ENVIRONMENTAL RISK MANAGEMENT AUTHORITY DECISION

Amended under s67A on 18 November 2006, 23 August 2007 and 2 November 2009

18 August 2003

Application code	GMC03001
Application type	To import into containment new organisms under section 40(1)(a) of the Hazardous Substances and New Organisms (HSNO) Act.
Applicants	The University of Otago, Genesis Research & Development Corporation and Malaghan Institute of Medical Research
Purpose	A generic application to allow for importation of laboratory mice with specific genetic modifications to be used in a range of studies of gene or cell function and as models for human diseases.
Date received	4 February 2003
Consideration period	14 May – 4 August
Considered by	A Committee of the Genetically Modified Organisms Standing Committee of the Environmental Risk Management Authority (the Committee).

1 Summary of Decision

The application to import into containment genetically modified mice is **approved,** subject to the **organism description** (refer **appendix 1)** and with **controls** (refer **appendix 2**), having been considered in accordance with section 45(1) and other relevant provisions of the Hazardous Substances and New Organisms (HSNO) Act 1996 and the HSNO (Methodology) Order 1998 (the Methodology).

Note that, the approval is subject to additional controls above PC2 Vertebrate containment (controls 6.1 –6.3, **appendix 2**).

The organisms have been given the following generic identifier for the ERMA New Zealand Organism Register:

> *"Mus musculus* Linneaus *1758 modified by targeted or random insertions of non-infectious gene constructs that fall within the limits of the organism description in application GMC03001"*

A unique identifier for each specific mouse strain to be imported under this approval will be added to the ERMA New Zealand Organism Register at a later date, after verification, but prior to importation. Once verified by ERMA New Zealand and added to the ERMA New Zealand Organism Register, any person may import that strain of mouse provided that they meet the containment requirements and any MAF Biosecurity Authority requirements.

2 Legislative Criteria for Application

The application was lodged pursuant to section 40(1)(a) of the HSNO Act. The decision was determined in accordance with section 45, taking into account additional matters to be considered under section 44, and matters relevant to the purpose of the HSNO Act, as specified under Part II of that Act. Unless otherwise stated, references to section numbers in this decision refer to sections of the HSNO Act.

Consideration of the application followed the relevant provisions of the Methodology with particular regard to clauses 12 (dealing with assessment of risks and costs) and 13 (dealing with assessment of costs and benefits). Unless otherwise stated, references to clauses in this decision refer to clauses of the Methodology.

The terms 'risks', 'costs' and 'benefits' used in the Methodology (and this decision) are analogous to the terms 'adverse effects' and 'beneficial effects' used in section 45 of the HSNO Act under which the application is determined. The Methodology functions as a decision making framework.

2.1 Legal and Jurisdictional Issues

The Committee gave consideration as to whether or not it was within the Committee's jurisdiction to consider an application for importation into containment which was generic in its description of the organism.

The Committee considered the relevant statutory provisions including sections 20 and 40 of the HSNO Act and concluded that there is nothing in the HSNO Act to preclude the consideration of this application, provided that the key matters within that Act were addressed and the risks and costs of the organisms could be assessed.

The extent of the range of possible genetically modified mice encompassed by the application introduced a very high level of uncertainty about the organism and therefore the ability to confidently weigh risks and costs and benefits under section 45 of the Act. An organism description was developed which had the effect of delineating the range of organisms so that the potential risks, costs and benefits could be identified and assessed.

Risk characteristics were then established in accordance with clause 33 of the Methodology, taking into account the containment regime. Finally the combined impact of risks, costs and benefits was evaluated in accordance with clause 34 of the Methodology. Benefits were weighed against the adverse effects in terms of section 45(1)(a)(ii) of the HSNO Act and clause 27 of the Methodology; and the adequacy of containment considered in accordance with section 45(1)(a)(iii) of the HSNO Act, in order to determine whether the application should be approved or declined.

Section 20 of the HSNO Act requires the Authority to maintain a register of all applications. The register must contain a sufficient description of the organism to enable unique identification of that organism to occur with regard to the requirements of section 20(2)(b) of the HSNO Act, the description of allowable organisms is broad in that it encompasses mice with a range of modifications, but at importation each genetically modified mouse will be described, verified as being in accordance with the allowable organism description and uniquely identified and recorded on the register. Thus the Committee decided that the requirements of section 20(2), in relation to maintaining of a register have been adequately met. A control has been set requiring

reporting of particular constructs prior to importation (refer **appendix 2**, additional control 6.1).

3 Application Process

3.1 Application Receipt

The application was formally received on 4 February 2003 and verified by ERMA New Zealand as containing sufficient information to proceed on 4 February 2003. A waiver was granted to reduce the time from 10 working days to 4 for the distribution of the E&R report, in accordance with section 59(5) of the HSNO Act. Two further waivers were granted to extend the decision notification date. The first waiver was sought on the 8 July 2003 to extend the notification date to the 30 July 2003. The second waiver sought to further extend the notification date by 10 days to 13 August 2003. The Committee then elected to have a further consideration on the 4 August 2003, due to the refinement of the organism description made in the earlier considerations, this further extended the notification date to 25 August 2003.

It was considered there was unlikely to be significant public interest in this application. Therefore, the application was not publicly notified, in accordance with ERMA New Zealand policy.

3.2 Consultation with Departments and Crown Entities

In accordance with clauses 2(2)(e) and 5 of the Methodology and section 58(1)(c) of the HSNO Act the Department of Conservation (DoC) and Ministry of Agriculture and Forestry (MAF) Biosecurity Authority were invited to comment on this application.

DoC raised the following three points (from section 1.10 of the Evaluation & Review Report, "E & R Report").

"…The background information indicates that the mice are not necessarily sourced from specific pathogen free facilities. Provided that ERMA is confident that the 30 day quarantine period will be sufficient to ensure all infectious diseases are expressed the department would have no concerns…"

"…Provided that the organism description is sufficiently detailed to ensure that imported GM mice meet either category A or B genetic modifications (as described in the HSNO Low Risk Genetic Modification Regulations), then the department has no concerns with this".

"…As long as containment is not breached, there does not appear to be any significant conservation risks and costs associated with these application".

MAF Biosecurity Authority raised no new concerns other than a previously provided comment about general mouse import applications in an Email dated 2 August 2002 (quoted in section 1.11 of the E & R report):

"…We don't need to see all of the mouse applications but would like to see those that are novel or are associated with infectious agents"

3.3 Information Available for Consideration

The information available for the consideration was as follows:

- The application prepared by the applicant.

- ERMA New Zealand prepared an Evaluation and Review (E&R) Report to assist and support the Committee's decision-making. The E&R Report consolidated and evaluated the relevant information in a format and sequence consistent with the decision making requirements of the HSNO Act and Methodology. Recognised techniques were used in identifying, assessing, and evaluating the relevant information, as required under clause 24 of the Methodology. These techniques are based on internal procedures as specified in the ERMA New Zealand Technical Guides. The documents available for the preparation of the E&R Report were the application (including copies of each institutions containment manuals) and published references as cited in the application and comments provided by those agencies notified of the application (section 3.2).

- The Committee sought advice from an external expert, Professor Garth Cooper, appointed in accordance with clause 17 of the Methodology. As required by clause 18, the applicant was informed of the Committee's intention to appoint an expert and given opportunity to comment on the advice received.

- At the Committee's behest ERMA New Zealand also consulted an ecologist at Landcare Research during the refinement of the organism description during the consideration period.

3.4 Decision Making Committee

The application was considered by the Genetically Modified Organisms Standing Committee of the Authority appointed under Schedule 1 of the HSNO Act and in accordance with the delegation made under section 19(2)(b). The Committee comprised of the following members: Ms Jane Lancaster (Chair), Dr Lin Roberts and Professor George Clark.

4 Consideration

4.1 Purpose of the Application

The University of Otago, Genesis Research & Development Corporation, and Malaghan Institute of Medical Research sought approval to import into containment a range of genetically modified (GM) mice that contain specific genetic modifications; under section 40(1)(a) of the Hazardous Substances and New Organisms (HSNO) Act 1996.

The purpose of this work is to allow for importation of laboratory mice with specific genetic modifications to be used in a range of studies of gene or cell function and as models for human diseases. The Committee considered the purpose of the application fell under sections 39(1)(h) of the HSNO Act 1996: *such other purposes as the Committee thinks fit*.

4.2 The Sequence of Steps in the Consideration

In accordance with clause 24 of the Methodology, the approach to consideration adopted by the Committee was to first examine the scope of the application, and the range of organisms applied for, then to look sequentially at identification, assessment and evaluation of risks, costs and benefits. Qualitative scales used by the Committee to measure likelihood and magnitude of risks, costs and benefits are provided in **appendix 3** of this decision.

In assessing risks and costs, issues affecting the adequacy of the containment regime and potential for population establishment and population eradication were considered (as required by section 37 and 44 of the HSNO Act and clause 10(e) of the Methodology). The containment regime was considered in the context of a risk management regime for controlling the identified risks and costs (clauses 12(d) and 24). In doing so, the Committee set controls to satisfactorily provide for the matters in the Third Schedule (Part I) of the HSNO Act. It was then considered whether or not there were any residual risks that required further consideration.

Benefits associated with this application were considered in accordance with Methodology clauses 9, 10, 13 and 14 and section 6(e) of the HSNO Act.

4.3 Scope of Application and Organism description

This application sought approval to import mice strains (*Mus musculus*) with a broad range of modifications. This included strains of mice that have not been developed yet, and may not be in development for some time.

The generic nature of the application created some significant initial difficulties for the Committee. A decision can only be made at one point in the process – there is no scope for later secondary decision making processes once more information on a specific importation is received. The decision must therefore be based on an assessment of the full range of potential risks, costs and benefits of the full range of organisms potentially covered by the application. The Committee obtained further advice on the range of potential risks and costs from Professor Garth Cooper.

