

ENVIRONMENTAL RISK MANAGEMENT AUTHORITY DECISION

Amended 18 November 2005, 22 August 2007, 14 December 2007 and 11
March 2010

Date Signed 30 September 2002

Application code:	GMD02028
Application category:	Develop in Containment any New Organism under the Hazardous Substances and New Organisms (HSNO) Act 1996
Applicant:	AgResearch Limited
Purpose:	To develop transgenic cattle that can express functional therapeutic foreign proteins in their milk, and to develop transgenic cattle to study gene function and genetic performance
Date application received:	1 May 2002
Hearing	13 - 15 August 2002
Considered by	A Special Committee of the Authority comprising Authority members Jill White, Colin Mantell, Lindie Nelson and Jane Lancaster, and appointed member Manuka Henare.

Summary of the Decision

The application received was for the development in containment of *Bos taurus* cells and animals modified with a range of genes derived solely from humans, mice, cattle, deer, sheep, and goats and other genetic sequences, including reporter and selectable marker genes and expression control sequences, derived from both specified and non specified organisms.

In relation to the legal and jurisdictional issues raised, it was decided that the application could be validly considered as a development, as defined in section 2 of the HSNO Act, and that a generic application could be validly considered.

The application was considered in accordance with the relevant provisions of the HSNO Act and the HSNO (Methodology) Order 1998.

It was decided that the extent of the range of possible genetically modified organisms encompassed by the application introduced too great a level of uncertainty to enable risks, costs and benefits to be confidently weighed. The scope of the organism description was accordingly reduced and additional controls imposed, to reduce the level of uncertainty to a point where risks, costs and benefits could be weighed in a

manner satisfactory for decision-making. The organism description resulting is set out in Annex 1 and is the basis for this decision. The controls are set out in Annex 2.

On this basis, i.e. the organism description in Annex 1 and the controls set out in Annex 2, it was decided that the benefits of having the organism in containment outweighed the risks and costs, and that the organism was adequately contained by the controls. In accordance with sections 45 and 45A of the HSNO Act and the relevant clauses of the Methodology, the application was thus approved with controls.

Section 45(3) of the HSNO Act and clause 36 of the Methodology require the Committee to give the reasons for its decision in writing. These are provided in the body of this decision document.

The Application

The application is for approval to develop in containment genetically modified *Bos taurus* (cattle) cells and animals that can express functional therapeutic foreign proteins in their milk, and to develop genetically modified cattle to study gene function and genetic performance. The genetically modified cattle will contain genes from cattle, sheep, goat, deer, human or mice, as well as other sequences identified in terms of desired function. Genetically modified embryos will be produced and will be transferred to conventional cattle and the resulting transgenic¹ calves will be tested to evaluate whether the transgenesis and expression in transgenic calves has been successful.

The development of genetically modified cattle will span three to four years. Genetically modified cattle will be produced in the first year and if applicable the analysis of inheritance, phenotype and protein expression in milk will be done in the second, third and fourth years. The application sought approval for a period of 10 years.

There are six parts to this proposed research:

- a) the isolation and culture of cell lines
- b) the isolation of DNA, libraries and gene constructs
- c) the transfection and selection of stable cell clones
- d) nuclear transfer
- e) the generation of live offspring from cultured embryos
- f) the checking of gene stability through reproduction

The application has two components: an initial laboratory phase where genetically modified embryos are to be created (steps a - d) followed by an outdoor phase where the genetically modified animals are to be developed to fully grown animals (steps e and f).

¹ In this decision the term “transgenic” is used interchangeably with “genetically modified”

Process and criteria for evaluating, hearing and considering the application

Application Process

The application was verified on **13 May 2002** by ERMA New Zealand as containing sufficient information for processing.

The Authority has discretion on the notification of a development application. In this case the Authority decided that there would be sufficient public interest to warrant notification. The application was notified on **15 May 2002** in *The Dominion*, *The New Zealand Herald*, *The Press* and *The Otago Daily Times*. The submission period closed on **27 June 2002**. Of the 863 submissions, 391 stated that they wished to be heard. All submitters who indicated that they wished to be heard were asked to confirm their intention to appear at the hearing. Submitters were also asked to indicate in writing if they would need longer than the allocated 15 minutes for the presentation of their oral submission. One person requested a time extension.

In accordance with *section 19(2)(b)* of the Hazardous Substances and New Organisms (HSNO) Act 1996, the Authority appointed a Committee to determine the application. The Committee comprised members from the Authority, who were: Mrs Jill White (Chair), Professor Colin Mantell, Dr Lindie Nelson, Ms Jane Lancaster, and one external member, Dr Manuka Henare (appointed for his expertise and knowledge in Māori culture and traditions).

The hearing was held **13 - 15 August 2002** at the Quality Hotel, Hamilton. The following people were present and made contributions for AgResearch, ERMA New Zealand and Ngā Kaihautū:

For AgResearch:

Paul Atkinson	General Manager Science
Goetz Laible	Scientist
Warren Parker	General Manager Science
Peter Moore	Farm Manager
Justin Smith	Legal Counsel, Russell McVeagh
Kerry Marshall	Legal Counsel, Russell McVeagh
Sophie East	Legal Counsel, Russell McVeagh
Tony Conner	Horizontal Gene Transfer expert from Crop and Food Research

For ERMA New Zealand:

Suzanne Lambie	Project Leader
Robert Hickson	Advisor (Science & Analysis Group)
Parekura White	Senior Advisor (Science & Analysis Group)
Celia Haden	Acting Office Solicitor
Joseph O'Keefe	Virology expert from Ministry of Agriculture and Forestry, National Centre for Disease Investigation

For Ngā Kaihautū Tikanga Taiao (Ngā Kaihautū)

Sam Napia

Ngā Kaihautū Tikanga Taiao

Submitters:

The following people gave an oral submission on the legal and jurisdictional issues relating to this application:

Submitter	Organisation	Witness	ID No
Wendy McGuinness		Jamie Ferguson	4250
Gareth Bodle	Bio-Gro New Zealand, the Biodynamic Farming and Gardening Association in New Zealand (Inc)		3497
Jeanette Fitzsimons	Green Party NZ		3542

The following people gave oral submissions in relation to the application:

