ENVIRONMENTAL RISK MANAGEMENT AUTHORITY
NGĀ KAIWHAKATŪPATO WHAKARARU TAIAO

FORM NO2G

Application for approval to

IMPORT INTO CONTAINMENT ANY NEW ORGANISM THAT IS GENETICALLY MODIFIED

under section 40 of the Hazardous Substances and New Organisms Act 1996

Application Title: Import of GM mice

Applicant Organisation: University of Otago, Genesis Research & Development and the Malaghan Institute of Medical Research

ERMA Office use only

Application Code: ☐☐☐☐☐☐☐☐ Formally received:____/____/____

ERMA NZ Contact: _____ Initial Fee Paid: $

Application Status:

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ENVIRONMENTAL RISK MANAGEMENT AUTHORITY
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Application for approval to import into containment any new organism that is genetically modified, under Section 40 of the Hazardous Substances and New Organisms Act 1996

IMPORTANT

1. An associated User Guide is available for this form. You should read the User Guide before completing this form. If you need further guidance in completing this form please contact ERMA New Zealand or your Institutional Biological Safety Committee.
2. This application form covers importation into containment of any new organism that is genetically modified, under section 40 of the Act.
3. If you are making application to import into containment an organism that is **not a genetically modified organism** you should complete **Form NO2N** instead of this form (Form NO2G)**.**
4. This form, together with form NO2N, replaces all previous versions of Form 2. Older versions should not now be used. You should periodically check with ERMA New Zealand or on the ERMA New Zealand web site for new versions of this form.
5. You can talk to an Applications Advisor at ERMA New Zealand who can help you scope and prepare your application. We need all relevant information early on in the application process. Quality information up front will speed up the process and help reduce costs.
6. This application form may be used to seek approvals for importing more than one new organism into containment where the organisms are of a similar nature.
7. Any extra material that does not fit in the application form must be clearly labelled, cross-referenced, and included as appendices to the application form.
8. Commercially sensitive information must be collated in a separate appendix. You need to justify why you consider the material commercially sensitive, and make sure it is clearly labelled as such.
9. Applicants must sign the form and enclose the correct application fee (plus GST). The initial application fee can be found in our published Schedule of Fees and Charges. Please check with ERMA New Zealand staff or the ERMA New Zealand website for the latest schedule of fees. We are unable to process applications that do not contain the correct initial application fee.
10. Unless otherwise indicated, all sections of this form must be completed for the application to be progressed.
11. Please provide an electronic version of the completed application form, as well as sending a signed hard copy.

You can get more information by contacting us. One of our staff members will be able to help you.

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Section One – Applicant Details

1.1 Name and postal address in New Zealand of the organisation or individual making the application:

Name > Three Institutions are joint applicants
1: University of Otago
2:Genesis Research and Development Corporation
3: Malaghan Institute of Medical Research

University of Otago

Postal Address > PO Box 56, Dunedin

Physical Address >
Department of Biochemistry, University of Otago, 710 Cumberland Street, Dunedin.

Phone > 03 479 7869

Fax > 03 479 7866

E-mail >

Genesis R&D

Postal Address > PO Box 50, Auckland

Physical Address > 1 Fox St., Parnell, Auckland

Phone > 09 373 5600

Fax > 09 373 2189

E-mail >

Malaghan Institute of Medical Research

Postal Address > PO Box 7060, Wellington

Physical Address > Level H, Wellington School of Medicine, Mein Street, Wellington South.

Phone > 04 389 5096

Fax > 04 389 5095

1.2 If application is made by an organisation, provide name and contact details of a key contact person at that organisation

This person should have sufficient knowledge to respond to queries and have the authority to make decisions that relate to processing of the application.

