ENVIRONMENTAL RISK MANAGEMENT AUTHORITY
NGĀ KAIWHAKATŪPATO WHAKARARU TAIAO

ERMA New Zealand

FORM 2

Application for approval to

IMPORT INTO CONTAINMENT ANY NEW ORGANISM

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

Office use only ☐☐☐☐☐☐☐☐

Fees $_____ Date received ___/___/___ Verified date ___/___/___ _____Job manager

Application for approval to import into containment any new organism under Section 40 of the Hazardous Substances and New Organisms Act 1996

IMPORTANT

Before you fill in this application form please talk to ERMA New Zealand. We can help you scope and prepare your application. The scale of information we need should match the potential significance of the application. For example, applications which may pose a significant risk to the environment or to human health need to be supported with more substantial information than applications which clearly pose a more minor risk.

We need all relevant information early on in the application process. Quality information up front will speed up the process.

Any extra material that does not fit in the application form must be clearly labelled and cross-referenced in the application form. Commercially sensitive information should be collated in a separate document.

All applicants must sign at the end of the form and enclose the correct application fee. The standard non-notified application fee is $750 (excl GST). We are unable to process applications that do not contain the correct fee.

All references to regulations in this form, unless otherwise noted, refer to the Hazardous Substances and New Organisms (New Organisms Forms and Information Requirements) Regulations 1998.

Copies of all our application forms will soon also be available on our website: www.ermanz.govt.nz, and also in electronic form (MS Word format).

If you have any suggestions for improvements to this form, please contact our operations staff at the address below.

You can get more information at any time by telephoning, writing to, or calling in at our Wellington office. One of our staff members will be able to help you.

List of application forms for new organisms:

These are all our application forms related to new organisms. Please check you have the right one.

Form 1 Application for approval under section 34 of the Act to import for release, or release from containment, any new organism—including rapid assessment.

Form 2 application for approval under section (40)(1)(a) of the Act to import into containment any new organism **(this form)**.

Form 3 application for approval under section 40(1)(b) of the Act to develop in containment any genetically modified organism – including rapid assessment.

Form 4 application for approval under section 40(1)© to field test (including large scale fermentation) in containment any genetically modified organism.

Form 5 application for approval under section 47 to use a new organism in an emergency.

Form 6 application for approval under section 62 for grounds for reassessment of a new organism in containment.

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NGĀ KAIWHAKATŪPATO WHAKARARU TAIAO

Application for approval to import into containment any new organism under Section 40 of the Hazardous Substances and New Organisms Act 1996

Applicant details

1. Name and address in New Zealand of the applicant:

This should be the organisation or person formally responsible for this application.

Name: University of Otago

Address:

PO Box 56, University of Otago, Dunedin

Phone: 03- 479-7846

2. The applicant's address for service in New Zealand (if different from above):

Address:

3. Name of the contact person for the application (if different from applicant): **This person should have sufficient knowledge to respond to queries and have the authority to make decisions on behalf of the applicant that relate to processing the application.**

Name:

Position:

Phone:

Fax: **Email:**

4. Summary

Provide a summary of the information contained in this application relating to the identification of the organism.

The information should include summaries of:

- the identity of the organism;
- if it is a genetically modified organism, the source of the donor nucleic acid material and the purpose of the modification;
- what the organism will be used for and why it has been selected.

Provide a summary of the information contained in this application relating to the assessment of the effects of the organism.

The information should include summaries of:

- the risks, costs and benefits and the assessment of these;
- the containment system proposed.

This summary will be used to provide information to people and agencies who may request it. Applications to import any new organism into containment will not be publicly notified. However, as the information in this section may be released upon request, applicants should ensure that this summary does not contain any commercially sensitive information.

[Yes/No?] further information

The Malaghan Institute of Medical Research, Wellington and Christchurch Medical Schools and the University of Otago conduct research into several areas of experimental biology, immunology, disease treatment and behavioral sciences.

Murine cell lines are used to model the biochemical events which occur inside normal cells, as an alternative to using actual rodents. The results of this research may be applied to improving human/animal health through the development of diagnostic tests, therapies or vaccines against disease.

The murine cell lines will be modified by genetic constructs encoding eukaryotic and/or prokaryotic DNA sequences inserted at sites within the genome. The cell lines are derived from various mouse strains, engineered using promoters, reporter genes and selection markers described in Appendix one.