Submitter	Organisation	Witness	ID No
Steve Abel	Greenpeace		3452
Kevin Marshall	Fonterra		4294
Gareth Bodle	Bio-Gro New Zealand, the Biodynamic Farming and Gardening Association in New Zealand (Inc)		3497
Sandy Wendt		Peter Maddison	3977
Jon Carapiet	Himself Friends of the Earth GE Free NZ GE Free Northland		3511
Noel Wierzbicki			3834
Tremane Barr	Groundswell Suzie Lees GE Free NZ (Nelson)		3493
Mary Gardner			3959
Ema Aitken	MadGE		3591
Wendy McGuinness		Jamie Ferguson	4250
John Forman	New Zealand Organisation for Rare Disorders		3477
Claire Bleakley			3541
Gaye Dyson			3887
Peter Harrison			3936
Joanna Paul		Matiu Tawera	3897
David Foote			3814
Yannick Wakelam			3466
Peter Wham			3932
James Valley			3979
Catherine Petrey	Federated Farmers	Charlie Pederson	3623

William Rolleston	Life Sciences		4136
Jill Brown		Proxy Karyn	3514
Steve Howell		Amoore	3515
Nannette Doering			3908

Consultation with Crown Entities and Government Departments

In accordance with clause 2(2)(e) and 5 of the Methodology and section 58(c) of the HSNO Act, 99 Crown entities and Government departments that were likely to have an interest in this application were notified of the application. Of these, only the Department of Conservation, the Fish and Game Council, and the Land Transport Authority provided comments for the consideration process.

Waivers of time

Section 59 of the HSNO Act sets out time limits for various parts of the processing and consideration of applications. Sections 59(4) and (5) provide for time limits to be waived. The time frames were extended by two waivers, one to waive the time with which to hold the hearing made on 31 July and the other to release the decision on 30 September.

The waivers were authorised by ERMA New Zealand acting under delegated authority. In authorising these waivers ERMA New Zealand was satisfied that the interests of the applicant and other parties to the application, were not unduly prejudiced and the Authority's duty under section 59 (5) of the Act to ensure the matter is carried out as promptly as is reasonable in the circumstances was met.

Information available for the consideration

An evaluation and review (E&R) report was prepared by the staff of ERMA New Zealand to assist and support the Committee's decision-making. The E&R report consolidated and evaluated relevant information in a format and sequence consistent with the decision-making requirements of the HSNO Act and the Methodology. The staff of ERMA New Zealand had available to them the application, published references cited by the applicant, the submissions and additional references.

The Committee had available for its consideration the application, the E&R report, the Ngā Kaihautū Tikanga Taiao (Ngā Kaihautū) report, and submissions and additional information provided by submitters prior to the hearing. During the hearing the Committee considered the evidence presented by the applicant, ERMA New Zealand staff, Ngā Kaihautū, and submitters.

Legislative basis for consideration

The application was lodged pursuant to section **40(1)(b)** and **40 (2)(a)** of the Hazardous Substances and New Organisms Act 1996, and determined in accordance with section **45 and 45A**, the additional matters contained in sections **37, 44, 44A**, and the matters set out in Part II of the Act being sections **5, 6, 7, 8, and 9**. 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 Hazardous Substances and New Organisms (Methodology) Order 1998 (the *Methodology*). Unless otherwise stated references to clause numbers in this decision refer to clauses of the Methodology.

Consideration approach and sequence

Before considering the application itself, the Committee considered legal and jurisdictional issues. This was done to enable the Committee to be sure that the application could be validly considered. The purpose of the application was validated as required by section 45(a)(i) of the Act.

In accordance with clause 24 of the Methodology, the approach to the consideration was then to identify the potentially significant risks, costs and benefits of the application, and to then assess the identified risks, costs, and benefits in relation to:

- the containment regime considered to be appropriate, as specified in **Annex 2** of this decision and having regard to the requirements of section 45(1)(a) and section 45A(2) of the Act ; and
- the ability of the organism(s) to escape from containment and to form an undesirable self-sustaining population, and to be eradicated, as required by sections 37 and 44 of the Act.

The risks that were identified as significant were assessed in terms of clause 12 of the Methodology. Costs and benefits were assessed in terms of clause 13 of the Methodology.

The initial assessment of risks indicated that the scope of the application (the description of the organisms(s) covered) introduced too high a degree of uncertainty into the assessment of risks (clause 32 of the Methodology refers) to enable risks and costs to be confidently weighed against benefits under section 45 of the Act. Additional controls and restrictions on the organism description were thus introduced which had the effect of reducing the level of uncertainty to the point where risks, costs and benefits could be weighed.

Risk characteristics were then established in accordance with clause 33 of the Methodology, taking into account the containment regime.

Alternative methods of carrying out the research were considered as required by section 44A(2)(b) of the Act and a judgement made as to whether the alternatives were of a character that might justify declining the application.

Finally the combined impact of risks, cost and benefits was evaluated in accordance with clause 34 of the Methodology. Benefits were weighed against costs and risks in terms of section 45(a)(i) of the Act and clause 27 of the Methodology; and the adequacy of containment considered in accordance with section 45(a)(iii) of the Act, in order to determine whether the application should be approved or declined.

Details of the Committee's consideration of the application are discussed below under the following headings:

1. Legal and jurisdictional issues
2. Identification of the potentially significant risks, costs and benefits of the organism
3. Adequacy of the proposed containment regime and its ability to mitigate risks, including especially:
 - 3.1 Adequacy of indoor containment
 - 3.2 Adequacy of controls on the ability of the organism or any heritable material to escape from outdoor containment including:
 - i. general containment of cattle
 - ii. breach of containment following deliberate action
 - iii. containment of bulls
 - iv. containment of semen and ova
 - 3.3 Adequacy of mandatory controls set under section 45A(2) and other controls on the retention within the containment facility, or the disposal of, the organism(s) and any heritable material, including:
 - i. disposal of genetically modified cattle
 - ii. disposal of surrogate mothers, recipient cattle and non-transgenic offspring
 - iii. disposal of milk
 - iv. disposal of faeces
 - 3.4 Adequacy of controls on the escape of genetic elements into the site environment or beyond
 - 3.5 Adequacy of controls to monitor effects and associated elements
 - 3.6 Impact of restrictions on the scope of the organism description
4. Assessment of the significant risks (magnitude and probability of adverse effects) of the organism, including:
 - 4.1 Establishment of a self-sustaining population and ease of eradication

- 4.2 Risks to the biological and physical environment
- 4.3 Risks to public health
- 4.4 Unintended effects
- 4.5 Animal welfare issues
- 4.6 Relationship of Māori and their culture and traditions with their ancestral lands, water, sites, waahi tapu, valued flora and fauna, and other taonga; risks to their economic, social and cultural wellbeing
- 4.7 Application of the principles of the Treaty of Waitangi
- 4.8 Ethical issues
- 4.9 Economic risks
5. Assessment of the significant benefits associated with the application
6. Establishment of appropriate approach to risk
7. Alternative methods to achieve the research objectives
8. Measures to reduce risk and uncertainty
9. Overall evaluation and weighing up of risks, costs and benefits, and the adequacy of containment
10. Decision

Consideration of the application

1. Legal and Jurisdictional issues

A number of submitters raised two fundamental legal and jurisdictional issues for the Committee's consideration:

- 1) whether AgResearch's application was properly for development of a genetically modified organism in containment, or a field test;
- 2) whether it was within the Committee's jurisdiction to consider an application which was generic in its description of the organism.