University of Otago

Name > Dr. Iain Lamont

Position > Biological Safety Officer

Address > Department of Biochemistry, University of Otago

Phone > 03 479 7869

Fax > 03 479 7866

E-mail > iain.lamont@stonebow.otago.ac.nz

Genesis R&D

Name > Dr. Hilary Sheppard

Position > staff scientist

Address > As above

Phone > 09 373 5600

Fax > 09 373 2189

E-mail > h.sheppard@genesis.co.nz

Malaghan Institute of Medical Research

Name > Professor Graham LeGros

Position > Director of Research

Address > As above

Phone > 04 389 5096

Fax > 04 373 5095

E-mail > glegros@malaghan.org.nz

1.3 If the applicant is an organisation or individual situated overseas, provide name and contact details of the agent authorised to transact the applicant's affairs in relation to the application

This person should have sufficient knowledge to respond to queries and have the authority to make decisions that relate to processing of the application.

Name > Not applicable

Section Two – Purpose of the Application

This form is to be used for an application to import into containment any new organism that is genetically modified. For an application to import into containment a new organism that is **not** genetically modified, use **Form NO2N**.

2.1 Give a short summary statement of the purpose of this application to be used on ERMA New Zealand's public register. (Maximum of 255 characters). Briefly describe the organism(s) to be imported into containment, and the purpose(s) for which you wish to import the organism(s).

> This application is generic in nature to allow for importation of strains of laboratory mice with specific genetic modifications to be used for a range of studies of gene or cell function and as models for human diseases.

2.2 Provide a short description of the background and aims of the project suitable for lay readers.

Describe the rationale for the overall project these organisms are to be used in so that people not directly connected with the research can understand why these organisms are required. This explanation is particularly important if the work involves DNA from native flora and fauna, or the use of human genes. In addition, discuss whether expression of the foreign genetic material is anticipated, and any unusual manipulative steps involved in the development.

> Genetically modified mice are now widely used in several areas of medical and other research. Such mice include (i) gene "knock-outs" where specific mouse genes are disrupted to investigate the role of that gene, (ii) gene "knock-ins" where mutations are introduced into specific genes or regulatory sequences in specific genes, and (iii) transgenic mice, where foreign genes may be introduced at a random location within the mouse genome. These mice are used to study specific gene or cell function, often in relation to increasing knowledge about human gene functions or diseases. Hundreds of GM mice are now commercially available, and new types are developed every year. Since GM mice are commonly used in many projects in our institutes, we wish to get an approval for importation to cover all GM mice that have similar levels of risk. This will enable us to have the necessary flexibility in our research projects, while not increasing the level of risk. The imported mice are laboratory strains (often highly in-bred), and will be placed in quarantine when they first arrive to check that they do not have infectious diseases. Small numbers of each type will be imported and will be bred when necessary to

produce mice for specific projects. In some cases different strains may be crossed after importation to achieve the desired type of mouse – such cross-breeding requires separate approval, and this will be applied for when necessary.

2.3 Public interest in the application

Provide comment on whether there is reason to believe or not to believe that there is potential for public interest in any aspect of the application. This may be related to any novel or unusual genetic manipulation, use of species or subjects of cultural significance, intended use of the GMO, level or nature of the risks involved, extent to which the application sets a precedent.

> GM mice have been routinely used in several areas of basic research for many years now, and the types of manipulations are not novel or unusual. The mice are not native or generally valued by Maori, and will only be used for contained laboratory research. Contained laboratory research appears to be widely accepted by the public. Conditions of animal use come under the jurisdiction of the Animal Welfare Act. Many imports of GM mice have been previously approved by ERMA, and several generic type applications for other organisms have also been approved, so this application does not set any precedents. Consequently, public notification of this application is unlikely to provide relevant information.

Section Three – Information on the Organism(s) to be imported

If the application is for importation of more than one organism, information must be provided separately for each organism. If there are commercial reasons for not providing full information here, alternative approaches must be discussed with and agreed by ERMA New Zealand.