These cells are fragile and require sophisticated culture systems to maintain viability. They cannot survive outside of this fragile environment. They cannot transmit to other organisms and thus pose no threat to the environment, ecosystem or people.

Organism details

5. The identification of the organism:

This should include all information necessary to identify the organism and should include:

- The taxonomic classification and name of the organism;
- The essential characteristics that identify the organism and its behaviour in the environment;
- Sufficient information to enable the Authority to uniquely identify the organism in the register as required by section 20(2)(b) of the Act.

(This section may also include the name by which the organism is generally known.)

The information in this section would include, for example, information on the habitat range and climatic sensitivity of the organism. References to the scientific literature supporting this information should be given here if appropriate.

In the separate box below the applicant should provide the name of the organism suitable for inclusion in the Authority's public register.

Information that is commercially sensitive should be clearly identified. If supplied separately, a cross-reference to it should be included.

Taxonomic Name: **Mus Musculus**

Characteristics: **See description**

Organism details

This application covers murine cell-lines and primary cultures modified by transfection of genetic constructs encoding eukaryotic and/or prokaryotic DNA sequences inserted at non-functional sites within the genome. All cell lines referred to in this application have identical or near identical risk assessments.

Each cell-line represents an immortalised clone that can only be grown under specified culture conditions, typically in a defined culture medium at a constant temperature with regulated CO_2 levels. The cultures have the potential to grow indefinitely under these conditions, or can kept as frozen stocks in liquid nitrogen.

No information regarding the construction of these cell lines is considered commercially sensitive.

[Yes/No?] further information [Yes/No?] commercially sensitive information

Name of the organism that may be used for the Authority's public register: Mus Musculus

6. If the organism is a genetically modified organism, information on the details of the genetic modifications:

This information shall include full details of the genetic constructs and modifications and the source and characteristics of the foreign nucleic acid.

This information should clearly identify the source of the donor genetic material and the characteristics. The desired characteristic (eg, herbicide resistance) and any other significant characteristics that may be expressed by the donor genetic material in the organism should be described.

Information on the stability and homogeneity of the construct should be given, if known. If this information is not known then this should be explicitly stated. References to the scientific literature supporting this information should be given here if appropriate.

Information that is commercially sensitive should be clearly identified. If supplied separately a cross-reference to it should be included.

[Yes/No?] further information [Yes/No?] commercially sensitive information

Genetic modifications

The cell-lines and primary cultures considered in this application carry genetic constructs containing eukaryotic and/or prokaryotic DNA sequences inserted at non-functional sites within the murine genome. The cell lines included have the same or very similar risk assessments.

The cell lines are derived from various mouse strains as described in Appendix One.

The cell lines will be modified with promoters, reporter genes, selectable markers and donor DNA as described in Appendix One

The source for the donor material may be from commercial laboratories, other researchers or research institutes.

Each cell-line represents an immortalised clone that can only be grown under specified culture conditions. No information regarding the construction of these cell lines is considered commercially sensitive.

7. The reason why an application is necessary for the organism:

Refer to the definitions set out in Section 2 of the Act, to the prohibited organisms in the Second Schedule of the Act, and for genetically modified organisms, to the exemptions in the HSNO (Organisms Not Genetically Modified) Regulations 1998.

Under the HSNO Act 1996 permission is needed to import any genetically modified organism. These murine cell lines are low risk yet need permission. The cell lines considered in this application carry genetic constructs and therefore can be classed as genetically modified organisms as defined under the Act. It should be noted that murine cell lines are not on the list of prohibited items as defined under the second schedule of the HSNO Act 1996.

8. The purposes for which an approval is sought:

Reference should be made to the purposes specified in section 39(1) of the Act and the information should also provide sufficient details on the purpose of the application to enable the Authority to provide the information required in the register (under section 20(2)© of the Act).

The information in this section should be as expansive as possible. While the applicant may have only one potential use in mind, an approval would enable other uses as well. To enable the Authority to have access to all relevant information all the potential uses of the organism should be provided. The information on how well the organism performs these uses is necessary to enable the Authority to determine the performance characteristics of the organism.

Information that is commercially sensitive should be clearly identified. If it is supplied separately a cross-reference to it should be included.