The Committee heard submissions on these issues at the beginning of the hearing and adjourned to consider these matters before proceeding further.

The Committee concluded there were issues relevant to the legal and jurisdictional issues that it expected to hear further evidence about, and that it was useful to consider that evidence. It therefore reserved its determination on the legal and jurisdictional issues, resumed the hearing and proceeded to hear all the evidence.

Having taken into account all written submissions and all evidence presented at the hearing, the following decision has been made regarding these legal and jurisdiction issues.

Development or field test

Of the six steps proposed for the work, steps (e) and (f) were contended by some submitters to be tantamount to a field test rather than a development. These two steps involve the generation of live transgenic offspring, and the reproduction and milking of transgenic animals. These steps are proposed to largely take place outside, in paddocks within the secure Ruakura facility.

The Committee noted a lack of clarity within the Act definitions:

“Develop” in relation to organisms, means genetic modification of any organism; but does not include field testing (section 2(1))

“Field test” means, in relation to an organism, the carrying on of trials on the effects of the organism under conditions similar to those of the environment into which the organism is likely to be released, but from which the organism, or any heritable material arising from it, could be retrieved or destroyed at the end of the trial; and includes large scale fermentation of microorganisms (section 2(1))

The Committee noted that the amendment to the Act (HSNO (genetically modified organisms) Amendment Act 2002) confirms that development can occur when not in a containment structure (but remaining in containment).

The Committee concluded that all steps (a) to (f) of the application could be regarded as development. In reference to step (e), the Committee is satisfied that generating live, genetically modified calves clearly pertains to developing a genetically modified organism. In reference to step (f), the Committee was satisfied that milking is necessary to demonstrate expression of the therapeutic proteins in milk, and that some breeding is reasonable to determine which constructs show stable inheritance. However, the Committee accepts that step (f) has elements of examining the effects of the organism. Since “develop” does not include field testing, and field testing was not applied for or considered, it is essential to set boundaries on this development application to ensure that it does not include field testing.

In this application, where part of the development occurs outdoors, the determinant difference between a field test and a development is whether “trials” are being carried out on the effects of the organism. The Committee is of the view that a trial, in the context of the HSNO definition of field test, involves research procedures aimed at providing statistically valid results about the effects of the organism (including animal or herd performance).

To ensure that the research undertaken pursuant to this application does not go beyond development (to become field testing) any approval must be subject to restrictions on breeding. Such restrictions should prevent any additional increase in numbers of lines of genetically modified cattle, and thereby preclude statistically valid research on the effects of the organism.

For this application, the Committee concluded that the following restrictions should be applied to breeding to ensure that the development does not include field testing:

- a) no breeding of cattle modified to study gene function and genetic performance, unless animals with homozygous replacement of cattle genes are required, since the phenotype is expected to be expressed in the first generation;
- b) cows modified to express therapeutic proteins in milk may, where necessary, be bred to investigate stability of inheritance or to develop cattle homozygous for the genetic modification.

The Committee is of the view that these restrictions on breeding will not interfere with the stated objectives of the application. Allowing subsequent generations of cattle modified to express therapeutic proteins will enable initial identification of constructs showing stable inheritance and generation of homozygous genetically modified cattle.

In conclusion the Committee was satisfied that steps (e) and (f) are part of the investigative process of establishing whether the modifications gave rise to expression of therapeutic proteins or alterations of the bovine genome. Therefore the application could be considered as a development, provided breeding restrictions ensure the applicant does not increase, beyond that necessary for development, the number of animals of a particular construct.

Jurisdiction of the Committee to hear and consider a generic application

The Committee considered the relevant statutory provisions including sections 20 and 40 of the Act and concluded there is nothing in the Act to preclude a generic application provided the application is in an approved form and there is sufficient information to meet the requirements of section 40(2)(a) and section 20(2)(b) as follows:

1. For the purpose of making an application for the development of a genetically modified organism (section 40(2)(a)), information on:
 - (i) the identification of the organism;
 - (ii) the description of the project and the experimental procedures to be used;
 - (iii) the details of the biological material to be used;
 - (iv) the expression of foreign nucleic acid material; and,
 - (v) all possible adverse effects of the organism on the environment.
2. For the purpose of maintaining a register of all applications under section 20(2)(b), a sufficient description of the organism to uniquely identify that organism.

With regard to GMD02028, the issue is whether the requirements under sections 20 and 40 have been met. The Committee in its deliberations on this matter was conscious that there is a distinction between the level of information required to determine the validity of an application and the information required to assess and evaluate all adverse and beneficial effects to determine whether an approval with controls can be granted.

The following analysis was made of the compliance with the information requirements in section 40(2)(a).

- (i) Identification of the organism is stated as “*Bos taurus* modified with vectors containing ...”. The host organism is clearly cattle but individual animals may contain a range of potential modifications. The precise modifications can be specified before individual animals are created because the genetic construct introduced will be able to be precisely described. The Committee concluded that there was sufficient information to meet the requirements.
- (ii) In regard to the description of the project, the application form asks for information on “... the experimental plan, any unusual manipulative steps and any special factors affecting the risk”. The applicant gives experimental procedures for each step (a) to (f). The application notes that there are two broad aims of the application - some proteins will be expressed in milk and other genes will be introduced to study gene function in cattle. The Committee noted that s40 is not specific on how much information is required but were satisfied this requirement was sufficiently met.
- (iii) Details of the biological material were provided in Appendix 1 of the application, describing the types of genetic elements that would be used in the vector. Sources of some elements are not always specifically identified, but the functions and purposes are. It is also clear that certain types of genetic elements are included and certain types are excluded. Because the source species of some organisms are not specified (such as those covered by “other features” in Appendix 1 to the application), it is possible for some elements such as transcriptional and translational elements, homologous recombination signals, reporter and selection marker genes, to potentially come from species other than those listed as “donor DNA”. Consequently, genetic material, in addition to that derived from the six named mammalian species, may potentially be derived from a very broad range of other non-pathogenic prokaryotes or eukaryotes.

It is noted however that modifications must comply with the requirements of category A or B experiments as defined in the HSNO (Low-Risk Genetic Modification) Regulations 1998. Some bounds are provided in that only well characterised sequences can be introduced into the cattle.

The Committee accepted that there was sufficient information provided, although with reservations about the potential to use unspecified source species for some sequences.