3.1 Give the unequivocal identification of the organism(s) to be imported

Please provide details of the following:

Latin binomial, including full taxonomic authority:

> *Mus musculus* Linnaeus 1758

Common name(s), if any:

> House mouse, laboratory mouse

Type of organism (eg bacterium, virus, fungus, plant, animal, animal cell):

> animal

Taxonomic class, order and family:

> Mammalia; Rodentia; Muridae

Strain(s) and genotype(s), if relevant:

> various

Other information, including presence of any inseparable or associated organisms:

> Mice to be imported will not knowingly contain infectious agents. All mice will be quarantined for 30 days after importation so that it is likely that any infectious diseases will be able to be identified. In many (but not all) cases the mice will be derived from specific pathogen free facilities, and in these cases there will be little uncertainty about the absence of associated organisms.

3.2 Provide unique name(s) for the new organism(s) to be imported for entering in the public register.

These name(s) should clearly identify the species and strain(s) and genetic modification(s).
For example, "*Escherichia coli* DH5α modified by pBluescript containing cholera toxin gene"

> *Mus musculus* modified by targeted or random insertions of non-infectious gene constructs

3.3 How were the new organism(s) developed?

Provide details of the following:

Vector system(s):

> microinjection or transfection of DNA into mouse embryos or embryonic stem cells.

Type and source of additional genetic material:

> See appendix 1

Use of special genetic material of significance to Maori:
Please complete this table by marking the correct box

	Yes	No
Were native flora or fauna used as **host organism(s**)?		**X**
Was **genetic material** from native flora and fauna used in developing these GMOs?		**X**
If native flora and fauna were involved, are the species concerned endemic to New Zealand?		**X**
Was **human** genetic material involved in developing these GMOs? *Answer Yes if human genetic material in any form was used, ie obtained directly from humans (either Maori or non-Maori), from a gene bank, synthesised, copied and so on.*	**X**	
Was genetic material obtained **directly** from human beings used in developing these GMOs? *If Yes, provide additional details below.*		**X**

If native flora and fauna were involved (either as host organisms or as a source of genetic material), from where in New Zealand or elsewhere, was this material obtained? Be as specific as possible as this information may be needed to decide whether Maori have been appropriately consulted.

> No material from native flora or fauna will be used

If human genetic DNA was obtained directly from human beings, please provide details.

> To the best of our knowledge no material sourced directly from humans will be used. Instead human genetic material will be sourced from genebanks. If genetic material soureced directly from humans was used, there may be situations (due to the when the original sample was collected), where documents of informed consent may be difficult to source. Consequently, while every endeavour will be made to ensure that relevant documentation comes with the mice, we cannot provide an assurance that this will always be the case because it depends on other parties. We will be importing mice from reputable commercial suppliers or researchers that we expect will comply with requirements for consent associated with the use of human genetic material.

Other details of the genetically modified organism(s) (such as whether the modification is stably inherited, if the foreign genetic material is to be expressed, and anticipated characteristics resulting from such expression)**:**

> The modifications are introduced into cells or embryos and will be stably inherited if the modification is in germ line cells. Some modifications may not be in germ line cells, and so will not be stably inherited. Some of the modifications will result in disruption of an endogenous mouse gene and so a particular gene or genes may not be expressed, some of the modifications will results in modification of an endogenous mouse gene, while other mice will (also) express specific marker or reporter genes and/or specific genes from other organisms (or modified genes from mice). Characteristics will depend upon the gene(s) expressed.

In some cases mice to be imported may be derived from two (or more) different strains of GM mice that have been mated so that the offspring may contain multiple genetic modifications. In some cases the mice to be imported may be derived from different strains of mice (not necessarily genetically modified) to produce a desired strain.

An example of the type of mouse that may be imported is given below:

B6;129 Pluto tm This mouse strain has been modified by the introduction of loxP sites flanking exons 3 and 4 of the mouse pluto gene. The loxP sites contain a 34 bp sequence derived from bacteriophage P1. These are target sites for recombination by cre recombinase, a 343 amino acid protein that mediates recombination events, also derived originally from bacteriophage P1. This mouse will express pluto normally since the cre recombinase is not normally present in mice. However, if this mouse is crossed with a strain of mouse that has been genetically modified to express cre recombinase, exons 3 and 4 of pluto will be excised, thereby effectively deleting expression of this gene.