The Committee found there were too many uncertainties about the range of risks and costs that could be associated with the possible range of organisms covered by the original organism description submitted by the applicant to allow meaningful risk assessment. The Committee therefore invited the three applicant organisations to further particularise or confine the range of organisms covered by the application to eliminate some areas of potential risk, but the applicants did not make any such refinement. The Committee therefore spent considerable time more precisely delineating the range of organisms so that the range of potential risks and costs, costs and benefits could be identified and evaluated.

The potential range of organisms to be covered by the decision was defined in such a way that, if the application was approved, the decision on whether any specific genetically modified mouse being considered for importation conformed with the organism description could be made on a **verification** basis, and did not require a secondary risk assessment process.

Independent authoritative verification that any prospective genetically modified mouse to be imported conforms to this approval is not a function that can realistically be undertaken by MAF Biosecurity Authority at the border. Therefore, the Committee has imposed, by way of controls (**appendix 2**, additional control 7.1), a mechanism requiring the importer to obtain such verification from ERMA New Zealand prior to importation. The verification process functions as a mechanism whereby persons with appropriate knowledge and expertise confirm (or otherwise) that the specifications of the organism, as described in this approval (organism description is found in **appendix 1**), have been met.

The following paragraphs outline the changes made to the organism description by the Committee during the consideration process.

The Committee raised concerns that the broad nature of this approval meant that genetically modified mice could potentially be sourced from any facility, raising the possibility that mice could be imported that could bring in infectious or associated organisms.

To address this risk the Committee inserted the following phrase into the organism description, "The animals must be certified specific-pathogen-free and may be sourced from commercial farms, research institutes or private researchers, provided these sources carry out regular monitoring of known infectious agents".

Many of the residual risks and costs the Committee identified in the consideration stemmed from potential unexpected effects from genetic modification (discussed in section 7.2.6). Because of the wide range of potential modifications that could occur under the organism description, the Committee felt the degree of uncertainty was large. The uncertainty stemmed from two sources. Firstly, the Committee needed to identify all the modifications and anticipate the potential risks and costs associated with them. Secondly, the scientific uncertainty associated with the potential risks and costs (particularly unexpected effects from genetic modification as by their very nature, they introduce a larger degree of uncertainty).

In turning their minds to this risk, the Committee chose to focus on the phenotypes of the genetically modified mice that could be imported under this application. By focusing on phenotypes, the Committee focused on features that are more readily demonstrated and most relevant to the risks they wished to exclude.

The Committee chose to exclude phenotypic features from the organism description that they considered more likely to give the genetically modified mouse selective advantages, or present a higher level of risk to: the environment, Māori culture; the economy; human health and safety; or society and the community, in the event of an escape. On this basis, the Committee excluded from the organism description phenotypes (a) to (d) in **appendix 1**. The reasons for these exclusions from the organism description will be elaborated and discussed in more detail, in the context of risk and risks and costs, in section 7 of this decision.

5 Identification of risks and costs

The Committee identified risks and costs related to the application in accordance with clauses 9 and 10 of the Methodology, which incorporate sections 5, 6, 8 and 43 of the HSNO Act.

The Committee considered Section 7 of the E&R Report when carrying out an assessment of the adverse environmental effects. In addition, they also consulted an external expert for advice (refer to section 3.3).

Risks and costs were identified in relation to potential impacts on the:

- Environment;
- Māori culture;
- Economy;
- Human health and safety;
- Society and the Community.

The following table (Table 1) lists the risks and costs identified by the Committee and subsequently assessed under the relevant area of impact:

Table 1: Risks and costs and Areas of impact identified by the Committee

Sources of Risk	**Risk**	**Area of impact**	**Further discussion**
Importation of animal diseases or associated organisms, either separable or inseparable	Associated organisms could potentially cause animal or human disease and/or other effects to laboratory workers and to members of the public and to other animals in the event of escape.	Environment and/or human health and safety	Section 7.2.1
Genetically modified mice producing toxins	The genetically modified mice could potentially be toxic to laboratory workers or to members of the public and other animals in the event of escape.	Environment and/or human health and safety	Section 7.2.2

Sources of Risk	Risk	Area of impact	Further discussion
Genetically modified mice producing infectious viral particles or viruses	The genetically modified mice could potentially spread viral particles causing disease to laboratory workers or to other members of the public in the event of escape.	Environment and/or human health and safety	Section 7.3.2
Imported genetically modified mice being reproductively more efficient than wild type laboratory mouse	Could breed more efficiently and in the event of an escape, result in large populations of genetically modified mice	Environment	Section 7.2.4
Risk of genetically modified mice having a greater ability to survive outside of containment	In the event of escape, could potentially damage crops and native species in the environment	Environment and/or human health and safety	Section 7.2.5
Genetically modified mice being imported that have unexpected effects from transposable elements	Consequences uncertain, but could potentially generate unexpected phenotypes with impact on laboratory workers or members of the public or the environment in the event of escape.	Environment and/or human health and safety	Section 7.2.6.1
Genetically modified mice being imported that have unexpected effects from insertional mutagenesis	Consequences uncertain, but could potentially generate unexpected phenotypes or Activate endogenous viruses with impact on laboratory workers or members of the public or the environment in the event of escape.	Environment and/or human health and safety	Section 7.2.6.2

Sources of Risk	Risk	Area of impact	Further discussion
Genetically modified mice being imported that have unexpected effects from recombination	Consequences uncertain, but could potentially Activate a virus that may cross the species barrier with impact on laboratory workers, or members of the public or the environment in the event of escape.	Environment and/or human health and safety	Section 7.2.6.3
Genetically modified mice being imported that over-express cytokines	Consequences uncertain if breed with population of wild mice.	Environment and/or cultural	Section 7.2.6.4
The risk of genetically modified mice being imported that carry DNA of human origin	Potentially significant adverse cultural effects.	Cultural	Section 7.4

6 Containment

In assessing risks and costs, the Committee considered issues affecting the adequacy of the containment regime (in accordance with section 45(1)(a) of the HSNO Act); the potential for population establishment and population eradication (sections 37 and 44 of the HSNO Act and clauses 10(e) and 10(f) of the Methodology); and other matters in order to give effect to the purpose of the HSNO Act (section 45(2)(b)). Risk management techniques were used in relation to the identified risks and costs (clauses 12(d) and 24 of the Methodology). As such, the assessment of risks and costs (refer to section 7 of this decision) was taken into account in setting the containment requirements that are discussed in this section.

6.1 Ability to Escape from Containment

The controls imposed by this approval (as specified in **appendix 2**) address the matters detailed in the Third Schedule Part I of the HSNO Act: Matters to be addressed by containment controls for importing, developing or field testing of genetically modified organisms under the Act, plus other controls to give effect to the purpose of the Act. These controls incorporate requirements for the management of risks and costs (under clauses 12(d) and 24 of the Methodology) posed by the genetically modified mice subject to this approval. The controls have been imposed to ensure that exposure of laboratory workers and other persons, and the outside environment, to risks and costs posed by the organisms is negligible.

The basis for the containment regime is that the imported genetically modified mice shall be held in a containment facility that is registered and operated in accordance with the MAF Biosecurity Authority/ERMA New Zealand Standard 154.03.03 (Containment Facility for Vertebrates) PC2. General containment requirements for the safe management of vertebrates in the laboratory environment are addressed in this Standard, with cross-reference to detailed physical containment (PC) requirements in the Australian New Zealand AS/NZ Standard (refer control 1.2, **appendix 2**). The controls in **appendix 2** emphasize and/or clarify how the above containment standards address the matters required under the Third Schedule (Part I) of the HSNO Act.

The Committee also considered the likelihood of genetically modified mice escaping during transit (i.e. during import or transfer between facilities) or from the containment facilities. The Committee took into account sections 6.9 to 6.15 of the E & R Report. The Committee noted that organisms imported into containment are also controlled by the Biosecurity Act 1993. The applicant, having obtained verification from the Authority for the importation into containment of a new organism, would require:

- an import health permit (including ERMA approval of the organism); and
- an animal health certificate from the registered Specific Pathogen Free (SPF) Animal Facility or laboratory of purchase; and
- transportation to be approved by the Chief Veterinary Officer; and,
- on arrival imported mice to be placed into a quarantine room for 30 days; and,
- any animal showing signs of sickness or death, must be reported to MAF.

The Committee also noted the general requirements for transport of vertebrates, including their transfer between containment facilities, are covered under sections 4.4 and 4.6 of the Vertebrate Standard 154.03.03. The minimum requirement is for animals to be transported and held in cages which meet International Air Transport Association (IATA) Live Animal Regulations. Section 4.6 of the Vertebrate Standard 154.03.03 addresses the supervisor's responsibilities regarding transfer of animals between containment facilities. The supervisor is an enforcement officer appointed under the Biosecurity and/or HSNO Act, and must supervise operation of containment facilities (including inspections and response to non-compliance). The supervisor must be satisfied that the method of transfer ensures that animals cannot escape and must issue a written authority for any such transfer. Other conditions of transfer are:

- transfer occurs under MAF/ERMA standard 154.03.03 at PC2 level.
- in addition to the facility staff, only trained staff have access to the facility.

Within the containment facility, mice are held singly or in groups in cages in rooms fitted with rodent barriers on the doors. Drains are covered by a mesh or grill to prevent rodent escape or entry.

The Committee considered the skills and experience of the organisations involved, as well as the current public climate related to contained research Activities. The Committee has no reason to think that the risk of deliberate removal of organisms by facility workers, or external saboteurs, would be any higher for the research Activities associated with this application, than for other similar applications. There have been no reported incidents of genetically modified mice being deliberately removed from containment in New Zealand.

The Committee has imposed three additional controls (refer **appendix 2**: Section 6 "Additional controls") to manage risks and costs associated with this application. The Committee considered that, taking into account the organism description (refer **appendix 1**) and containment controls it imposed, it was very unlikely that mice would escape the containment.

6.2 Ability of Organism to establish a self-sustaining population and the ease of eradication

In accordance with section 44 and 37 of the HSNO Act the Committee considered the ability of the organism to establish undesirable self-sustaining populations, should it escape from containment, and the ease with which such populations could be eradicated.