- (iv) In regard to the expression of foreign nucleic acid material, the applicant indicated that proteins would be expressed in milk, and that expression of other

genes elsewhere in the cattle is likely to occur. The Committee was of the view that the information on the expression of foreign DNA was barely adequate. However it was satisfied that the legal requirements were met sufficiently to allow the application to be considered.

- (v) The requirement in the Act for information on “all possible adverse effects of the organism on the environment” sets a high standard. The application addressed adverse effects to some extent and the E&R report discussed potential adverse effects not covered by the applicant.

The Committee was of the view that the broadness and lack of specificity of the organism description and the fact that the organisms were to be outside rather than in a contained laboratory made assessment of all possible adverse effects on the environment very difficult. On a strict interpretation of the requirements, AgResearch had possibly failed to identify all possible adverse effects. However the Committee acknowledged that a standard of reasonableness should be applied when assessing the extent to which identification of adverse effects was required. On this basis it was decided that on balance the application could be regarded as valid.

Therefore while a bare minimum level of information had been provided in some respects, the Committee concluded that this was a valid application to be considered.

In relation to the requirements of section 20(2) of the HSNO Act reference to the list of features in the vector as part of the description of the organism can be made, so that while the organism description is broad, some information on the types of modifications is included in the organism description, and so that the organism description is distinguishable from other applications. The Committee notes that many types of genetic modifications can be difficult to identify uniquely in the way that some submitters suggested. For example, a description for a genomic library of cattle sequences in *Escherichia coli* could not identify the individual genes of cattle that were introduced. The Committee decided that the requirements of section 20(2), in relation to maintaining a register of applications, were adequately met. To ensure that the register remains an accurate record of approved organisms that are sufficiently described to enable unique identification, controls can be set requiring reporting of particular constructs before nuclear transplantation (see control 9.2).

2. Identification of the potentially significant risks, costs and benefits of the organism

The Methodology defines costs as values of negative effects (expressed in monetary or non-monetary terms). Costs most often arise from risks. No costs were identified in relation to this application that did not arise from risks. Therefore both risks and costs are addressed together in this decision and references to risks should be taken to include the associated costs. The Methodology defines benefits as values of positive effects (expressed in monetary or non-monetary terms). Benefits are addressed under the heading of Benefits in this decision. Qualitative scales used by the Committee to measure likelihood and magnitude of effects are provided as Annex 3 of this decision.

The Committee conducted an identification of potential risks, costs and benefits related to the application, based on the requirements of the HSNO Act and the Methodology. Those risks, costs and benefits identified as being significant are highlighted and a discussion of their assessment and evaluation is given in the following sections (following clauses 9 and 10 of the Methodology, which incorporate sections 5, 6 and 8 of the HSNO Act).

Risks (and costs)

Potentially significant risks identified for assessment and evaluation were as follows, following clauses 9 and 10 of the Methodology, which incorporates sections 5, 6, 8 and 44 of the Act.

- Risks to organisms in the environment within the containment facility, from the transfer of transgenic material from animal waste and the disposal on site of milk and carcasses (in accordance with clause 9(a), (b)(i), (c)(iii), (c)(iv), clause 10(b), 10(d))
- Risks to water, notably groundwater, arising from transgenic material from animal waste and the disposal on site of milk and carcasses (in accordance with clause 9(a), (b)(i), (c)(ii), (c)(iii), and (c)(iv), clause 10(b))
- Risks arising from the mating of genetically modified and non-genetically modified cattle (in accordance with clause 9)
- Risks to the welfare of the cattle (in accordance with clause 9(c)(i))
- Risks of a long term, unintended nature (potentially in accordance with clause 9 or 10)
- Risks to public health arising from the consumption of milk or meat or products containing these, derived from genetically modified cattle (in accordance with clause 9(b)(i), 9(c)(iii), 9(c)(iv); clause 10(c))
- Risks to Māori (in accordance with clauses 9 (b)(i), (c)(iii), (c)(iv), clause 10(c) and the treatment of those risks in accordance with the principles of the Treaty of Waitangi (section 8 of the Act refers); including:
 - spiritual beliefs, through interference with the mauri and whakapapa of valued species,
 - degradation of tūpuna land,
 - metaphysical effects on health,
- Risks arising from the failure to proceed with this type of research, including loss of scientists and scientific expertise
- Risks to New Zealand farming and tourism.

Benefits

Potentially significant benefits identified for assessment and evaluation were as follows:

- Benefits of scientific knowledge arising from the carrying out of the research including the acquisition of new skills (in accordance with clause 9(b)(i) and 9(c)(v)).

The applicant and others made reference to the specific downstream economic and health benefits to be gained from the products that might result from the commercial use or release of the genetically modified cattle. These products might especially include biopharmaceuticals. The Committee did not consider these downstream benefits to be relevant to this application, because it was for scientific development and not for release or commercial production.

3. Adequacy of the proposed containment regime and its ability to mitigate risks

In assessing risks, the impact of the containment regime was considered (section 45(1)(a)(iii) of the HSNO Act) in relation to the ability of the organisms or any heritable material to escape from containment; the ability to meet the requirements of s45A(2) in regard to removing or destroying material; the management of risks and other factors. The risks considered were those identified in Section 2 above and assessed in detail in Section 4 below (clause 24 of the Methodology refers).

3.1 Adequacy of indoor containment, i.e. the containment structure

Control 1.2 in Annex 2 sets out the containment requirements for the laboratory phase of the work. The controls require that steps (a) to (d) of the development (that is, production of genetically modified cattle cells and embryos) be carried out in a PC1 containment facility approved by the Ministry of Agriculture and Forestry (MAF) under the Biosecurity Act 1993, in accordance with the MAF/ERMA Standard 154.03.02 *Containment Standard for Microorganisms*. The Committee notes that the proposed modifications are Category A or B experiments as described in the HSNO (Low-Risk Genetic Modification) Regulations 1998, and thus require a PC1 level of containment.

Based on the dependence of cell cultures on special temperature and nutrient requirements, and the fact that genetically modified mammalian cell lines have a documented history of being able to be contained in such a facility, the Committee considers that with the proposed controls it is very unlikely that the cells or embryos will escape from containment. Modifications that result in the production of infectious particles are not permitted under this approval.

3.2 Adequacy of controls on the ability of the organisms or any heritable material to escape from outdoor containment, i.e. when contained outside of the containment structure

The controls 1.3 and 1.4 require that the production and maintenance of live genetically modified cattle from embryos be carried out in a containment facility approved by the Ministry of Agriculture and Forestry (MAF) under the Biosecurity Act 1993, in accordance with the MAF/ERMA New Zealand Animal Health and Welfare Standard 154.03.06: *Containment Standard for Field Testing Farm Animals*. Additional controls are also specified to manage the risks of escape of animals or heritable material.