3.4 Identify the category or categories of genetic modification(s) as described in the current HSNO (Low-Risk Genetic Modification) Regulations, had the genetic modifications been carried out in New Zealand.

Identify specific class of modifications(s) as described in the Regulations and explain your characterisation.

> Category B(b)(ii)(C) – production of genetically modified whole animals

3.5 Characteristics of the organism(s) to be imported

Provide information on the biology, ecology and the main features or essential characteristics of each organism(s) to be imported. For example, note production of spores/seeds/pollen, conditions for growth and reproduction. Also provide information on affinities of the organism(s) with other organism(s) in New Zealand. This information should be relevant to the identification of the risks of the organism (section 5).

> Laboratory mice. Some of these are highly in-bred. These mice are often raised in specific pathogen-free environments, and have been kept for many generations in containment. Most mice will be fertile, although they may have lower fertility than wild mice. Some may have suppressed immune systems or congenital defects associated with the specific genetic modifications. The mice are derived from the house mouse, which is the same species introduced into New Zealand during human colonisation.

Section Four – The Proposed Containment System and its Effectiveness

4.1 Describe the proposed containment system (physical and operational) and the ability of the organism(s) to escape from this system. The adequacy of the containment regime is a principal consideration so you need to provide comprehensive information on the containment system. Containment facilities must be registered by MAF, and you should provide documentary evidence of this. Refer to relevant containment manuals as appropriate. Please also ensure that ERMA New Zealand has an up-to-date copy of the containment manual relating to this facility. Identify possible pathways of escape of the organism(s) from containment, including through lapses of security or sabotage. Describe the biological features of the organism(s) that might affect its ability to escape from containment.

> The mice will be kept in PC2 animal houses that are registered by the MAF Biosecurity Authority in accordance with the MAF Biosecurity Authority/ERMA New Zealand Standard 154.03.03 (Containment Facilities for Vertebrate Laboratory Animals). The University of Otago (on each of the Dunedin, Christchurch and Wellington Campuses), Genesis R&D and The Malaghan Institute all have suitable animal houses that are registered with MAF under this Standard and are regularly monitored by MAF as required under the Standard.. Standard containment requirements include rodent barriers on doors.

A study done by ERMA New Zealand noted that the likelihood of escape is a function of the number of animals contained rather than the number of different types of GM mice. The number of mice able to be held is controlled by the MAF registration and inspection process under the Biosecurity Act. Our experience, and that of other reputable research facilities holding GM mice, is that the risk of accidental escape of mice from PC2 containment is very low. Access to the animal facilities is controlled so that unauthorised people do not have easy access to the mice.

The containers used for shipping the mice are escape proof and are lined with metal wire mesh and securely sealed to prevent escape, as prescribed by IATA regulations.

The mice are laboratory strains that are used to being handled by humans. As such they may lack certain behaviours - the loss of which may increase the probability that they will be preyed upon, or otherwise decrease their competitive ability. In our experience mice outside of their cages are easy to re-capture.

Section Five - Identification and Assessment of Risks, Costs, and Benefits

This section must include information on the beneficial and adverse effects referred to in the HSNO Act. It is easier to regard risks and costs as being adverse (or negative) and benefits as being positive. You should consider costs and benefits with respect to both non-monetary and monetary (dollar) terms and also consider the distribution of their incidence. Provide a brief description of where the information in the application has been sourced from, e.g. from in-house research, independent research, technical literature, community or other consultation.

5.1 Ability of organism(s) to establish a self-sustaining population.

Discuss the ability of the organism(s) to establish an undesirable self-sustaining population, should an escape from containment occur, and the ease with which such a population could be eradicated. You should consider the ability of the organism to survive and reproduce if it did escape from containment.