[NO] further information [NO] commercially sensitive information

As defined under Section 39(1) of the HSNO Act 1996, the approval for these organisms is primarily for the purpose of (h) and (f), as listed in this section.

The cell lines will be used to carry out research into the biochemical and cellular events underlying mammalian physiological processes. The cells in vitro will be used in studies on viability, proliferation, death and other responses to various stimuli. At a basic level these cells will be used in vitro to study biochemical and immunological function. They may also be used in vitro to produce proteins, cytokines and antibodies. In vivo these cells will be used to study cancer, blood cell formation and the immune system. The results of this research may be applied to improving human/animal health through the development of diagnostic tests, therapies or vaccines against disease.

Provide in this box a statement describing the purpose for making the application. This statement may be included in the Authority's public register (please use a maximum of 255 characters):

To import into containment genetically modified murine cell lines for use in research into the biochemical and cellular events underlying mammalian physiological processes. Results of this research may be applied to improving human/animal health.

9. Information on any likely inseparable organisms:

Information should be provided on any organism which is unable to be separated from any new organism at the time of making the application. Examples may include foot and mouth and scrapie causing organisms in animals and viruses in plants.

[Yes/No?] further information

These are kept sterile and contain no inseparable organisms.

Assessment of Effects

The information to be provided in these sections should cover the assessment of effects (both adverse and positive) of the organism. Where appropriate these sections may be combined in section 13 below.

Effects should be clearly assessed where relevant, including details as to how the risks will be controlled by the proposed containment system. **Where these adverse effects are identified, in the first instance by the applicant, as being minor then these do not require in-depth assessment.**

10. Information on all the possible adverse effects of the organism on the environment:

This should include information on the effects of the organism on ecosystems, public health, and Maori culture and taonga. It should also include information relevant to the matters in sections 4, 5, 6, 7, 8, and 37 of the Act and any regulations made under section 41 of the Act. The assessment should identify and assess risks, costs and benefits.

The information should give particular regard to:

Environmental and ecosystem effects (section 6(a) and (b) of the Act)

- assessment of the known and possible adverse effects throughout the life cycle of the organism on the sustainability of native and valued introduced flora and fauna and on the intrinsic value of ecosystems. *[Include an assessment of the ability of the organism to establish an undesirable self-sustaining population and the ease with which the organism could be eradicated if it was established.]*

Public health effects (section 6© of the Act)

- assessment of the known and possible adverse effects throughout the life cycle of the organism on public health. *[Assessment should take account of aspects of public health and safety including, where appropriate, effects from occupational exposure and effects from environmental exposure to the organism.]*

Relationship of Maori with taonga (section 6(d) of the Act)

- assessment of the known and possible adverse effects throughout the life cycle of the organism on the relationship of Maori and their culture and traditions with their ancestral lands, water, sites, wahi tapu, valued flora and fauna, and other taonga. [Include details of consultation (if any) carried out.]

The ability of the organism to escape from containment.

11. In the identification and assessment of risks, costs and benefits and other impacts, which may occur should the organism escape, include those matters set out below.

The information should comprise of the risks identified and include:

- the nature of the adverse effects of the organism.
- the probability of occurrence and the magnitude of each adverse effect.
- the risk assessed as a combination of the magnitude of the adverse effect and the probability of its occurrence.
- the options and proposals for managing the risks identified.
- the uncertainty bounds on the information contained in the assessment, expressed quantitatively where possible but otherwise through narrative statements.

The identification and assessment of costs and benefits required in each application must include.

- the nature of the costs and benefits associated with the proposed new organism and whether they are monetary or non-monetary;
- the magnitude or expected value of the costs and benefits and the uncertainty bounds on the expected value.

Relevant costs and benefits will be those which pertain to the New Zealand economy, society and environment and which would not arise if the application was not approved (ie the opportunity cost to New Zealand). They shall include the long term as well as short term, and consequential as well as direct costs and benefits.

The information on risks, costs and benefits shall include the distributional effects over time, space and groups in the community. It shall also include the uncertainty intervals associated with these estimates.

Risks

There are no perceivable risks to individuals, including staff who work with murine cell lines using the appropriate physical containment procedures. Likewise there is no perceivable risk to the environment, ecosystem or public health related to the import of these organisms, as they cannot survive outside a strictly controlled laboratory environment.