In considering the ability of the organism or any heritable material to escape from containment, the Committee considered, amongst other things, the following specific points:

- i. general containment of cattle
- ii. breach of containment following deliberate action
- iii. containment of bulls
- iv. containment of semen and ova.

(i) General containment of cattle

The Committee is satisfied that the containment regime set out in the MAF/ERMA New Zealand Standard 154.03.06, plus further controls imposed in this decision, can adequately contain cattle.

Additional measures already exist over and above the requirements of the Standard that further reduce the probability of any escape of cattle from the containment facility. These include the erection of two 2-metre high perimeter fences (instead of the single 2 metre fence required in the MAF/ERMA Standard 154.03.06), and the installation of a system to electronically monitor the perimeter fencing in order to promptly detect any interference or break in the fence. These measures also form part of the proposed controls for this decision (control 1.5).

In addition, identification measures in place for genetically modified cattle, including ear tags and sub-cutaneous microchips, facilitate rapid identification of any animals should a breach of containment occur (control 4.3).

The Committee acknowledges that AgResearch's track record provides a basis for concluding that under this regime the probability of an escape from the outdoor facility is very low

(ii) Breach of containment following deliberate action

The Committee was satisfied that the construction, operation and management of the outdoor containment facility minimises the likelihood of any deliberate action or sabotage resulting in a breach of containment. In reaching this decision the Committee took into account the nature of the fencing, electronic monitoring, and the location of the containment facility within the Ruakura Research Centre (RRC).

For any potential saboteurs to gain access to the outdoor containment facility they would need to breach a number of levels of security. They would need to gain access to the RRC (which is monitored outside of working hours by a security provider on-site), gain access to the containment facility without triggering the security system, and exit without being detected.

Nevertheless the Committee acknowledged that it is almost impossible to protect against well-planned, deliberate action to breach containment. However, the Committee considers that, even were such a breach to occur, the adverse effects of the limited number of uncontained GM cattle would be negligible.

The Committee once again acknowledges that AgResearch's track record provides a basis for concluding that under this regime the probability of a breach of containment following deliberate action is low.

(iii) Containment of bulls

Bulls, being larger and potentially more aggressive, can make containment more difficult. However, taking into account the requirements of the standard and the proposed containment regime, as well as the fact that AgResearch presently successfully keeps sexually mature bulls in containment, the Committee concluded that the probability of bulls escaping from containment is very low. In addition the Committee acknowledges that the number of bulls produced will be kept to a minimum and they will be slaughtered after semen has been collected (control 1.7).

(iv) Containment of semen and ova

For the purposes of publication and verification of any research results, the applicant may retain semen and/or ova from genetically modified cattle following the conclusion of the development. Any semen or ova retained shall be held in accordance with the MAF/ERMA standard 154.03.02 at PC1 (control 8.1(b)). These provisions are considered to be adequate to securely contain the semen and ova.

3.3 Adequacy of mandatory and other controls on the retention, removal or destruction of the organisms and any heritable material

Section 45A of the Act requires the Committee to include controls to ensure that, at the end of the development or field test, the organisms and any heritable material from the organisms are removed or destroyed. Controls 1.8 to 1.13 and control 8.1 have been included to meet this requirement and to more generally deal with issues of retention, removal or destruction. In setting these controls consideration was given to the following aspects of containing the organisms and any biological material:

- i. disposal of genetically modified cattle
- ii. disposal of surrogate mothers, recipient cows, and non-transgenic offspring
- iii. disposal of milk
- iv. disposal of faeces.

i. Disposal of genetically modified cattle

The Committee acknowledges that Ngāti Wairere wished for genetically modified cattle to be buried in lined offal pits and note AgResearch's willingness to accommodate their wishes. However, both AgResearch and the Ngā Kaihautū report stated a preference for use of unlined offal pits since this would expedite decomposition and, in the case of Ngā Kaihautū, enable return of material to *Papatuanuku*. In their report, Ngā Kaihautū writes:

“Whereas the culture, traditions and the relationship of Māori with Papatuanuku, as inferred by the Te Runanga o Ngai Tahu submission, includes recognition that in death all living things should eventually return to her; the apparent position of Te Kotuku Whenua Consultants is that dead and defunct transgenic material ought to be disposed of in lined offal holes, thus denying the purpose and function of Papatuanuku in this regard.

The cultural inconsistency identified here is that Ngāti Wairere propose to deposit dead material into the te kopu o te whenua, the belly of Papatuanuku, but will allow it to sit there for all time thus remaining uncleansed by Papatuanuku.”

The Committee accepts the cultural position of Ngā Kaihautū. In addition, the Committee agrees that use of unlined offal pits will expedite decomposition. The Committee is therefore of the view that offal pits should be unlined (control 1.9). As noted in section 4.2, and given the restrictions on the approved scope of the organism and controls 9.1 and 9.2, the Committee does not consider that disposal in unlined offal pits poses any significant additional likelihood of adverse effects attributable to horizontal gene transfer (HGT).

The Committee is also of the view that incineration will render genetic material non-viable and is therefore an acceptable disposal method. However, the Committee acknowledges that Ngāti Wairere has expressed concern about incineration and its potential cultural offence. It is possible that Ngāti Wairere may not have concerns about incineration of recipient cows or surrogate mothers, or about cattle which do not have human genes inserted.

Because of the uncertainty about Ngāti Wairere’s possible response to further discussions with AgResearch, incineration is not included in the controls as a disposal option. However, should AgResearch and Ngāti Wairere subsequently agree on the suitability of incineration, AgResearch may apply to the Authority for a minor change to the controls under s67A of the Act.

The Committee requires AgResearch to consult further with Ngāti Wairere regarding culturally appropriate mechanisms and protocols for disposal of the animals used in the research. For instance planting of trees may be a culturally appropriate method of cleansing any burial sites.

ii. Disposal of surrogate mothers, recipient cows, and non-transgenic offspring

The applicant requested that any controls imposed by the Committee regarding the disposal of surrogate mothers and recipient cows no longer required for the development allow for the their transfer or sale off site.

Consideration was given to whether the sale of conventional cattle that have failed to carry a GM embryo to term (“recipient cows”) or which have given birth to genetically modified calves (“surrogate mothers”) would result in any breach of containment. A key issue was the possibility of surrogate mothers and recipient cows carrying cells or other genetic material from genetically modified embryos or foetuses following embryo transfer or the birth of a genetically modified calf. This was based on a recent paper² reporting the presence of human foetal material in mothers sometimes many years after the birth.