> It is considered very unlikely that the GM mice will be able to establish self-sustaining populations. As noted above, rodent barriers in the facility are likely to prevent escape of any mice. There is a possibility that some of the mice may be able to survive and reproduce if they did escape, but many will be moderately or severely incapacitated by the genetic modifications, making it very unlikely that they will be able to breed with wild mice. For mice that do escape and survive, the genetic modifications are very unlikely to provide a selective advantage because they either involve knocking out of a mouse gene or introduction of genes from other organisms that by themselves would be very unlikely to provide selective advantages. In cases where modifications may result in more agile mice, extra precautions (such as stronger cages, and handling requirements) will be taken.

Studies of the ability of lab GM mice to survive if they escape do not appear to have been published. However, a paper Hendrick *et al*. 2000[1] may be relevant. They studied the survival of in-bred laboratory white-footed mice and laboratory bred wild derived mice in a nonlab environment where low numbers of true wild mice existed. Over the 10 week study the weekly survival rate of the inbred mice was estimated to be 56% that of the none inbred mice, and inbred male mice lost significantly more body mass throughout the experiment. If these results are extrapolated to *Mus musculus* (and the results of Meagher *et al*. 2000[2] suggest that they can be), it can be inferred that in-bred lab mice will do less well in the wild, even without the genetic modifications as discussed above. For laboratory mice that are not extensively in-bred their ability to compete and survive with wild mice may not be so compromised, so there may be some slightly greater uncertainty over their ability to establish self-sustaining populations

5.2 Identify all potential adverse effects of the organism(s).

Identify potential adverse effects associated with the organism(s) and with any inseparable organisms, both within containment, and outside of containment (should an escape occur). Consider effects on the environment, human health and safety (e.g. of

[1] Hendrick PW, Kalinowski ST (2000). Inbreeding depression in conservation biology. Annual Review of Ecology and Systematics 31, 139-162

[2] Meagher S, Penn DJ, Potts WK (2000). Male-male competition magnifies inbreeding depression in wild house mice. Proc. Natl. Acad. Sci USA 97, 3324-3329.

workers in the containment facility), and ethical and cultural effects. It is important to think about the source of the risk, i.e. the way in which the risk is created (the exposure pathway), and then the consequences of exposure. Adverse effects should be identified for the following categories:

A. Potential adverse effects on the environment, in particular on ecosystems and their constituent parts (e.g. adverse effects on: life supporting capacity of air, water, soil and ecosystems; native and valued introduced flora and fauna; natural habitats and the intrinsic value of ecosystems; New Zealand's inherent genetic diversity; animal or plant health)

> It is very unlikely that any adverse effects on the environment will result since the animals will be from reputable suppliers and will not have infectious diseases. The only identifiable risk from the importation of these modified mice into New Zealand is their accidental escape from the contained facility in which they will be housed, or during transport from the containers in which they will be shipped.

B. Potential adverse effects on public health (including occupational exposure)

> It is very unlikely that the animals will have adverse effects on human health since they will not contain infectious diseases or agents able to infect humans.

C. Potential adverse effects on the relationship of Māori and their culture and traditions with their ancestral lands, water, sites, waahi tapu, valued flora and fauna and other taonga (taking into account the principles of the Treaty of Waitangi). For example, you should consider whether the organism(s) would have an effect on specific native flora or fauna if they escaped from containment.

> No adverse effects on Māori are expected since the mice do not contain genetic material sourced from native flora or fauna, and the mice are to remain in containment. The animals will not breed with native fauna, and much of the research is directed towards treatment of human diseases.

D. Other potential adverse effects (such as New Zealand's international obligations, social or economic adverse effects, ethical issues)

> No other adverse effects are anticipated.

