvals, a situation has developed whereby the same low-risk host organism is described in multiple low-risk approvals with varying purposes. The applicant believes that this has resulted in an increased administrative burden for little mitigation in risk(s). In addition, the applicant believes that the situation has increased the administrative burden on managing compliance to the defined scope of these approvals, for both internal audits and external (MPI) audits. ▪ To address this situation, MPI understands that the applicant is applying to the EPA to replace all of its low-risk HSNO approvals (import and development) with three approvals, the purposes for which shall be streamlined into one – for research and teaching. ▪ The applicant is also applying to 'future-proof' further research and teaching work through applying to import an additional 17 host organisms, many of which have previously been assessed by the EPA or a delegated IBSC. ▪ The applicant is proposing that, if approved, one set of containment controls apply for all three approvals; these controls being outcome-focused (results-based), rather than prescriptive, as most of the controls applying to the existing low-risk organisms at present.
Section 2.3	▪ The applicant has highlighted the fact that many of the existing approvals have a restricted purpose and that this has resulted in a limitation of the research that can be conducted, either in developing organisms or with the developed organisms themselves. ▪ Noting that the Schedule in the HSNO (Low-Risk Genetic Modification) Regulations 2003 identifies those developments that are not low-risk genetic modifications, MPI urges the EPA to consider how the applications, if approved, will ensure that the permitted developments do not include those within that Schedule. ▪ The applicant has highlighted that single low-risk organism import and development approvals with one set of controls will facilitate and simplify both the internal and external auditing processes that ensure compliance. While MPI agrees that there will be a degree of facilitation and simplification, it has reservations about how much of a degree that will be. The following points are relevant. **- Effectively auditing to outcome-based controls may take some time to achieve -** A single set of outcome-focused controls means that internal and external auditing can only be effectively carried out by auditing to the Quality Management System (QMS), which identifies and describes the management structure, policies, procedures and operational methodology put in place to meet those outcome-focused controls. Instead of auditing against the prescriptive-based controls, currently within most of the current HSNO approvals, the prescription has to be within the QMS (proposed controls 3 and 4). This then requires that the QMS details all the prescriptive requirements for each organism. - **There is an increased reliance on maintaining an effective QMS under an outcome-based controls system –** While the QMS should provide sufficient operational detail to identify how the controls of the current suite of low-risk organism approvals will be met, MPI cannot currently verify

	that the applicants QMS does this. MPI has conducted one audit of approvals APP201030-33 during the period of the trial. While the applicant has stated that the trial was successful, it failed the audit because the QMS was inadequate. There will need to be a substantive amount of work done on improving the QMS if the applications are approved. However, this work will still need to be done even if they are not. - **Internal auditing against the QMS will involve more work –** Because the QMS will be more detailed and comprehensive and there is greater reliance on internal audits, MPI will be looking for evidence that the prescriptive requirements of the QMS are effectively applied to each organism in the internal audit process. - **The applicant will need to operate dual compliance systems –** While the replacement of the existing low-risk organism approvals with the three that are proposed in these applications may facilitate and simply aspects of the compliance regime, the applicant will still need to ensure adequate systems are in place for meeting the requirements of the various standards the facility is approved to as a transitional and containment facility. This includes the requirements for non low-risk organisms, unwanted organisms and other risk goods imported under the Biosecurity Act. Therefore, the QMS will still need to address these requirements, as well as those for low-risk organisms. ▪ In short, it is not entirely clear to MPI that the replacement of the current low-risk organism approvals with the three approvals applied for will *'make life significantly easier'* since the applicant still has a degree of work ahead in developing a more robust QMS to meet outcomes. While the current work involved in complying with the various 'purposes' of the existing low-risk approvals will disappear, the applicant will still need to ensure that the requirements of the Schedule in the HSNO (Low-Risk Genetic Modification) Regulations 2003 are complied with. ▪ The applicant has stated that, if the applications are approved, they will replace all existing low-risk organism import and development approvals. However, it appears that this will be by choice, rather than a requirement, since the proposed controls do not include a provision (if this is permitted?) to expire those existing approvals. MPI advises the EPA to consider this.
Section 2.4	▪ The applicant has attached a Management Plan (Appendix 3) showing how the proposed outcome-based controls in Appendix 2 will be met. However, because MPI, as the enforcement agency, is requiring more evidence-based verification to be confident that compliance is being met, the Management Plan only gives a high-level overview of the actions and expectations of compliance. There will need to be substantially more work into identifying how compliance is verified and what evidence will be provided to show that. Noting that the applicant failed the audit during the trial period, it has good systems in place and MPI is confident that, further work will 'bring it all together'. The following points should be noted: - Although little detail is provided, the Management Plan describes what will be done but not what evidence will be provided to demonstrate that it is effective – this is why the prescriptive detail of the QMS becomes so important to show that the outcome-based controls will be met. - Control 2 – Because the control subverts the accountability of the operator, as mandated under the Biosecurity Act, the way the control is to be met only assumes that the operator is responsible (through delegation) for ensuring compliance (see later comment on Control 2). - Control 3 – The specified procedures must be shown to be effective and the applicant will need to provide the evidence to show this. While new laboratories will be built to international best practice and older laboratories will be upgraded to meet 'this standard', no standard is specified and it remains uncertain who will decide that the proposed 'best practice' is effective.

	▪ If the applications are approved, MPI will expect a detailed expectations plan to support the Management Plan, preferably through, and supported by, a comprehensive QMS.
Section 3.1	▪ The new organisms intended to be imported and/or developed are extremely extensive and broadly grouped. Without being more specific about the actual species of organism to be imported, MPI can provide no information to the EPA on risk. Because the applications are so generic, MPI will need to undertake a risk assessment of each imported new organism upon application for a Permit to Import. ▪ If the applications are approved, MPI will expect the applicant to provide adequate evidence showing that the imported organisms meet the criteria for either a Risk Group 1 or 2 organism.
Proposed controls	▪ Control 2 – Under the Biosecurity Act, the operator is ultimately accountable and responsible for the control and management of a containment facility. Control 2 extends that responsibility to include any (other) organisation, entity or person(s) with responsibility for the ownership, control and management of the containment facility, including Board members and/or directors). The applicant has included in Control 2 in Appendix 3 that *'The University of Otago must ensure compliance with the controls of this approval'*. Note that this addition is not included in Control 2 of the Controls attached to the applications. MPI believes that the proposed control confuses the provisions of accountability and responsibility for new organisms and the containment facility. It would be more appropriate that control 2 addresses the organisation, entity or person(s) which have responsibility for the new organism, rather than the containment facility. That would then leave the accountability and responsibility for the containment facility to the provisions of the Biosecurity Act, where it belongs. Suggest amending control 2 to the following: *The organisation, entity or person(s), including Board members and/or directors, responsible for the approved organisms must ensure compliance with this approval.*

Environmental Protection Authority
Te Mana Rauhī Taiao

Level 10, 215 Lambton Quay, Wellington 6011, New Zealand

New Zealand Government