The applicant originally requested approval for conventional recipient cows to be sold or otherwise disposed of off-site. The release of such animals from the containment facility would be contingent on the animal producing three negative pregnancy scans (using ultrasonography) performed at approximately 28, 35 and 50 days post-embryo transfer, and, following the third negative pregnancy scan, holding the cows for a further period of 50 days prior to removal from the containment facility. The applicant also proposed that conventional surrogate mothers be disposed of off site, with a withholding period for such cows of at least 100 days in order to provide consistency with the measures applied to recipient cows, and to ensure that no foetal blood cells derived from the genetically modified calf remain in the cows.

Based on the paper by Invernizzi *et al.*, the ERMA New Zealand E&R Report suggested a control proposing that all cattle receiving genetically modified embryos be disposed of within the containment facility to prevent genetically modified cattle cells being inadvertently removed from containment. The Committee notes that Ngā Kaihautū also recommended on-site disposal of all mothers.

The applicant stated that this disposal requirement would reduce AgResearch’s income (through loss of revenue from animal sales) and would create difficulties in burial capacity within the containment facility. The applicant also noted that the results of Invernizzi *et al* need to be confirmed. They proposed that surrogate mothers and recipient cows be tested for foetal material using PCR techniques at 100 days after birth (or 50 days after 3 failed pregnancy tests). If animals gave a positive result for foetal material they would be disposed of on-site, otherwise they should be able to be sold off-site.

At the hearing ERMA New Zealand staff noted that the PCR test has limits of detection so that it can only be claimed that no foetal material was detected rather than the animals contain no foetal material. Consequently, there would be some uncertainty over whether animals containing foetal material could inadvertently be allowed outside of containment. Many submitters expressed concern at consuming material derived from the genetically modified animals or the surrogate mothers. Invernizzi’s paper reported the presence of foetal material in lymph and blood tissue. Although such tissues would not generally be consumed by humans, or passed on to subsequent offspring, the Committee recognises the public concern.

² Invernizzi P. *et al.* (2002). Presence of fetal DNA in maternal plasma decades after pregnancy. *Human Genetics* 110, 587-591

The Committee is of the view that given the Invernizzi *et al.* paper and AgResearch's acceptance of the extrapolation of these results from humans to cattle, it is not appropriate to distinguish between recipient cows and surrogate mothers for the purposes of disposal. Based upon the limitations of the PCR testing the Committee is of the view that only cattle that have received an embryo that did not implant can be removed from containment and sold off-site. Cattle in which the embryo has implanted (determined on the basis of demonstrable placentation at or before the 35 day scan) should be disposed of on-site regardless of whether they have gone to term or not (control 1.8). Conventional cattle that fail to implant a genetically modified embryo may be disposed of off-site.

The Committee also notes that breeding may result in offspring that are non-transgenic. For the same reasons discussed above, such calves are to be maintained in containment and disposed of on-site in accordance with control 1.9.

iii. Disposal of milk

Additional information supplied by the applicant proposed several methods of disposal of milk derived from genetically modified cows. These included, incineration or autoclaving of small quantities of milk from induced lactation of genetically modified cows at 6-9 months of age, and for surplus milk from lactation of mature genetically modified cows, disposal via incineration, digestion in an effluent digester (either on-site or by a local effluent disposal company), or by spraying onto pasture within the containment facility following denaturation of the milk.

Issues were raised by a number of parties to the application regarding the potential risk of contamination of groundwater as a result of spraying milk derived from genetically modified cattle onto pasture. The issue of pollution of groundwater (or other water) as a result of the land disposal of milk is a matter that is managed under the Resource Management Act (RMA) 1991.

Disposal of milk via treatment and spraying onto pasture is not a route for the escape of heritable material since the milk is treated prior to disposal, and is therefore a matter more appropriately dealt with under the RMA. The Committee notes that the milk will be denatured by autoclaving. Autoclaving does not completely destroy DNA but is likely to break it into small random fragments. As discussed elsewhere in this decision, and given the approved organism description, the risk arising from HGT of such fragments from genetically modified cattle in this application is considered to be negligible.

Controls on this approval therefore provide for disposal of waste milk and cream by effluent digester or incineration within the indoor containment facility, or spraying onto pasture within the outdoor containment facility following treatment in order to destroy any cells present in the milk (control 1.12). Any milk derived from genetically modified cattle and used in further experimentation must be retained within the indoor containment facility and be disposed of in the same manner, or by sterilization, when no longer required for experimental purposes (controls 1.11, 1.12 and 8.1(b)).

iv. Disposal of faeces

The applicant indicated that effluent from cattle in the cattle yards would be collected into effluent tanks and then sprayed onto pasture. Faecal material from grazing animals would not be collected or treated and would be left to decompose as is the practice in normal farming.

Some submitters expressed concern that faeces from genetically modified animals would be left on, or returned to, pasture. Their concern was based on the potential for horizontal gene transfer (HGT) and/or adverse environmental effects resulting from material from the GM cattle.

The Committee noted the concern but considered, as discussed in sections 4.2 and 4.3, that the likelihood of HGT and unintended production of toxins to both be very low, given the restrictions on the approved scope of the organism and controls 9.1 and 9.2. In addition, given the small number of genetically modified animals of each type, and the local nature of the experiments it was considered that even if faeces from GM animals had adverse effects on the environment it was very likely that such effects would be restricted to the area where faeces were deposited and so be of minimal magnitude. Consequently, no additional controls on the treatment or disposal of faeces are included.

3.4 Adequacy of controls on the escape of genetic elements into the site environment or beyond

Section 45A(2)(b) of the Act provides the Committee with discretion to include or not include controls to ensure that after the end of the development (or field test) and after heritable material is removed or destroyed, some or all of the genetic elements remaining from the organisms are removed or destroyed.

The organism description excludes the use of inherently mobile genetic elements (such as transposable elements) and viruses, so that escape of infectious genetic elements is very unlikely to occur. Some of the controls set in place for other reasons will have the effect of inhibiting the movement of genetic elements off site, or of assisting their destruction on site. Thus the general containment regime will prevent the movement of genetically modified cattle off-site. Any carriage of genetic elements off site must be by other means, e.g. blood-sucking arthropods. Similarly, the requirement to provide for the decomposition of carcasses (and disposal of milk) on-site, will ensure that any genetic elements derived from the genetically modified animals are likely to remain on-site until they decompose.

Given the scope of the approved organisms (Annex 1), and controls 9.1 and 9.2 which limit use of bacterial sequences in the vector insert and require the characterisation of the genetic material to be inserted, no further controls have been included specifically for the purpose of dealing with any genetic elements, other than a control for monitoring micro-organisms to detect HGT (control 6.4).