The Committee recognises that should a genetically modified mouse/mice escape from the containment facility it is unlikely to be recovered. It is generally accepted that mice bred and raised in sheltered conditions are unlikely to survive in the external environment for more than a few days. In accordance with clause 12(e) of the Methodology, the Committee recognised the scientific uncertainty attached to this contention, as it would depend on whether the genetically modified mouse gained a selective advantage from the modification. The Committee considered that if genetically modified mice did escape and breed with endemic mice, the distinctive genetic traits of the genetically modified strains could be lost, or fixed in the population during subsequent breeding depending on any selective advantage conferred on the mice containing them.

In evaluating these matters, the Committee took into account the nature of the organisms. The organism description was developed to exclude genetically modified mice that demonstrate evidence of increased survival ability, increased aggressiveness, enhanced reproductive success or increased breeding capacity when compared to unmodified laboratory mice. The Committee considers that in the very unlikely event of accidental (or deliberate) removal of genetically modified mice and breeding with wild mice, that they would very unlikely to confer any selective advantage for survival in the wider environment.

The Committee is satisfied that the controls within this decision address and limit the possibility of escape and subsequent establishment of self-sustaining populations outside of containment.

7 Assessment of Risks and Costs and Benefits

7.1 Characteristics of the organism

In assessing the nature of the risks and costs, the Committee considered the characteristics of the genetically modified mice allowable under the organism description and the likely potential genetic modifications allowable under the organism description. The Committee notes the assessment of organism characteristics provided in section 2 of the E&R Report. The Committee also noted that genetically modified mice developed under the Low Risk Regulations (B)(b)(ii)(C) and/or B(b)(ii)(B) of the

HSNO (Low-Risk Genetic Modification) Regulations 1998[1] (the Low-Risk Regulations), would be eligible for consideration via the rapid assessment route if they were developed in New Zealand. Genetically modified mice meeting the requirements of Category (C) of the Low-Risk Regulations are excluded from the organism description. The Committee noted that some phenotypes were identified by the applicant (more agile mice, page10; mice with increased reproductive output, page 12) and the external referee as having greater risk, but that these were not identified or specifically excluded under the low risk criteria of the Low-Risk Regulations. The Committee also noted that (B)(b)(i)of the Low-Risk Regulations pertains to a risk assessment process, and thus to use the Low-Risk Regulations to specify the organism description, would be to invoke a secondary decision making process at a later stage. Therefore the Committee used the Low-Risk Regulations to inform the organism description, but not to solely specify it.

The Committee considered and assessed the specific risks and costs identified in section 5. Other risks and costs that are mentioned within the E&R Report are not further elaborated in this decision; the Committee considered them insignificant and concurred with the analysis in the E&R Report.

The Committee also considered the revised organism description in **appendix 1**, and the impact the revisions have in assessing and evaluating the adverse effects and beneficial effects.

7.2 Adverse environmental effects

7.2.1 Inseparable or associated organisms

In assessing risks and costs, the Committee considered the nature of organisms that might be associated with the import of genetically modified mice. The Committee concurs with the assessment provided in sections 7.41 and 7.42 of the E&R Report, that any pathogen or parasite associated with the genetically modified mice (i.e. separable or inseparable) is very unlikely to pass undetected through the quarantine regime required by MAF Biosecurity Authority (in accordance with an Import Health Standard issued under the Biosecurity Act). In accordance with clause 12(c) of the Methodology, the Committee assessed the risk as a combination of magnitude of the adverse effect and the probability of occurrence using table 4 (**appendix 3**).

As outlined in section 4.3, the Committee considered the generic nature of this approval and noted that genetically modified mice could potentially be sourced from any facility. In order to ensure that mice were sourced from only reputable suppliers, the Committee inserted the following sentence into the organism description:

"The animals must be certified specific-pathogen-free and may be sourced from commercial farms, research institutes or private researchers, provided these sources carry out regular monitoring of known infectious agents".

[1] The Committee recognized that the Hazardous Substances and New Organisms (Low-Risk Genetic Modification) Regulations 1998 were revoked on the 31st July 2003 and replaced by the Hazardous Substances and New Organisms (Low-Risk Genetic Modification) Regulations 2003. The Committee considered that as the majority of their consideration of this application was took place under the 1998 Regulations that these would referenced in this decision

The Committee was satisfied that the controls and the organism description reduced the risk of mice being imported with associated organisms to a negligible level.

The Committee also evaluated this risk according to clause 13 of the Methodology. The Committee considered that there may be costs associated with genetically modified mice being imported with associated organisms. The cost is likely to be monetary and be borne by the applicant or MAF Biosecurity Authority, as any mice that are imported with inseparable or associated organisms will be quarantined and either treated or destroyed.

7.2.2 Toxins

The Committee identified and discussed the risks and costs that genetically modified mice could be imported that contain sequences that result in the production of vertebrate toxins (E&R Report sections 1.3, 1.4, 2.3, 7.15, 7.43 and 7.47). In accordance with clause 12(a) of the Methodology, the Committee considered the risks and costs that potentially result from the genetically modified mice producing toxins. Firstly, people who handle the mice could potentially become ill through exposure to the toxin. Secondly, in the event of escape, any animals that came into contact with the toxic mice might become ill through exposure to the toxin.

The Committee noted these risks and costs and further noted that sequences that produce high level toxins or low levels of potent toxins are prohibited by the organism description. The Committee further considered the event of vertebrate toxins being inadvertently expressed in the genetically modified mice. As required by clause 12(b) of the Methodology, the Committee considered the probability and magnitude of the risks and costs associated with this event. It is assumed that any toxic effects in the mice are likely to be inadvertent, the probability is considered to be very unlikely and the magnitude of the risks and costs are considered to be minimal, given that they would be expected to affect only the modified animal and in the event of an escape, confined to the individual and/or if interbreeding occurred, be confined to a local area and self-limiting.

It is also assumed that such inadvertent ill effects would be exhibited in the phenotype and picked up in the course of regular monitoring of the mouse containment facility. Given the containment regime, the organism description and controls imposed by this decision, the Committee considered it very unlikely that toxins or other noxious compounds inadvertently and unexpectedly produced by genetically modified mice would enter the uncontrolled environment.

In accordance with clause 12(c) of the Methodology, the Committee assessed the risk as a combination of magnitude of the adverse effect and the probability of occurrence. Therefore, the Committee concluded the level of overall risk was insignificant and that no additional controls were necessary for managing the risks and costs, in accordance with clause 12(d) of the Methodology.

As required by clause 12(e) of the Methodology, the Committee noted, the degree of uncertainty surrounding the likelihood of a sequence giving rise to a toxic effect within a mouse and uncertainty surrounding the magnitude of any adverse effect as this would depend on the level of expression of the toxin and the effects it had on the genetically

modified mouse, or in the event of escape, other animals or people that the genetically modified mouse came into contact with.

In accordance with clause 25 of the Methodology, the Committee noted the uncertainty of the scientific evidence of the likelihood of a sequence to give rise to toxic effect within the mouse. As required by clause 29 of the Methodology, the Committee considered the materiality and significance of the scientific uncertainty to the application. The Committee considered that although uncertainty surrounded likelihood of a sequence to give rise toxic effects on the mouse and the severity of these effects on the mouse, it noted that it was likely to be confined to the genetically modified mouse affected and not transmitted to other mice. In addition, toxic effects on mice are likely to be picked up in the regular course of monitoring the genetically modified mice, required by the containment regime. Therefore, in the context of the application and given that sequences that produce high level toxins or low levels of potent toxins are prohibited by the organism description, the Committee considered that the scientific uncertainty was material to the application, but was not of large significance.

In accordance with clause 13 of the Methodology, the Committee also considered the likely cost of genetically modified mice being imported that produce toxins. The Committee considered that costs could potentially be both monetary and non-monetary. Monetary costs could arise if mice are imported producing toxins, become ill and die. In this event, the Committee considered this cost would be borne by the applicant. Non-monetary costs could arise in the event of the genetically modified mouse/mice escaping into the environment; they could potentially harm other animals or people that came in contact with them. Given that the probability of genetically modified mice escaping into the environment and having an adverse effect on the environment was considered by the Committee to be very unlikely, it is considered that costs associated with this occurrence are also unlikely to eventuate. The Committee found it difficult to give the magnitude of any costs or the expected value (clause 13(b) of the Methodology).

The Committee recognised the potential for risks and costs to human health in the event that mice did produce toxins. This is discussed later in section 7.3 of this decision.

7.2.3 Expression of viral particles

The Committee identified and discussed the risk of Active viruses being produced in an imported genetically modified mouse as discussed in the E&R Report (sections 1.3, 1.4, 2.3, 7.14, 7.43 and 7.46). The Committee discussed two pathways for the expression of viral particles. Firstly, that sequences encoding viruses may be deliberately put into a mouse, or secondly, that while inserting sequences inadvertent Activation of a retrovirus could occur.

In accordance with clause 12(a) of the Methodology, the Committee considered the potential for mice to potentially spread viral particles causing disease in animals and humans. This event could affect laboratory workers in close contact with the mice, or if the mouse escaped the containment facility (very unlikely) any other members of the public or animals that came into contact with it. The effect would also depend on the type of virus particles produced.

The Committee noted that sequences that result in the production of infectious viral particles or viral packaging signals are excluded by the organism description and in

particular by the requirement that donor genetic material does not meet the requirements criteria of category (C) of the Low-Risk Regulations, given that category (C) is excluded from the organism description. Given this, it is assumed that any viral particles produced by genetically modified mice are likely to be inadvertent. Therefore, as required by clause 12(b) of the Methodology, the Committee considered the probability of the occurrence of viral particles being inadvertently expressed in the imported genetically modified mouse to be very unlikely, and the magnitude of such an event uncertain as it would depend on the type of virus generated.