5.3 Provide an assessment of the adverse effects identified in Section 5.2.

The assessment should include the nature, likelihood or probability of occurrence, and magnitude of each adverse effect (i.e. **the risk**), and the value (in monetary or non-monetary terms) of a particular adverse effect (i.e. **the cost**). The uncertainty bounds of the information contained in the assessment should also be discussed. The assessment should consider options and proposals for managing risks identified and consider whether the identified risks can be adequately managed by the proposed containment system. Adverse effects should be assessed in relationship to:

A. Potential adverse effects on the environment, in particular on ecosystems and their constituent parts (e.g. adverse effects on: life supporting capacity of air, water, soil and ecosystems; native and valued introduced flora and fauna; natural habitats and the intrinsic value of ecosystems; New Zealand's inherent genetic diversity; animal or plant health)

> It is very unlikely that any adverse effects on the environment will result since the animals will be from reputable suppliers and will not have infectious diseases. Mice will be kept in quarantine for a period of 30 days after importation, and observed for any sign of disease. Shipping materials will be labelled and destroyed as bio-hazardous materials.

In the event of an escape from containment, adverse effects are considered very unlikely. This is because, as already noted, in the event of escape the animals will be very unlikely to establish a self-sustaining population. Animals will either be readily recovered within the facility, or if they evade recapture most will probably not survive and reproduce either because the genetic modifications may be detrimental to their survival in the wild, or because they are laboratory strains that have limited competitive abilities in the wild. Laboratory mice have been transported using the standard transport procedures for many many years and have been demonstrated to provide effective containment of the mice, so that we consider it very unlikely that mice will escape during their transport.

Should accidentally released mice succeed in surviving outside of containment or transmitting their genetic traits to progeny, it is considered very unlikely that there will be any long-term adverse effects. Some of the traits will probably impose disadvantages to survival in the wild as they are likely to have adverse effects on the tissues in which they are expressed, while others may result in no beneficial or adverse effects to mice containing them. None of the modifications are such that the impact of these genetically modified mice on the environment would be predicted to be greater than the impact of wild mice. Introduction of traits associated with increasing reproductive output or otherwise enhancing mouse survival in the wild are prohibited in the organism description. Consequently the magnitude of any adverse environmental effects are very likely to be minimal.

B. Potential adverse effects on public health (including occupational exposure)

> Since the mice will be free of infectious diseases, no infectious pathogenic traits will be introduced, and bedding and other material associated with the mice will be disposed of by incineration or sterilization, it is very unlikely that there will be any adverse effects associated with the handling of these mice. Any adverse effects on human health (if they occur) are likely to be limited to those directly handling the mice, so will be local, and based on past experience with mice, treatable. Consequently the magnitude of any adverse effects are expected to be minimal. Based on many years of handling such mice there is little uncertainty associated with this.

C. Potential adverse effects on the relationship of Māori and their culture and traditions with their ancestral lands, water, sites, waahi tapu, valued flora and fauna and other taonga (taking into account the principles of the Treaty of Waitangi). For example, you should consider whether the

organism(s) would have an effect on specific native flora or fauna if they escaped from containment. If consultation with Maori has been undertaken, provide details of the process of consultation and the outcome.

> It is very unlikely that the importation of these mice will adversely affect the relationship of Māori and their culture and traditions, since they are for contained laboratory use and do not contain material from native biota. Genetic material sourced from Māori will not be used. Consequently, the magnitude of any adverse effects are considered to be minimal.

D. Other potential adverse effects (such as New Zealand's international obligations, social or economic adverse effects, ethical issues)

> No other potential adverse effects have been identified.

5.4 Identification of beneficial effects (benefits)

Identify and describe monetary and non-monetary benefits associated with importing the organism(s) into containment. Outline and discuss the purpose(s) for the importation and the potential use of the organism(s). Focus on the immediate benefits, as well as longer-term benefits. For example, "increase in scientific knowledge", "increased production of agricultural produce". Substantiate claims by reference to sources of information. Specify whether the benefits identified are environmental, public health or economic benefits; and/or are specific benefits to Maori.