3.5 Adequacy of controls on monitoring of effects and associated elements

The Committee's view is that every reasonable opportunity should be taken to monitor developments such as this for the occurrence of adverse effects and for information on the significance of pathways such as HGT. As well as providing an assurance on the effectiveness of controls, the information is potentially valuable for future applications.

Controls 9.5 (animal welfare), 1.14 (incineration of any cattle diagnosed with transmissible spongiform encephalopathies – “TSEs”), 9.2 (characterisation of genetic material), and 6.4 (monitoring micro-organisms) have been included to monitor, and manage, potentially adverse effects associated with this application. Controls 9.2 and 6.4 were also recommended by Ngā Kaihautū.

The Committee notes that, in its closing submission, AgResearch confirmed its intent to work toward developing the procedures and capability to monitor insertion sites of the genetic material. The Committee accepts that, while desirable, a control requiring monitoring of insertion sites would be impractical at this time.

Several additional controls of this type were recommended in the Ngā Kaihautū report, including monitoring decomposition in both lined and unlined offal pits, monitoring insertion sites, and studies on horizontal gene transfer in cattle intestinal bacteria and parasites. The Committee's view was that the additional controls recommended were not practicable, while appreciating the legitimate concern (shared by the Committee) that monitoring should be as extensive as possible. Ngā Kaihautū also recommended monitoring development of resistance to tetracycline. The Committee notes that, given the restrictions on the approved organisms, this recommendation is unnecessary since tetracycline resistant markers cannot be used (Annex 1).

3.6 Impact of restrictions on the organism

The generic nature of this application has led the Committee to the view that, while there is sufficient information in the application for it to be validly considered, the generality and breadth of the organism description leads to significant uncertainty as to the magnitude and likelihood of the adverse effects arising. These uncertainties are discussed in more detail in the detailed assessments in section 4 below.

The Committee has decided to restrict the scope of the approved organism and add further controls to reduce uncertainty by:

- a) restricting the use of bacterial and viral sequences (Annex 1 and control 9.1), to reduce uncertainty related to the likelihood and consequences of HGT due to homologous recombination;
- b) excluding known human and animal viral cell receptors (Annex 1), to reduce the likelihood of genetically modified cattle becoming new reservoirs for human or animal viral diseases;

- c) requiring genetic material to be characterised with respect to sequence and potential functions (control 9.2), so that only elements of known function are inserted into the cattle genome, thereby reducing the likelihood or consequence of unintended effects;
- d) restricting the range of selection markers to genes which do not confer resistance to human or veterinary antibiotics and will not provide selective advantages to micro-organisms in the environment (Annex 1), thus reducing the consequences of any HGT events; and
- e) excluding all material that could potentially cause prion diseases, i.e. transmissible spongiform encephalopathies (Annex 1).

4. Assessment of the significant risks (probability and magnitude of adverse effects) of the organism

4.1 Establishment of an undesirable self-sustaining population and ease of eradication

Section 37 of the Act requires that the Committee consider the ability of the organism to establish an undesirable self-sustaining population, and the ease with which it could be eradicated if a self-sustaining population was formed. It is valid to do this in advance of assessing risks, because the information is relevant to that assessment.

The Committee's view is that it is very unlikely that the genetically modified cattle could form a self-sustaining population in the wild. While there are some feral cattle populations these occur only in a few isolated areas, and the nature of the animals (large and not especially agile herbivores that are suited for flatland grazing) would make it unlikely in any case. As noted previously, the genetically modified animals will be closely monitored and any escaped animals noticed and searched for.

If a feral population did form it would be relatively easy to identify and eradicate. The animals are large and generally slow moving, and given the location of the containment facility, unlikely to be found in broken or bush clad country.

It is possible that any escaped cows could join another domestic herd. However, even given modestly good farming practices, which include animal identification procedures as well as animal recognition, it is very unlikely that this would go unnoticed.

Control 5.2 requires that, in the event of unintended or accidental release or escape of genetically modified cattle, the applicant shall recover the escaped animals. Furthermore, if there has been any possibility of mating occurring, any potentially affected cows shall be identified, destroyed, and disposed of in accordance with the provisions specified in the controls.

These conclusions have been reached with reference to clause 10(e) and (f) of the Methodology.

4.2 Risks to the biological and physical environment

The following risks to the biological and physical environment are assessed below:

- (i) risks from the introduction of viral cell receptors
- (ii) risks from HGT
- (iii) development of new diseases.

(i) Viral cell receptors

The Committee notes that there is the potential for viral cell receptors from other mammalian species to be introduced into cattle as a result of the genetic modifications. As noted in the Evaluation and Review report and comments from a virologist who provided a discussion of this topic for the report, such receptors have the potential to create a new disease in cattle or enable the development of a new reservoir for an existing virus.

The applicant stated that they would not introduce known human viral receptors, but the Committee notes that not all viral cell receptors have been identified so that there is the potential for inadvertent introduction of viral receptors (from humans or the other mammals acting as sources of DNA) into the cattle. This issue is discussed in detail on pages 36-40 and in Annex 3 of the E&R report. In addition the E&R report identified that experience with laboratory mice could not be fully applied to an outside situation since animals outside could be exposed to a greater range of viruses. The applicant noted that the relatively few cattle involved limited the magnitude of effect since viruses would only be able to infect animals containing the receptors. The Committee notes that the potential exists for some viruses to be transmitted off-site by biting arthropods (flies, ticks, etc) but that other conventional cattle would not be susceptible without the specific cell surface receptors.

The Committee noted that the magnitude of adverse effects due to incorporation of a new viral receptor while potentially major were more likely to be minor since they would involve only a small number of animals. The Committee did note, however, that if by creating a new reservoir of such viruses there is the potential for the virus to change and adapt to cattle without the need for the introduced viral cell receptor, adverse effects may occur beyond the containment facility. The Committee identified this as an area of significant uncertainty. The application does not exclude cell surface receptors because the application has a broad scope. The Committee has, however, restricted the organism description to exclude “known human and animal viral cell receptors”, where known is defined in terms of there being published material in peer-reviewed scientific literature indicating that the gene is or may be associated with a viral cell receptor. This will prevent use of sequences that are known in the scientific literature to be involved in viral entry. Since not all viral cell receptors have been identified a control preventing the use of “viral cell receptors” is not meaningful.

The Committee acknowledges that the exclusion of known viral cell receptors from the genetic modifications does not eliminate uncertainty but given the requirement that all introduced sequences must be characterised it reduces the likelihood of viral cell receptors being introduced. Furthermore, in the event that a genetic modification resulted in the animal(s) becoming infected with a non-cattle virus the magnitude of effect is considered by the Committee to be minimal or minor because of the small number of animals involved, and the fact that the virus would be unlikely to infect non-modified cattle since they would lack the appropriate receptor. The overall risk, having regard for the controls imposed, is thus considered to be low to a reasonable degree of certainty (clause 12 of the Methodology refers).