Costs

The cost to New Zealand, should this application not be approved would be significant. Biomedical research is reliant on cell lines for research into mechanisms of disease. As technology grows, cell lines will be able to be used more and more for higher level research. Without access to the latest murine cell lines this type of work can not be continued. This would delay understanding of disease and possible treatments, as well as pushing up the number of animals that must be used in biomedical research.

Benefits

The benefits of these murine cell lines is in the use they are to research and adding to the knowledge base. That is, they help in testing how diseases respond under certain conditions and treatments. There are no real perceived financial benefits connected to the use of these organisms. Financial gains would be along the lines of attracting funds from granting bodies due to progress of research.

12. Information on the positive effects of the organism:

Use of these organisms will assist in the identification of biological, immunological, behavioral and disease processes and development and testing of possible treatments for common diseases. The use of cell lines can also reduce the number of laboratory animals needed to carry out research.

13. Assessment of effects

If the assessment of effects is combined into this section, applicants should clearly indicate how the information requirements in sections 10, 11 and 12 of this form are addressed.

[Yes/No?] further information [Yes/No?] commercially sensitive information

Environmental and ecosystem effects

Cell lines require specified culture conditions, typically in sterile culture in a constant temperature incubator with regulated CO_2 levels. Under these conditions the organisms can theoretically survive indefinitely. However outside of these conditions there is no practical chance of survival. Even if these organisms were accidentally released there is no chance of adverse effects on the environment and ecosystem. The fragile nature of these cell lines makes the risk assessment identical or near identical for all cell lines. Were a cell line to contain genetic material from a prohibited organism, which they will not, it would have no greater chance of surviving outside of the controlled laboratory environment than any other cell line. Due to the nature of the medical research undertaken with murine cell lines, no dangerous toxins or virulent microorganism will be produced. All work with imported murine cell lines will be conducted in an approved containment facility for microorganisms under MAF/ERMA standard 154.03.02.

Public Health Effects

As with environmental and ecosystem effects, no adverse public health risks are envisaged. Staff working with the cell lines are all trained and operating to procedures such as those outlined in A/NZS 2243.3 standard for microbiology.

Relationship with Maori Taonga

Mouse cell lines do not pose a threat to traditional Māori food sources, natural resources, indigenous flora and fauna or the purity of water, land and air. Nor does the importation of mouse cell lines impose any restrictions on the rights of control of natural resources embodied in the Treaty of Waitangi. The aim of research with these cell lines will impact on the physical health of Māori, by adding to the understanding of disease mechanisms and applying this understanding to the treatment, cure and diagnosis of disease.

Professor xxxx has made contact with Kamatua xxxx of Iwi Nagti Tuwharetoa and discussed the use of imported organisms in the research conducted at the Malaghan Institute. Kamatua xxxx expressed his full support for the purpose of importing such organisms, to help understanding of diseases relevant to the Maori population. There

are no written records of the above mentioned conversations. Other such consultations are in progress with the University of Otago and local Iwi.

Assessment of risks, costs and benefits

The murine cell lines that we wish to import are necessary for the type of research conducted at the Malaghan Institute, University of Otago and its Medical Schools. Therefore the costs to this research, should this application be declined, are potentially very high. Many research projects will be stalled. The benefits are the understanding achieved through our research into biological and disease systems and their possible treatments. The risks to the environment, public health and staff health are negligible, yet the possible benefits to public health are significant if the research is successful at combating diseases common to the New Zealand public.

Containment System

14. Information about proposed containment system:

Provide information on how it is proposed that the organism be adequately contained including how the proposed containment system conforms to the requirements of the Parts I and II of the Third Schedule of the Act as appropriate.

This may include reference to, and outlines of, appropriate standards and codes of practice.

[Yes/No?] further information

Containment

The murine cell-lines and vectors are in Schedule 2 of the Low Risk Regulations, this work falls into Category A of the Regulations. Therefore the containment level for the organism is PC1 of A/NZS 2243.3. . The work will be carried out in a containment facility registered under the Biosecurity Act 1993. All studies will be directed by well-trained staff and will be subject to the strict safety guidelines outlined by The University of Otago safety committees. Access to the containment laboratories is restricted to staff.