> The mice will be used for laboratory research, aimed primarily at the understanding of human diseases and gene function. As such the immediate benefit will be an increase in scientific knowledge related to these diseases and genes. Some of the research may eventually lead to improved medical treatments.

An example of the utility of GM mice is the fact that the New Zealand Transgenic Animal Users Group did a survey in the year 2000 and found that over 5000 publications dealing with transgenic or knockout mice appeared in Pubmed (A citation index listing published papers related to medicine). This led to the observation that on average, a scientific paper based on these mice is published every 2 hours.

5.5 Provide an assessment of the benefits identified in Section 5.4.

Estimate the likelihood that the benefits will be realised, the magnitude of benefits associated with importing the organism(s) into containment, and any uncertainties associated with this assessment. You should also indicate who would receive the benefits and the expected time-course of delivery of the benefits.

> As has been shown in the scientific literature, the use of mice to increase our understanding of some diseases and gene function is very likely, and there is little uncertainty over this. The magnitude of such benefits are, however, difficult to predict.

5.6 Overall evaluation of risks, costs, and benefits

This overall evaluation is the main task of the Authority. The Authority has to decide whether the beneficial effects of having the organism in containment outweigh the adverse effects of the organism and inseparable organism(s). The Authority must also be satisfied that the organism can be safely contained. You may wish to express a view on the relative importance of the different risks, costs and benefits and how they should be brought together in making a decision.

> The principal benefits are increase in scientific knowledge. Since mice are demonstrably able to be securely contained, and the modifications are not expected to increase pathogenicity or survival ability there are no significant risks. The inability to use such mice in our research would severely hamper research projects and the potential to win research funding.

Section Six – Additional Information

6.1 Do any of the organism(s) need approvals under any other New Zealand legislation or are affected by international obligations? For example, indicate whether the organism is subject to other New Zealand legislation, e.g. the Biosecurity Act 1993, or Animal Welfare Act 1999; or if the organism(s) are listed in CITES, then approval is required from both the importing and exporting countries.

> No. Material from CITES-listed species is specifically excluded from the organism description. Research involving the mice will be subject to the requirements of the Animal Welfare Act, and projects approved by the Institution's Animal Ethics Committee.

6.2 Have any of the new organism(s) in this application previously been considered in New Zealand or elsewhere? For example, has the organism(s) been previously considered for import (e.g. under the Plants Act)?

> Many applications for the importation of GM mice have been made in the past.

6.3 Is there any additional information that you consider relevant to this application that has not already been included?

> No

6.4 Provide a glossary of scientific and technical terms used in the application.

> N/A

6.5 List of appendices. List any appendices included with this application. Any information that is commercially sensitive, or additional material included with the application (such as details of consultations, referenced articles) should be contained in appendices. The main application should refer to the relevant appendices but be able to be read as a stand-alone document.

> Appendix 1 – Organism description
> Appendix 2 Paper by Meagher *et al*. 2000.
> Appendix 3 Paper by Hendrick and Kalinowski 2000.

Section Seven – Application Summary

Summarise the application in clear, simple language that can be understood by the general public. Include a description of the organism(s) to be imported into containment, and any risks and benefits associated with their importation. This summary will be used to provide information for those people and agencies who will be notified of the application (eg Ministry of Agriculture and Forestry, Department of Conservation, Crown Research Institutes) and for members of the public who request information. Do not include any commercially sensitive information in this summary.

> This application is for approval to import a broad range of genetically modified strains of laboratory mice for research on gene and cell functions. The mice are often used to aid medical research, but may also be used for helping understand more general cellular behaviour. New strains of such mice are being constantly developed and this application would allow rapid and cost-effective access to such strains without increasing levels of risk. The range of modifications are described in general terms, similar to previous applications approved by the Environmental Risk Management Authority, and exclude mice that have been modified so that they produce infectious agents or would be more able to survive outside of the laboratory. The mice will be maintained within registered laboratory animal containment facilities (physical containment level 2) in cages and rooms that are demonstrably able to contain the animals. Based on many years research with such mice it is very unlikely that any of the mice will escape from containment, or if they did escape would establish self-sustaining populations.