It is assumed that in the event of a virus being generated that ill effects would be exhibited in the phenotype and picked up in the course of regularly monitoring of the mouse containment facility. As required by clause 12(c) of the Methodology, the Committee assessed the probability and magnitude of the adverse effect occurring. The Committee concluded that the risk to the environment presented by genetically modified mice expressing viral particles was insignificant.

The Committee then considered the risk that a sequence of DNA being inserted into a mouse inadvertently activated a retrovirus resulting in an adverse environment effect. In accordance with 12(b) of the Methodology, the Committee considered the probability of this event to be very unlikely. The organism description prohibits the use of sequences that give rise to infectious viruses. As well, there is a long history of safety in genetically modified mice, with no documentation of the production of retroviruses as a result of genetic modifications. The Committee noted that large numbers of genetically modified mice have been generated over twenty years without the apparent creation of new viruses. The Committee notes that should a new virus be created the possible risks and costs could potentially be of a high magnitude. Control 6.2 requires that if any traits unexpectedly occur that fall outside of the organism description this shall be notified to ERMA New Zealand and MAF Biosecurity Authority immediately the trait becomes apparent.

As required by clause 12(c) of the Methodology, the Committee considered the probability of occurrence and the magnitude of the adverse effect and concluded that it was insignificant, particularly in light of the controls and the unlikelihood of escape of the mice.

In accordance with clause 12(d) of the Methodology, the Committee is satisfied that the controls imposed in this decision aimed to reduce the risks and costs as much as possible, by excluding the use of viral particles or packaging signals from the organism description and reducing the risk of escape from the containment facility. The Committee recognizes, as required by clause 12(e) of the Methodology, that there is uncertainty when assessing the risk of the genetically modified mice imported inadvertently producing viral particles, and the potential impact on the environment and human health, as any risks and costs would depend on the type of virus produced.

In accordance with clause 25 of the Methodology, the Committee noted the uncertainty of the scientific evidence of the likelihood of a sequence to give rise to genetically modified mice producing viral particles that cause disease in humans or animals. As required by clause 29 of the Methodology, the Committee considered the materiality and significance of the scientific uncertainty to the application. The Committee considered that although uncertainty surrounded likelihood of a sequence to give rise viral particles, and the uncertainty surrounding the nature of any potential adverse

effect. Therefore, in the context of the application, the Committee considered that the scientific uncertainty was material to the application and was significant. The Committee again noted that sequences that result in the production of infectious viral particles or viral packaging signals are excluded by the organism description and noted that although this reduced the overall risk, it did not reduce the uncertainty associated with the potential adverse effects that could occur.

The Committee also considered costs associated in the event that genetically modified mice spread viral particles causing disease in animals and humans. The Committee considered there was potential for costs, both monetary and non-monetary to be generated in the very unlikely event of genetically modified mouse/mice producing viral particles that caused disease in both animals and humans. However, the Committee agreed that it was difficult to assign any magnitude or expected value to those costs, in accordance with 13(b) of the Methodology, due to the uncertainty of the nature of the risk as it would depend on the type of virus produced. In accordance with clause 13(c) of the Methodology, the Committee considered the distributional effects of costs and benefits over time, space and groups in the community. Analogous to above, The Committee considered it was difficult to evaluate these cost due to the uncertainty surrounding the likely effects of the virus.

The Committee acknowledged the potential for risks and costs to human health in the event that mice inadvertently produced virus particles. This is discussed later in section 7.3 in the decision.

7.2.4 Reproductive efficiency

The Committee discussed a concern that a genetically modified mouse could be imported that had greater reproductive efficiency than the unmodified mouse. This was also identified by the applicant (page12). As required by clause 12(a) of the Methodology, the Committee considered the risk this could pose to the environment. In particular, the Committee expressed concerns that in the event of escape, the mice could breed prolifically and result in larger numbers of mice in the wider environment. As stated in section 7.2.5, it is recognised that mice are already widespread within the environment and in agriculture, and occupy a variety of niches, and that larger numbers of mice could potentially have a significant impact on the environment. For example, they could impinge on the habitats of native flora and fauna, or have a negative impact on agricultural crops.

As required by clause 12(b) of the Methodology, the Committee considered the probability of occurrence and the magnitude of the adverse effect. The probability that a mouse will be imported that has increased reproductive efficiency is considered very unlikely, particularly, given the organism description that states:

(a) The genetically modified mice shall not demonstrate evidence of enhanced reproductive success or increased breeding capacity when compared to unmodified laboratory mice and in particular:

   i. There shall be no evidence of a higher number of viable offspring produced per litter when compared to the unmodified strain, nor any evidence to indicate that the modifications might lead to such an increase or;

ii. There shall be no evidence of an increased number of viable litters produced per year when compared to the unmodified train, nor any evidence to indicate that the modifications might lead to such an increase or;

iii. There shall be no evidence of an extended age of reproduction when compared to the unmodified strain nor any evidence to indicate that the modifications might lead to such an increase, or;

iv. There shall be no evidence of an increased number of viable and reproductively fit offspring when compared to the unmodified strain nor any evidence to indicate that the modifications might lead to such an increase.

The magnitude of the effect is considered to be minimal, given the containment regime and organism description imposed by the Committee.

As required by clause 12(c) of the Methodology, the Committee took into account the combination of the magnitude of the adverse effect and the probability of occurrence and concluded that the overall risk of an adverse effect was insignificant.

In accordance with clause 13 of the Methodology, the Committee considered the likely costs associated with genetically modified mice being imported that were reproductively superior to wild type laboratory mice and concluded, given the organism description and containment regime that it was unlikely this event would generate any significant costs.

7.2.5 Greater ability to survive outside of containment

The Committee discussed the possibility that genetically modified mice could be imported with a greater ability to survive outside of containment in the unlikely event that they escaped. Such an enhanced ability could be because of greater ability to tolerate extreme wet, cold or dry environments, greater health through decreased disease susceptibility, changed dietary preferences or being more vigorous or aggressive than an unmodified laboratory mouse.

As required by clause 12(a) of the Methodology, the Committee considered increased aggression could pose a risk to workers that handle the genetically modified mice (i.e. bites, etc).

In the event of escape from the containment facility the genetically modified mouse could also potentially pose a risk to the wider environment. It is recognised that mice are widespread within the environment and in agriculture, occupy a variety of niches, including some close to people (albeit inadvertently) and tend to share a common food supply. New Zealand's native fauna evolved in the absence of rodents and other small mammals and has been shown to be particularly vulnerable to rodent predation, to competition with rodents for food sources, and to predation by rodent predators that build up in numbers following peaks in mouse numbers. It is also noted that a range of mammalian and avian predators of rodents, which are common in other countries, are absent in New Zealand.

The Committee noted these risks and costs, and that such genetically modified mice are prohibited by the organism description (refer **appendix 1**). As required by clause 12(b)

of the Methodology, the Committee considered the probability of occurrence and the magnitude of the adverse effect. The probability that a mouse will be imported that has increased vigor or aggressiveness is considered very unlikely, particularly given item 4(c) of the organism description. The magnitude of these effects is considered to be minor.

As required by clause 12(c) of the Methodology, the Committee took into account the combination of the magnitude of the adverse effect and the probability of occurrence and concluded that the overall risk of an adverse effect was insignificant. In accordance with clause 33 of the Methodology, the Committee considered both involuntary and voluntary exposure to risk (clause 33 will be discussed further within section 10.1 of this document).

In accordance with clause 13 of the Methodology, the Committee considered the likely costs associated with genetically modified mice being imported that were reproductively superior to wild type laboratory mice and concluded, given the organism description and containment regime that it was unlikely this event would generate any significant costs.

7.2.6 Unanticipated adverse environmental effects associated with genetic modification

The Committee broadly discussed the risk that genetically modified mice could potentially have unanticipated effects in their genome as a result of their modification (discussed in sections 7.23 to 7.29 of the E&R Report). The Committee then proceeded to identify the particular elements as recombination, insertional mutagenesis, transposable elements and cytokines as having potential for unanticipated effects and these will be discussed below.

As noted in the E & R Report, modifications to mice may include knocking out endogenous genes, introducing copies of equivalent genes from other species or introducing genes with no counterparts in mice. The Committee noted that some knock-outs or other modifications to endogenous genes may have a minor effect if one copy of the endogenous mouse gene is not modified. The unmodified endogenous copy may be able to compensate for the absence of function in the disrupted gene. However, in some cases disruption of only one copy of the gene will have an effect.

In accordance with clauses 12(e) and 25 of the Methodology, the Committee noted the scientific uncertainty over the effect of knocking-out or introduction of genes in mice, since for many genes, the mode of effect is unknown.

The E&R Report noted that unanticipated effects resulting from the interruption of a gene can result in:

(a) Higher or lower levels of expression of a gene than normal;

(b) Expression in tissues where the gene is not normally expressed;

(c) Disruption of other genes due to location of insertion;

(d) Unknown functions or interactions of the disrupted or introduced gene.

The likelihood of unanticipated effects is dependant on these factors:

(a) The nature of the introduced genetic material;

(b) Location(s) of insertion;

The Committee noted that the effects depend on the pattern and timing of the expression of foreign genetic material.

The Committee discussed several adverse elements resulting from unanticipated effects from genetic modification: transposable elements, insertional mutagenesis and recombination, in the following paragraphs. The Committee did note that unanticipated effects could also result in beneficial effects in some circumstances.

7.2.6.1 Transposable elements

The Committee considered sections 4 and section 7.11 of the E&R Report. The organism description does not exclude the incorporation of sequences that may contain transposable elements or mobile elements.

In accordance with clause 12(a) of the Methodology, the Committee considered the potential risks and costs arising from transposable elements. They considered the affected mouse may potentially demonstrate a range of abnormal features. The magnitude of the adverse affects can vary from no observable adverse phenotypic effect, to a range of morphological, physiological, or behavioral abnormalities (dependant on the genes involved), to premature death of the animals (due to serious disruption of cellular functions).