Each murine cell-line represents an immortalized clone that can only be grown under specified culture conditions, typically in sterile culture in a constant temperature incubator, and with regulated CO_2 levels. Although the cell-lines have the potential to grow indefinitely under these conditions, untended cells will become overgrown and die. Cells removed from these culture conditions will rapidly die. These cells have no potential to self-propagate and therefore present negligible risk of release from containment.

The Malaghan Institute, University of Otago, Christchurch School of Medicine and the Wellington School of Medicine all have approval as transitional facilities under MAF standard 154.02.17. The Malaghan Institute, University of Otago and Christchurch School of Medicine also have approval as Containment facilities under MAF/ERMA standard 154.03.02.

International and related matters

15. Information on all occasions where the organism has been considered by the government of any prescribed State or country or by any prescribed organisation and the results of such consideration: Where no countries or organisations are prescribed by regulations made under section 140(1)9k) of the Act, this section can be omitted.

If the applicant is aware that the organism has previously been considered by, for example, any OECD or APEC country, information on the nature of that consideration, including the result, should be provided if known.

[NO] further information

There will have been many considerations and acceptances of most of the types of cell lines contained in this application. Many of these murine cell lines are commonly used in comparable research.

16. Information on New Zealand's international obligations that may be relevant to the application:

Where the applicant is aware that New Zealand's international obligations may be relevant to the application, indicate the nature of the obligation and the effect this may have on the application.

If the applicant is aware of obligations such as the WTO Agreements, the Convention on International Trade in Endangered Species (CITES), Trans Tasman Mutual Recognition Agreement and the like that may be relevant to the application, then information on these obligations should be provided, if known.

[NO] further information

To the best of our knowledge no organisms involved with this application involve any international obligations.

Previous considerations

17. If the application relates to an organism that has been previously considered by the Advisory Committee on Novel Genetic Techniques or the Minister for the Environment on the recommendation of the Interim Assessment Group, details of the consideration and its results:

[NO] further information

To the best of our knowledge no organisms involved with this application have been considered by the advisory committee on novel genetic techniques or the Minister for the Environment.

Other relevant legislation

18. Information on other legislation relevant to the organism and its use throughout its life cycle.

If the organism is also subject to other legislation (eg. an Import Health Standard under the Biosecurity Act 1993, or resource consent under the Resource Management Act 1991), details should be provided.

[NO] further information

Besides the HSNO Act 1996, other legislation relevant to importing murine cell lines are the Biosecurity Act 1993 and Import Health Permits issued by MAF. The Malaghan Institute and Otago University comply with the conditions of both of these pieces of legislation.

Glossary

19. A glossary of scientific and technical terms used in the application.

This may be appended to the application on a separate form if desired.

[NO] further information

germ-line - unmodified genetic material transmitted to progeny via gametes.

homologous recombination - The exchange of DNA fragments between two DNA molecules or chromatids of paired chromosomes (during crossing over) at the site of identical nucleotide sequences.

murine - relating to, affecting, resembling, or derived from a rat or mouse.

mutation - a heritable change in DNA sequence resulting from mutagens. Various types of mutations include frame-shift mutations, missense mutations, and nonsense mutations.

plasmid - autonomously replicating, extrachromosomal circular DNA molecules, distinct from the normal bacterial genome and nonessential for cell survival under nonselective conditions. Some plasmids are capable of integrating into the host genome. A number of artificially constructed plasmids are used as cloning vectors.

recombination - The process by which offspring derive a combination of genes different from that of either parent. In higher organisms, this can occur by crossing over.

selectable marker - an approach to facilitate the detection of targeted cells by decreasing the detection of random integrants rather than increasing targeting efficiency. Positive selector genes, such as neomycin^{r}, confers resistance to drugs normally lethal to the cell. Negative selector genes, such as HSV tk, confers sensitivity to certain drugs (cells expressing HSV tk are sensitive to gancyclovir) resulting in cell death when the drug is included as a supplement of tissue culture media.

Other relevant information

20. Provide here any other information required by the Act or regulations not included under any other section of this form.

[NO] further information

[NO] commercially sensitive information

No other relevant information

Summary of Application Contents

(Please check the application is complete and identify attachments)

[ ] Fees enclosed

[ ] Assessment of effects included

[ ] Confidential information supplied

[ ] Signed and dated

[NO] Appendices attached and cross-referenced (list below)
Appendix One – Organism Description NOC99008

Signature of applicant or person authorised on behalf of applicant _____ **Date:**

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