Risks to the environment will be minimal since the mice will not express sequences that will be pathogenic or infectious to other organisms, and in some cases the genetic modifications will severely compromise the animals survival or competitive ability. Modifications to increase the reproductive abilities of the mice or to otherwise enhance their ability to survive in the wild will not be introduced. Potential risks to human health will also be minimal since the mice will not be modified to produce human infectious particles. Bedding and material associated with the mice, as well as dead mice, will be disposed of in a safe manner. The mice will not contain genetic material from native flora and fauna, or be used in ways that are likely to adversely affect the relationship of Maori with their culture and traditions.

Checklist

Please check and complete the following before submitting your application:

All sections completed	Yes
Appendices enclosed	Yes
Confidential information identified and enclosed separately	NA
Copies of additional references attached	Yes
Cheque for initial fee (incl. GST) enclosed	Yes
If "yes", state amount:	$3375
Direct credit made to ERMA bank account:	Yes/No
If "yes" give date of direct credit …/…/… and amount deposited:	$…….
Application signed and dated	Yes
Electronic copy of application e-mailed to ERMA New Zealand	Yes

*NA – not applicable

Signed: **Date:**

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Cnr Waring Taylor & Customhouse Quay
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Phone: 04-916 2426 Fax: 04-914 0433
Email: info@ermanz.govt.nz
Website: www.ermanz.govt.nz

ENVIRONMENTAL RISK MANAGEMENT AUTHORITY
NGĀ KAIWHAKATŪPATO WHAKARARU TAIAO

Appendix One: Organism Description

The organism will be genetically modified mice derived from any laboratory strain of *Mus musculus* that is not known to contain infectious agents and modified by deletion and/or insertion of DNA integrated into the mouse genome.

Constructs to be introduced into the mice will only contain any or all of the following elements described below, so long as the genetic material is not sourced from New Zealand native flora or fauna, and does not increase the level of risk of the mouse in relation to its ability to escape from containment, establish a self-sustaining population, or increase its potential to cause adverse effects to the environment or human health above that of non-modified laboratory mice. Modifications to the mice shall only be those meeting the requirements of Category A or B genetic modifications as described in the HSNO (Low-Risk Genetic Modification) Regulations.

Transcriptional elements
Promoter, operator, regulatory element binding and enhancer sequences, other transcriptional responsive elements and/or terminator sequences derived from bacterial, viral, or mammalian genes.

Reporter genes
Well characterised[3] genes that can be easily assayed. So long as the genes are not sourced from NZ native flora of fauna, and do not produce proteins that have an oral or dermal vertebrate LD_{50} less than 100 micrograms/kg.

Selectable marker genes
Well characterised genes that confer any of the following:

- the ability to deactivate antibiotics
- the ability to deactivate specific metabolic inhibitors
- the ability to deactivate specific vertebrate toxins

Other Features
Other sequences may be included that are:

- Polyadenylation signals
- Splice sites
- Secretory and targeting signals
- Intron signals that function to increase gene expression
- Homologous recombination sites and flanking sequences
- Ribosomal binding sites and/or Kozak sequences
- *Cre/Lox* or other recombinase systems
- Regulatory sequences for induced expression

[3] Well characterised means that the DNA has been sequenced and there is an understanding of the gene's function and, if relevant, the potential gene products

- Insulator elements

Other donor genetic material
The mice may also contain well characterized nucleic acids sourced from humans (provided that the human donor material shall not come from Maori), vertebrates, or bacteria.

The donor genetic material shall not include:

- Genes encoding vertebrate toxins that have an oral or dermal LD_{50} of less than 100 micrograms/kg
- Sequences that will produce particles able to infect humans, animals or plants
- Species listed by the Convention on International Trade in Endangered Species (CITES)