In the unanticipated event of mobilisation of a transposable element within the genetically modified mouse genome, the element would only move material within the mouse rather than between mice (i.e. is not heritable). Thus the effect of the modification would most likely be localised to the mouse itself. Therefore in accordance with clause 12(b) of the Methodology, the probability of an adverse effect on a genetically modified mouse was unlikely and the magnitude of the adverse effect was likely to be limited to the affected mouse. As required by clause 12(c) of the Methodology, the Committee considered the overall level of risk to be low to insignificant, but noted, in accordance with 12(e), the uncertainty surrounding what effects would occur as it depended on which genes are affected within the mouse and how important they are to its normal metabolic function.

To mitigate this risk, Control 6.2 requires that if any traits unexpectedly occur that fall outside of the organism description this shall be notified to ERMA New Zealand and MAF Biosecurity Authority immediately the trait becomes apparent.

The Committee considered that the likelihood of the occurrence was very unlikely, and its effect minimal or minor. The overall risk is low to insignificant. The Committee considered that no further options were necessary for managing the risks and costs, in accordance with clause 12(d) of the Methodology.

As required by clause 12(e) and clause 25 of the Methodology, the Committee noted the scientific uncertainty over whether the transposable elements that contained foreign DNA would remain viable and in fact, be able to move within the mouse genome. This uncertainty stems from the dependency on the type of transposable element and whether

it can accommodate additional features and remain functional. The Committee also noted uncertainty over the magnitude of the adverse affects as it would depend on the effect the transposable element had when inserting into the mouse genome.

The Committee considered that residual risk remained that could not be addressed by controls or modification of the organism description. This will be further discussed in section 11.

In accordance with clause 25 of the Methodology, the Committee noted the uncertainty of the scientific evidence of the effect the transposable element would have if inserted into the mouse genome. As required by clause 29 of the Methodology, the Committee considered the materiality and significance of the scientific uncertainty to the application. In the context of the application, the Committee considered that the scientific uncertainty was material to the application and was not of great significance, as any effect is likely to be localized to a particular genetically modified mouse.

In accordance with clause 13 of the Methodology, the Committee evaluated the likely costs arising from transposable elements. Given any adverse effect is likely to be limited to the individual mouse and not heritable, the Committee considered that the cost of this adverse effect happening will be borne by the applicant. The magnitude of the cost will be small and is not likely to be a long-term or an on-going cost.

7.2.6.2 Insertional mutagenesis

The Committee noted that insertional mutagenesis is generally an unanticipated result of genetic modification found particularly with mutagenesis, because the insertion of the gene is not always targeted. The likelihood of unanticipated effects is dependant on the nature of introduced genetic material, the location of insertion and pattern and timing of insertion.

As required by clause 12(a) of the Methodology, the Committee considered the nature of the adverse affects could vary from no observable phenotypic adverse effect, to a range of morphological, physiological, or behavioral abnormalities (dependant on the genes involved), to premature death of the affected animals (due to serious disruption of cellular functions). The Committee noted that it was very unlikely to transfer between animals.

Therefore in accordance with clause 12(b) of the Methodology, the probability of an adverse effect on a genetically modified mouse was unlikely and the magnitude of the adverse effect was likely to be limited to the affected mouse. As required by clause 12(c), the Committee considered the overall level of risk to be low to insignificant.

To mitigate the risk Control 6.2 requires that if any traits unexpectedly occur that fall outside of the organism description this shall be notified to ERMA New Zealand and MAF Biosecurity Authority immediately the trait becomes apparent.

The Committee considered that the likelihood of the occurrence was very unlikely, and its effect minimal or minor. The overall risk is low to insignificant. The Committee considered that no further options were necessary for managing the risks and costs, in accordance with clause 12(d) of the Methodology.

As required by clause 12(e) of the Methodology, the Committee noted the uncertainty surrounding what effects will occur as it depends on which genes are affected within the mouse and how important they are to its normal metabolic function. The Committee considered that residual risk remained that could not be addressed by controls or modification of the organism description. This will be further discussed in section 11.

In accordance with clause 13 of the Methodology, the Committee evaluated the likely costs arising from insertional mutagensis. Given any adverse effect is likely to be limited to the individual mouse and not heritable, the Committee considered that the cost of this adverse effect happening will be borne by the applicant. The magnitude of the cost will be small and is not likely to be a long-term or an on-going cost.

In accordance with clause 29 of the Methodology, the Committee considered the scientific uncertainty surrounding the likely effects of insertional mutagenesis. The Committee considered that the uncertainty was material, but was not of significance, to the application, as the Committee noted that any adverse effects are likely to be localised to the effected mouse.

7.2.6.3 Recombination

The Committee also discussed the importation of mice that could potentially include genetically modified mice that have undergone recombination giving rise to unanticipated effects in their genome, analogous in many respects to the risks and costs from insertional mutagenesis. Recombination also is an unanticipated result of genetic modification and can result in many of the same effects as insertional mutagenesis.

The likelihood of unanticipated effects is dependant on the nature of introduced genetic material, the location of insertion and pattern and timing of insertion. As required by clause 12(a) of the Methodology, the Committee considered the nature of the adverse affects could vary from no observable phenotypic adverse effect, to a range of morphological, physiological, or behavioral abnormalities (dependant on the genes involved), to premature death of the affected animals (due to serious disruption of cellular functions). The Committee noted that it was very unlikely to transfer between animals.

Therefore in accordance with clause 12(b) of the Methodology, the probability of an adverse effect on a genetically modified mouse was unlikely and the magnitude of the adverse effect was likely to be limited to the affected mouse. As required by clause 12(c) of the Methodology, the Committee considered the overall level of risk to be low to insignificant.

To mitigate the risk Control 7.2 requires that if any traits unexpectedly occur that fall outside of the organism description this shall be notified to ERMA New Zealand and MAF Biosecurity Authority immediately the trait becomes apparent.

The Committee considered that the likelihood of the occurrence was very unlikely, and its effect minimal or minor. The overall risk is low to insignificant. The Committee considered that no further options were necessary for managing the risks and costs, in accordance with clause 12(d) of the Methodology.

As required by clause 12(e) of the Methodology, the Committee noted the uncertainty surrounding what effects will occur as it depends on which genes are affected within the mouse and how important they are to its normal metabolic function. The Committee considered that residual risk remained that could not be addressed by controls or modification of the organism description. This will be further discussed in section 11.

In accordance with clause 25 of the Methodology, the Committee noted the scientific uncertainty over the effect of recombination. The Committee also noted uncertainty over the magnitude of the adverse affects as it would depend on what effect the recombination had when inserting into the mouse genome. The Committee also considered the materiality and the significance of the uncertainty, as required by clause 29 of the Methodology, in relation to the application. The Committee considered the uncertainty was material and of some significance to the application, as even though the event of recombination is very unlikely, the magnitude of the consequences is unknown as it would depend on the type of retrovirus Activated.

The Committee also noted that if an unanticipated recombination did occur between sequences, this could potentially result in a new viral pathogen (as discussed in 7.3.2).

In accordance with clause 13 of the Methodology, the Committee evaluated the likely costs arising from recombination. Given any adverse effect is likely to be limited to the individual mouse and not heritable, the Committee considered that the cost of this adverse effect happening will be borne by the applicant. The magnitude of the cost will be small and is not likely to be a long-term or an on-going cost that would be borne by the applicant or user of the approval

7.2.6.4 Cytokines

The Committee also discussed the importation of mice that could potentially include modified cytokine genes (as discussed in section 7.25 of the E&R Report). As required by clause 12(a) of the Methodology, the Committee considered the nature of the risks and costs. The modification of cytokine genes could result in over expression of cytokines, giving a predisposition for the genetically modified mice to develop tumors. It is considered that in the event of a genetically modified mouse developing a tumor that the effects would be localised to the affected mouse. The Committee noted that modification of cytokine genes can have uncertain effects because their individual functions are not always known. However, as it is expected the effect would be localised to a particular genetically modified mouse and unlikely to transfer between animals and unlikely to provide selective advantage, the Committee noted (in accordance with 12(c) of the Methodology) that it was very unlikely that cytokines will have significant adverse environmental effects or human health and safety effects in the event of escape and the establishment of self sustaining population. As required by 12(d) of the Methodology, the Committee considered no additional controls were necessary to manage this risk.

In accordance with clause 13 of the Methodology, the Committee evaluated the likely costs arising from cytokines. Given any adverse effect is likely to be limited to the individual mouse and not heritable, the Committee considered that the cost of this adverse effect happening will be borne by the applicant. The magnitude of the cost will be small and is not likely to be a long-term or an on-going cost.

7.3 Adverse public health effects

In accordance with clauses 9(b), 9(c), 10(c) (g), and 12 of the Methodology, the Committee assessed and evaluated potential adverse human health and safety effects associated with this application. In addition, the Committee has imposed additional control 6.2 and excluded phenotypes from the organism description that would give the genetically modified mice a selective advantage and pose higher levels of risk than wild type mice.

The Committee did briefly discuss genetically modified mice that produced toxins and viral particles and the adverse effects these could have on human health.

The Committee considers that it will be unlikely that infection of researchers will occur if proper procedures and controls are followed. In addition, the Committee also considered the requirements of the MAF Regulatory Authority Standard 154.03.03: Containment Facilities for Vertebrate Laboratory Animals. In particular, section 3.4 that outlined the training requirements for ensuring that all people who work in the facility are familiar with the principles of containment and the procedures of the facility, which ensure containment.

In addition, the Committee also considered relevant legislation relating to the workplace and in particular, the Health and Safety Employment Act (1992) and the Animal Welfare Act (1999).

The Health and Safety Employment Act (1992) binds employers and employees to the Occupational Health and Safety Guidelines (OSH) to ensure safety in the workplace. An employer must identify all hazards in the workplace and ensure that there are procedures in place to manage the hazards so as to not cause injury or illness, including identification of significant hazards. Once a significant hazard has been identified, an employer must take "all practicable steps" to eliminate, isolate or minimise the significant hazard. Part of an employer's responsibilities is to provide easily understandable information, on the steps to take with those hazards, to prevent harm. An employer must also ensure that workers have the knowledge, or are supervised by a person who has the knowledge, of the work they are undertaking. The employer must also ensure that staff are trained in the safe use of plant, any substances, protective clothing and equipment that they will be using or handling in their work. In addition, all accidents must be recorded in an accidents register and be reported to OSH.

The Committee also considered the Animal Welfare Act 1999, and in particular, National Animal Ethics Advisory Committee (NAEAC) [2]. The NAEAC recommends that any procedures should take into account the requirements of health and safety of the staff and procedures should be made known to all staff involved in the care and use of the animals and should be reviewed regularly. NAEAC also recommends that personnel employed in the care of animals should be instructed in how to recognise at an early stage changes in animal behavior, performance and appearance and new staff who will care for animals should be appropriately instructed in their duties and in institutional policy. Staff should be informed of hazards and diseases of animals under their care and

[2] National Animal Ethics Advisory Committee (2002). Good Practice Guide for the Use of Animals in Research, Testing and Teaching, Section 5.1, page 16 from http://www.maf.govt.nz/biosecurity/animal-welfare/naeac/papers/guide-for-animals-use.pdf [accessed August 8, 2003].

of precautions that should be taken. Regular health checks and appropriate immunisation of all staff who handle animals are recommended in the interest of both staff and animals.

The NAECA also has a section on experiments involving hazards to humans or other animals (6.4.19, page 29). Hazards may arise from sources that include, *inter alia*,:

- viruses;
- bacteria;
- fungi;
- parasites;
- toxins;
- allergens;
- carcinogens;
- recombinant DNA;
- physical injuries.

Any potential pathogenic effects of these hazards when used in experiments must (the minimum standards required under the Animal Welfare Act) be explained as far as possible to all staff. Tests before, during and after, the experiments may be required for staff. The investigator should inform the Animal Advisory Committee (AEC) that the advice of the institution's biohazards Committee (where it exists) has been sought and that appropriate measures for containment, disposal and decontamination have been established. Protocols should describe specific safety measures and disposal protocols used to prevent contamination of caging, other animals, research personnel and students. Animals being administered infectious organisms should be isolated as appropriate, taking into account risks to other animals and to people.

When considering the risks to human health posed by toxins and viral particles the Committee also considered that an element of exposure to the risk is voluntary, in the sense that people choose to work with mice, either as a scientist or a technician. Whereas, in the event of escape from containment, the general public does not choose to be exposed to genetically modified mice.

Therefore, taking account of the relevant information, the Committee concluded the level of overall risk was insignificant and that no additional options were necessary for managing the risks and costs, in accordance with clause 12(d) of the Methodology.

7.3.1 Toxins

In accordance with clause 12(a) of the Methodology, the Committee considered the risks and costs that potentially result from the genetically modified mice producing toxins that could potentially make people ill through exposure to the toxin. The Committee noted that any risks and costs are likely to be limited to the people handling the mice.

The Committee considers it unlikely that laboratory workers will be exposed to toxins if proper procedures and controls are followed. In addition, the requirements of the MAF Regulatory Authority Standard 154.03.03: Containment Facilities for Vertebrate Laboratory Animals (Section 3.4), outlines the training requirements for ensuring that all people who work in the facility are familiar with the principles of containment and

the procedures of the facility which ensure containment. Also, under the Health and Safety Employment Act (1992) employers and employees are bound by the Occupational Health and Safety Guidelines to ensure laboratory safety (as outlined earlier in section 7.3).

Therefore, taking account of the relevant information, the Committee concluded the level of overall risk was insignificant and that no additional options were necessary for managing the risks and costs, in accordance with clause 12(d) of the Methodology.

In accordance with clause 13 of the Methodology, the Committee evaluated the likely costs arising from the risk that people handling the mice are exposed to toxins. The Committee considered costs arising from laboratory workers being exposed to toxic mice. The Committee considered that given the containment regime, mice expressing toxins should be quickly picked up through regular monitoring and the number of people affected would be minimal. Therefore, the magnitude of the cost is likely to be small and accrue to the Institution.

In accordance with clause 25 of the Methodology, the Committee noted the uncertainty of the scientific evidence of the likelihood of a sequence to give rise to toxic effect within the mouse. As required by clause 29 of the Methodology, the Committee considered the materiality and significance of the scientific uncertainty to the application. The Committee considered that although uncertainty surrounded likelihood of a sequence to give rise toxic effects on the mouse and the severity of these effects on the mouse, it noted that it was likely to be confined to the genetically modified mouse affected and not transmitted to other mice. In addition, toxic effects on the mouse are likely to be picked up in the regular course of monitoring the genetically modified mice, required by the containment regime. In addition, the Committee considered that people who work with the genetically modified mice are trained in laboratory procedures and should recognise mice exhibiting a toxic phenotype. Therefore, in the context of the application and given that sequences that produce high level toxins or low levels of potent toxins are prohibited by the organism description, the Committee considered that the scientific uncertainty was material to the application, but was not of large significance.

7.3.2 Viral particles

When taking into account the adverse pubic health effects, the Committee considered the risks and costs of mice producing viral particles. The Committee discussed this matter in the context of the two pathways for virus expression, as discussed earlier in section 7.2.3. Firstly, that sequences encoding for viruses may be deliberately put into a mouse, or secondly that the insertion of sequences results in inadvertent Activation of a retrovirus.

As required by clause 12(c) of the Methodology, the Committee considered the probability of occurrence was very unlikely and the magnitude of the adverse effect minor to moderate. It was also noted that in the first instance, any adverse effect would be localized to the laboratory worker handling the mouse. Secondary, as discussed above in section 7.3, the Committee considered the relevant sections of the Health and Safety Employment Act (1992) and the Animal Welfare Act (1999) when taking account of the risk posed to laboratory workers. The Committee concluded that the

overall risk was low to insignificant, particularly in light of the organism description, controls and the laboratory handling procedures in place.

In accordance with clause 12(d) of the Methodology, the Committee is satisfied that the controls imposed in this decision reduce the risks and costs as much as possible, by excluding the use of viral particles or packaging signals from the organism description and reducing the risk of escape from the containment facility. The Committee recognised, as required by clause 12(e) of the Methodology, that there is uncertainty when assessing the risk of the genetically modified mice imported producing viral particles, as any risks and costs would depend on the type of virus produced.

The Committee also considered costs associated in the event that genetically modified mice spreading viral particles causing disease in humans. The Committee considered there was potential for costs, both monetary and non-monetary to be generated in the very unlikely event of genetically modified mouse/mice producing viral particles that caused disease in both animals and humans. However, the Committee agreed that it was difficult to assign any magnitude or expected value to those costs, in accordance with 13(b) of the Methodology, due to the uncertainty of the nature of the risk as it would depend on the type of virus produced. The Committee considered that people that handle the mice are likely to be the first affected, unless the affected mouse escaped containment. Escape from containment is considered very unlikely. In accordance with clause 13(c) of the Methodology, the Committee considered the distributional effects of costs and benefits over time, space and groups in the community. Analogous to above, The Committee considered it was difficult to evaluate these cost due to the uncertainty surrounding the likely effects of the virus.

In accordance with clause 25 of the Methodology, the Committee noted the uncertainty of the scientific evidence of the likelihood of a sequence to give rise to genetically modified mice producing viral particles that cause disease in humans or animals. As required by clause 29 of the Methodology, the Committee considered the materiality and significance of the scientific uncertainty to the application. The Committee considered that although uncertainty surrounded likelihood of a sequence to give rise viral particles, the likelihood of the viral particles to cause an adverse effect and the severity any potential adverse effect. Therefore, in the context of the application, the Committee considered that the scientific uncertainty was material to the application and was significant. The Committee again noted that sequences that result in the production of infectious viral particles or viral packaging signals are excluded by the organism description. The Committee also noted that although this reduced the overall risk, it did not reduce the uncertainty associated with the potential adverse effects that could occur.

7.4 Adverse cultural effects

The Committee considered the potential cultural effects in accordance with clauses 9(b) and 9(c)(iv) of the Methodology and sections 5(b), 6(d) and 8 of the HSNO Act.

The Committee noted the information provided by the applicant (Section 3.3 of the application) that stated that genetic material to be used in the proposed research is to be sourced from commercial gene banks. The human genetic material used in research is to be sourced from international gene banks. Genetic material sourced from genebanks is usually in the form of cDNA or expressed sequence tags (ESTs) and is a synthetic copy

of the gene, usually lacking intron sequences and so is not identical to the corresponding gene within a living organism.

The Committee noted that donor DNA and genetic sequences from any New Zealand native[3] or endemic[4] flora and fauna, or species valued by Māori that are sourced from New Zealand or human DNA of any origin are not allowed under the organism description. Therefore, the Committee considers that the application poses no risk to the relationship between Māori culture and their traditions with their ancestral lands, water, sites waahi tapu, valued flora and fauna and other taonga.

In accordance with clause 13 of the Methodology, the Committee evaluated the costs associated with any mice being imported that contain DNA or genetic sequences from any New Zealand native[5] or endemic[6] flora and fauna, or species valued by Māori. They noted that any costs is likely to be non-monetary, however, difficult to assign a magnitude or expected value to and difficult to evaluate the distributional effects as it would depend on the DNA used.

7.5 Summary of risks and costs

The Committee identified 10 significant risks and costs (as listed in section 5). The Committee considered that after restricting the organism description and in combination with the controls that only four classes of risk remained. These were: the risk of unexpected effects from transposons, insertional mutagenesis, recombination and the residual risk from the generic nature of the application.

8 Assessment of Benefits

The Committee agreed with the E&R Report and identified the following benefits associated with the application, in accordance with the Methodology clauses 9, 10, 13, and 14 and section 6(e) of the HSNO Act:

As noted in sections 7.52 – 7.58 of the E&R Report the Committee considered the main benefits of the application are scientific in nature, for instance, improved knowledge and understanding of disease processes. The Committee considered that the research may develop into health, welfare or economic benefits to New Zealand if the results of the research are suitable to translate into practical outcomes. In addition, the applicants note that the profile of New Zealand in the international scientific community would be raised, and that economic benefits may also occur in terms of the ability to attract funds from international organisations to support the progress of research. It is noted that due to the unpredictable nature of scientific research it is difficult to quantify the likelihood of success in terms of improvements in living standards. The Committee also recognised the difficulty in weighing the benefits. While these benefits are likely, their magnitude of effect is uncertain and may range from minimal (if the mouse strains do not substantially elucidate the understanding of a particular problem) or major (if, for example, the GM mouse leads directly to the development of an effective treatment for

[3] Native: Living or growing naturally in a particular region, not having been introduced from elsewhere.
[4] Endemic: Not naturally occurring outside of New Zealand.
[5] Native: Living or growing naturally in a particular region, not having been introduced from elsewhere.
[6] Endemic: Not naturally occurring outside of New Zealand.

a common human ailment). Indirect and/or longer-term benefits for human health and the economy are possible, but are also highly uncertain in terms of their magnitude of effect.

Under clause 13(a) of the Methodology, the Committee considered the primary benefit associated with this application to be increased scientific knowledge (non-monetary) gained through research. The Committee notes that while increased scientific knowledge likely, the magnitude and expected value of beneficial effects (clause 13(b) of the Methodology) is uncertain. Immediate benefits are likely to accrue directly to the applicant (clause 13(c) of the Methodology). But, in the event of some medical breakthrough, may potentially accrue to a wider section of the population.

9 Other matters

The Committee considered what other matters might be relevant in setting controls to provide for matters outside the Third Schedule, in order to give effect to the purpose of the HSNO Act (in accordance with section 45(2)(b)).

The Committee considers it inappropriate to impose a restricted time limit on this approval as it is likely to be repeatedly used over time.

The Committee noted that in order to fulfill its obligation under section 20 to maintain a register, all applications must contain a sufficient description of the organism to uniquely identify that organism. The verification mechanism discussed above (section 4.3) provides a mechanism for each strain that is imported to be recorded in the register (see control 6.1, **appendix 2**).

The genetic modifications allowed within the organism description include knocking out endogenous genes, introducing copies of equivalent genes from other species or introducing genes with no counterparts in mice. As noted in section 7.24 of the E & R Report, "there is likely to be uncertainty over the effect of knocking out or introducing genes in mice…" The Committee identified some unanticipated risks and costs associated with genetic modification, namely, unexpected effects arising from transposons, insertional mutagenesis and recombination. The Committee considered that these risks and costs could not easily be addressed within the organism description or by controls and therefore left residual risk. In order to address this residual risk the Committee imposed an additional control that (control 6.2) "If any traits unexpectedly occur that fall outside of the organism description this shall be notified to ERMA New Zealand and MAF Biosecurity Authority immediately the trait becomes apparent".

The Committee also imposed an additional control (6.3) that prevents development work from occurring with the imported strains. As this is an application to import mice only, this approval does not authorise the crossing of different strains to develop new strains of genetically modified mice. If such crosses are made at some future date they will need to apply for either IBSC or ERMA approval depending on their risk status.

10 International and Related Matters

The Committee considered international obligations relevant to this approval in accordance with clause 9(c)(vi) of Methodology and section 6(f) of the HSNO Act.

The Committee considered the organism description prohibiting the use of donor DNA from species listed by the Convention on International Trade in Endangered Species (CITES) (except where accompanied by appropriate letters of approval from the relevant agencies in the exporting and importing countries) and considered this adequate.

10.1 Approach to Risk

The Committee adopted a precautionary approach (in accordance with section 7 of the HSNO Act) when considering risk in accordance with clause 33 of the Methodology because of the particular vulnerability of New Zealand's unique biota to mice, in the very unlikely event of an escape. They also noted that a range of mammalian and avian predators of rodents, which are common in other countries, are absent in New Zealand.

The Committee had particular regard to the extent to which the following risk characteristics existed, particularly in its consideration of whether:

(a) Exposure to the risk is voluntary;

(b) The risk will persist over time;

(c) The risk is subject to uncontrollable spread and it likely to extend its effects beyond the immediate location;

(d) The potential risks and costs are irreversible;

(e) The risk is not known or understood by the general public and there is little experience or understanding of possible measures for managing the potential risks and costs.

The Committee considered that since people are informed of any risk when they work with the genetically modified mice, they are not exposed involuntarily (i.e. people choose to work with mice). Given the characteristics of the organism, the containment regime and controls imposed, the Committee considered that the wider community is unlikely to be involuntarily exposed to these risks and costs.

The Committee noted that in the event of some unanticipated effect occurring as a result of the genetic modifications, it is likely that it will be localised to the affected mouse, and in the event of escape from the containment facility, it is unlikely to be transferred via interbreeding. Taking that into account, the Committee considered that it was very unlikely that the risk would uncontrollably spread. Although, the Committee did note that wild mice are already widespread across New Zealand and tend to also be found in close vicinity to people.

In addition, the Committee noted that any health effects likely to be caused by the mice are likely to be treatable and reversible and not long term.

However, any adverse environmental effects may be difficult to reverse, given the general experience of the difficulty of eradicating rodent predators from the environment if they became established and the vulnerability of New Zealand's unique biota.

The Committee is willing to tolerate these risk characteristics because the key risks and costs identified are considered very unlikely to eventuate.

In regard to the approach to risk in this application, the Committee was also faced with judging the significance of the uncertainty generated by the lack of specificity in a generic application that defined its boundaries by exclusion rather than inclusion. Section 7 of the HSNO Act requires the Committee to take into account the need for caution where there is scientific or technical uncertainty about effects.

11 Overall Evaluation and weighing up of Adverse and Benefits and the overall adequacy of containment

In reaching its decision on this application, the Committee records that the following criteria in the HSNO Act and Methodology have been particularly relied on (in accordance with clauses 21 and 36(2)(b) of the Methodology):

The application has been considered in the context of the purpose and principles of the HSNO Act (sections 4-8 inclusive).

Pursuant to section 45(1)(a)(i) of the HSNO Act, the Committee is satisfied that the purpose of the application falls under section 39(1)(h): *Such other purposes as the Authority thinks fit*, that purpose being import of a GMO into containment for the purpose of scientific research.

In accordance with section 45 of the HSNO Act, and clauses 9, 10, and 12 of the Methodology, the Committee considered that while each of the risks and costs may be negligible on their own or cumulatively, for any particular strain or group of strains of mice, the broad nature of the application introduces a level of uncertainty that, in the Committee's view resulted in the overall risk being more than negligible. Thus, the Committee considered the application under clause 27 (not clause 26) of the Methodology.

The Committee identified 10 potentially significant risks and costs (as listed in section 5). The Committee concluded these risks and costs relate to the full range of organisms encompassed by the application. The Committee considered that after restricting the organism description and in combination with the controls, only four classes of risk remained. These were: the risk of unexpected effects due to transposable elements, insertional mutagenesis or recombination and the residual risk from the generic nature of the application.

As outlined in the body of this decision, the Committee considered (in accordance with clause 25 of the Methodology) that there was a degree of uncertainty relating to the scientific evidence on risks, particular in relation to transposable elements, insertional mutagenesis and recombination. The Committee also concluded (as required by clause 29 of the Methodology) that the uncertainty in each case was material to the application and (in some cases) overall gave a cumulative significant risk. Therefore, in the face of scientific uncertainty, the Committee took (in accordance with clause 30 of the Methodology) into account the need for caution in managing the adverse effects of the organism under approval.

Before evaluating and weighing the risks, costs and benefits, the Committee considered whether there were any measures that could be taken to reduced the identified areas of risk and uncertainty (as required by clause 33). The Committee considered that the organism description in the application resulted in an unacceptably high level of uncertainty. As discussed in section 4.3, the Committee has restricted the scope of the organism description in a number of ways in order to reduce risk and uncertainty. The Committee considers that, given the restrictions on the organism imposed by the organism description and controls, it is unlikely that unintended adverse effects will occur. Should they occur, the Committee considers that the effects will be primarily restricted to the genetically modified mouse/mice, and, as such, will be minor. As a result of the organism restrictions, the level of uncertainty has been restricted to an acceptable level (clause 12 of the Methodology refers).

The overall evaluation of risks, costs and benefits was carried out having regard to clause 22 and 34 of the Methodology.

Clause 34 of the Methodology sets out the approaches available to the Committee in evaluating the combined impact of risks, costs and benefits. It was not possible to use common units of measurement. However, it was possible to identify the dominant influence of the combined assessment of risks.

As indicated in the foregoing text, a number of potentially significant risks are considered to be negligible, after taking account of the organism description **appendix 1** and the impact of containment and other controls set out in **appendix 2**. These include risk of unexpected effects due to transposable elements, insertional mutagenesis or recombination and the residual risk from the generic nature of the application.

As assessed in section 8 of the decision the benefits are largely scientific. While these benefits are very likely to exist, their magnitude may range from minimal to moderate depending on the success of the research and the scientific value of the research results.

The Committee then considered whether, given the organism restrictions and the containment and controls proposed, the benefits outweigh the non-negligible risks and costs. The Committee's view is that the benefits do outweigh the costs and risks.

In order to reduce uncertainty associated with the assessment of effects of the organism to a level considered to be satisfactory for decision-making, the scope of the approved organism is reduced from that set out in the application and additional controls imposed. The resulting organism description is set out in **appendix 1**, and this is the organism description to which this decision applies.

The Committee is satisfied that the modified mice can be adequately contained (sections 45(1)(a)(iii) and 44(b) of the HSNO Act), by the controls required in this decision (refer to **appendix 2**). In relation to the additional matters to be considered under section 37 of the HSNO Act, the Committee considers it very unlikely for the genetically modified mice to escape or be removed (advertently or inadvertently) from the containment facility and form a self sustaining population. Eradication would be unnecessary given that the organism would be unlikely to survive outside of containment.

In accordance with clause 36(2)(b) of the Methodology, the Committee records that in reaching this conclusion, it has applied the balancing tests in section 45 of the Act.

12 Decision

The application to import into containment genetically modified mice (as described in **appendix 1** of this decision) is **approved** in accordance with section 45(1)(a) of the HSNO Act. As required under section 45(2) the approval is subject to **controls** (as listed in **appendix 2** of this decision).

Signed on behalf of the Authority

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Ms Jane Lancaster **Date** 18 August 2003
Chair, GMO New Organisms Standing Committee of the Authority

Approval code: GMC001197

Amendment: November 2006;
Control 3.3 amended to permit dead genetically modified mice or tissues from genetically modified mice to be held in a transitional facility registered in accordance with MAF Standard 154.02.17 for Transitional Facilities for Biological Products.

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Dr Kieran Elborough **Date: 18 November 2006**
Chair, GMO Standing Committee

Amendment: November 2006
Changes to controls:

- Addition of footnotes to the containment facility references and the Australian/New Zealand containment facility references to "future proof" the decision
- Standardise the wording of the breach of containment control
- Removal of the control regarding inspection of facilities by the Authority, its agent or enforcement officers

_____ Date: 23 August 2007

Dr Kieran Elborough
Chair, GMO Standing Committee

Amendment: April 2009

Changes to controls:
To remove the clause 'certified specific-pathogen-free' from Appendix 1 of the decision, to amend control 3.1, remove control 3.3 and review all other controls.

(References to the original controls in the body of this Decision document have not been removed).

_____ Date: 2 November 2009

Dr Kieran Elborough
Chair, Decision-making Committee

Appendix 1: Organism Description

1. Host organism

Mice (*Mus musculus* Linnaeus 1758; Family Muridae) strains, with genetic modifications that conform with the following:

2. Inserted construct

The strains of mice may be modified with vectors containing the following, whose introduction into the mice meet the requirements of Category A or B and do not meet Category C of the HSNO (Low Risk Genetic Modification Regulations) 1998[7]:

(a) **Promoter, operator and other regulatory elements** derived from bacterial, viral or mammalian genes. The regulatory elements used in the construction of the genetically modified mice shall be well characterized and their sequence and functions known.

(b) **Reporter genes** (genes encoding easily assayed proteins) that do not produce proteins that are pathogenic or toxic in vertebrates (have an LD_{50} less than 100 μg/kg). The reporter genes used in the construction of the genetically modified mice shall be well characterised and their sequence and functions known.

(c) **Selectable marker genes.** The selectable marker genes used in the construction of the genetically modified mice shall be well characterized and their sequence and functions known.

(d) "**Other features**" including:

i. Polyadenylation signals;

ii. Multiple cloning sites;

iii. Splice sites;

iv. Secretory and targeting signals;

v. Ribosomal binding sites and/or Kozak sequences;

vi. Homologous recombination sites and flanking sequences;

vii. Regulatory sequences for induced expression;

viii. Cre/Lox recombinase system;

ix. Intron signals;

x. Insulator elements.

[7] The Committee recognized that the Hazardous Substances and New Organisms (Low-Risk Genetic Modification) Regulations 1998 were revoked on the 31st July 2003 and replaced by the Hazardous Substances and New Organisms (Low-Risk Genetic Modification) Regulations 2003. The Committee considered that as the majority of their consideration of this application was done under the 1998 Regulations that these would apply to this decision.

3. Donor DNA

The donor genetic material shall be DNA and may be sourced from humans (provided that the human donor DNA shall not come from Māori), vertebrates or bacteria.

The donor DNA shall not include:

(a) Genes encoding vertebrate toxins that have an LD_{50} of less than 100 μg/kg, or high level expression of vertebrate toxins with an LD_{50} of more than 100 μg/kg.

(b) Sequences capable of giving rise to infectious particles pathogenic to humans, animals or plants.

(c) Known genes associated with the development of transmissible spongiform encephalopathies.

(d) Genetic sequences from any New Zealand native or endemic flora and fauna, or species valued by Māori that are sourced from New Zealand.

(e) Species listed by the Convention on International Trade in Endangered Species (CITES), except where accompanied by appropriate letters of approval from the relevant agencies in the exporting and importing countries.

4 Phenotypes

The genetically modified mice covered by this application shall conform to the following requirements:

(a) The genetically modified mice shall not demonstrate evidence of enhanced reproductive success or increased breeding capacity when compared to unmodified laboratory mice and in particular:

i. There shall be no evidence of a higher number of viable offspring produced per litter when compared to the unmodified strain, nor any evidence to indicate that the modifications might lead to such an increase or;

ii. There shall be no evidence of an increased number of viable litters produced per year when compared to the unmodified strain, nor any evidence to indicate that the modifications might lead to such an increase or;

iii. There shall be no evidence of an extended age of reproduction when compared to the unmodified strain nor any evidence to indicate that the modifications might lead to such an increase, or;

iv. There shall be no evidence of an increased number of viable and reproductively fit offspring when compared to the unmodified strain nor any evidence to indicate that the modifications might lead to such an increase.

(b) The genetically modified mice shall not demonstrate evidence of enhanced ability to survive outside of the laboratory when compared to unmodified laboratory mice and in particular:

i. There shall be no evidence of an increase in maximum life span nor any evidence to indicate that the modifications might lead to such an increase; or,

ii. There shall be no evidence of a decreased susceptibility to disease, nor any evidence to indicate that the modifications might lead to such an decrease; or,

iii. There shall be no evidence of enhanced survival in atypical environments (such as increase in their ability to tolerate extreme cold, wet, or dry environments) nor any evidence to indicate that the modifications might lead to such an increase; or,

iv. There shall be no evidence to indicate that the dietary preferences of the genetically modified mice are significantly altered nor any evidence to indicate that the modifications might lead to such an alteration.

(c) There shall be no evidence to indicate that the aggressiveness of the genetically modified mice is increased nor any evidence to indicate that the modifications might lead to such an increase.

(d) The genetically modified mice do not produce recombinant infectious viral particles.

Appendix 2: Controls required by this approval

In order to satisfactorily address the matters detailed in the Third Schedule Part II: *Containment controls for importing, developing or field testing of genetically modified organisms*, of the Act, and other matters in order to give effect to the purpose of the Act, the approved organisms are subject to the following controls:

The purpose of this approval is:

To allow for **importation** of laboratory mice with specific genetic modifications to be used in a range of studies of gene or cell function and as models for human diseases.

1) Requirements to meet the Standards:

1.1 The approved organisms must be held within a containment facility in accordance with the MAF-ERMA New Zealand Standard *Containment Facilities for Vertebrate Laboratory Animals*, at Physical Containment Level 2 (PC2), as defined in AS/NZS Standard 2243.3.2002, *Safety in Laboratories Part 3: Microbiological Aspects and Containment Facilities* or any subsequent equivalent updated standards.

2) Controls additional to the Standards

2.1 Any facility using this approval for the first time must notify ERMA New Zealand and the MAF Inspector responsible for supervision of the facility of their intention to do so in writing.

2.2 If a breach of containment[8] occurs the Approval holder must ensure that the MAF Inspector responsible for supervision of the facility has received notification of the breach within 24 hours.

[8] Breach of containment includes: the escape of an organism(s), unauthorised entry to the containment facility, or a failure in the structural integrity of physical containment mechanisms.

Appendix 3: Qualitative scales for describing risks and costs

The following qualitative scale has been used to describe the likelihood of an adverse or beneficial effect occurring:

Table 1: Likelihood of effect

Descriptor	**Description**
Very unlikely	Not impossible, but only occurring in exceptional circumstances
Unlikely	Could occur, but is not expected to occur under normal conditions
Equally likely or unlikely	50:50 chance of occurring
Likely	Will probably occur at some time
Very likely (almost certain)	Is expected to occur

The following qualitative scale has been used to describe the magnitude (or measure of the severity) of an adverse effect occurring:

Table 2: Magnitude of adverse effect

Descriptor	**Examples of descriptors for type and extent of adverse effect**
Minimal	Slight or insignificant, repairable or reversible, very localised (affecting only a few individuals, single plants/animals or individual businesses), no flow-on effects, acute rather than chronic, not affecting native or valued species
Minor	Small, reversible and short term, localised to small land area or local community, acute, possible affecting valued species but not native species
Moderate	Medium or mid range, largely but not completely reversible or medium term effect, some limited flow-on effects, slight effect on native species, affecting plants/animals/people/small industry over a wide area, but not necessarily over the whole country
Major	Large, long term effect, but no species loss, affecting the whole country, both acute and chronic health effects possibly leading to small number of deaths or reduced life expectancy
Massive	Huge and widespread, irreversible, national impact, considerable secondary effects, acute and chronic health effects leading to deaths, species loss, serious social and cultural damage with displacement of persons and loss of livelihood, major economic disaster

The following qualitative word scale has been used to describe the magnitude (or expected value) of a beneficial effect occurring:

Table 3: Magnitude of beneficial effect

Descriptor	**Examples of descriptors for type and extent of beneficial effect**
Minimal	Slight or insignificant, short term, very localised (affecting only a few individuals, single plants/animals), no flow-on effects
Minor	Small, reversible, localised to small land area, a group of individuals, a single company/organisation or a local community
Moderate	Medium or mid range, medium term, affecting plants/animals/people/small industry over a wide area, but not necessarily over the whole country, some flow-on effects, regional short/medium term reduction in a weed/pest
Major	Large, affecting large communities and industries, some national impact
Massive	Huge and widespread, long term, national impact, extensive secondary or flow-on effects, eradication of a weed/pest, large increases in employment, development of a new industry

Table 4: Calculating the Level of risk

Likelihood	**Magnitude of effect**				
	Minimal	**Minor**	**Moderate**	**Major**	**Massive**
Very unlikely	Insignificant	Insignificant	Low	Medium	High
Unlikely	Insignificant	Low	Low	Medium	High
50% chance	Low	Low	Medium	High	High
Likely	Low	Medium	High	High	Extreme
Very Likely (Almost certain)	Medium	Medium	High	Extreme	Extreme