(ii) Horizontal gene transfer (HGT)

Submitters expressed concern about the potential for HGT to occur and cause adverse effects, and the Committee has accordingly carefully reviewed relevant material in the application, the E&R report, and presented at the hearing.

HGT refers to the process whereby nucleic acid is transferred between organisms without recourse to sexual reproduction. It is now widely accepted that HGT occurs, most significantly within the prokaryote³ kingdom, but instances of nucleic acid transfer between prokaryotes and eukaryotes⁴ are documented in the scientific literature.

The Committee noted there was a range of scientific opinion about the frequency of HGT and the nature of the selection forces that enable a transferred sequence to become established in a population and give rise to effects that may be adverse. Thus the significance of HGT in creating unintended consequences is uncertain. The Committee noted that factors that may influence the likelihood of HGT include the presence of sequences similar or identical to those in the potential recipient. Transferred sequences that confer a benefit upon the organism are more likely to become established in the population than those conferring no benefit.

The Committee noted that the likelihood of HGT could be substantially reduced by controls on the nature of the DNA to be used. The organism description prevents the use of inherently mobile genetic elements (transposable elements and viruses), and genes conferring resistance to antibiotics of significant clinical or veterinary use. The applicant stated at the hearing that they would not include viral sequences in the vector insert (that is the genetic material introduced into cattle cells), except for the SV40 promoter.

³ prokaryote: A micro-organism whose DNA is not enclosed within a nuclear membrane. Prokaryotic organisms include bacteria and viruses.

⁴ eukaryote: An organism whose cells contain a true nucleus. Eukaryotic organisms include animals, plants and fungi.

The nature and magnitude of any adverse effects arising, should HGT occur, will depend upon the characteristics and function of the genetic material transferred. The application describes genetic material to be introduced into the cattle on the basis of function (for marker and reporter genes, promoters, transcriptional elements etc) or donor species (for material from the six mammalian species). Given the broad scope of the organism description in the application it is possible that some sequences to be introduced could provide selective advantages.

Based on available evidence, plausible selective advantages of transferred material could include, but not be restricted to, providing the recipient organism with an ability to exist in a new environment (such as a site with heavy metals) or to become resistant or tolerant to specific compounds in the environment. The applicant indicated that genes conferring resistance to antibiotics used in clinical medicine would not be used. This addressed one aspect of potential adverse effects related to HGT but the Committee notes that since other genes to be used are not clearly identified there is the potential that introduction of other genes may also provide potential selective advantages to micro-organisms that acquire them. Knowing specific details of the constructs involved may reduce the uncertainty associated with consequences of horizontal transfer, but the Committee notes that there may still be uncertainty over selective advantages associated with specific genes since selective processes in the environment (especially for micro-organism) are often not well known. This is an area of ongoing international research.

The Committee acknowledges that currently some bacterial sequences are routinely used in molecular biology and preventing the use of some of these in cattle may adversely affect the applicant's research capabilities in the short to medium term. However, given the broad nature of the application, the Committee has restricted the organism description by limiting the type of bacterial sequences in the vector insert to promoter elements, reporter genes, and selectable marker genes derived from non-pathogenic strains of *E. coli*. This provides clearer boundaries on the material to be used, and since the sequences are to be well characterised and derived from a common bacterium will reduce uncertainty associated with potential consequences of HGT.

The Committee is of the view that without a selective advantage occurring, and given restrictions of the approved organisms and controls 9.1 and 9.2, HGT is unlikely to lead to the establishment of a new trait in the population. The applicant will monitor for HGT at the disposal sites and in the event of HGT being detected the project will be halted and a remediation plan developed (control 6.4).

Given the evidence available at the moment and the restrictions on the types of genetic material able to be introduced into the cattle, both the likelihood of occurrence and the magnitude of adverse effects, and thus the risk, arising from HGT from genetically modified cattle to other organisms are considered to be low, even given the uncertainty involved (clauses 12, and 32 of the Methodology refer).

(iii) Development of new diseases

Many submitters expressed concern about the potential for new diseases or pathogens (especially of, but not restricted to, humans) to develop, with some referring to the report of the development of a more virulent mousepox virus after introduction of an interleukin gene⁵. The Committee notes that the mousepox example involves a replication competent and infectious virus and Application GMD02028 does not involve the genetic modification of viruses or other pathogenic organisms so that the mousepox virus example is not directly applicable.

There was also concern that use of other viral or bacterial sequences may, by for example recombination, generate new diseases. As an example, use of material from Simian Virus 40 (SV40) was viewed with concern by some submitters. The Committee notes, however, that only a promoter from SV40 is intended for use, and by itself the promoter is not pathogenic because it only regulates the expression of genes – the virus as a whole rather than this promoter can cause pathogenic effects. The promoter itself has no inherent ability for independent movement or infection.

Other viral sequences to be used are the EBV origin of replication. The EBV origin will not be introduced into the cattle.

The organism description prohibits the use of any other viral sequences, bacterial sequences derived from bacteria (with the exception of sequences from non-pathogenic strains of *E. coli*), genes associated with prions, or modifications leading to the production of infectious particles. The Committee considers that this reduces uncertainty associated with the potential for, and consequences of, HGT as well as that of introducing pathogenic traits into cattle. In the event that a new pathogen developed the magnitude of adverse effects would be dependent upon the nature and host range of the pathogen. The limits on the organism description (Annex 1) address this uncertainty

The overall risk, having regard for the controls imposed, is thus considered to be low to a reasonable degree of certainty (clause 12 of the Methodology refers).

4.3 Risks to public health

Risks to public health and safety are required to be considered under section 6(c) and section 44A(2)(a) of the Act. Issues considered below include:

- (i) development of antibiotic resistant bacteria;
- (ii) consumption of products derived from genetically modified animals, including allergenicity, prion diseases, and the production of toxins; and
- (iii) development of new diseases (this has already been considered above).

⁵ Jackson RJ *et al.* (2001). Expression of mouse interleukin-4 by a recombinant ectromelia virus suppresses cytolytic lymphocyte responses and overcomes genetic resistance to mousepox. *J. Virol.* 75, 1205-1210

(i) Development of antibiotic resistant bacteria

The applicant proposes to use antibiotic resistance marker genes that are not of clinical significance. The Committee is of the view that marker genes should also exclude the use of genes associated with antibiotics of veterinary significance (such as tetracycline) and, because of their clinical importance, genes conferring resistance to beta-lactam antibiotics shall not be used (Annex 1).

The Committee agrees with the discussion of antibiotic resistance that was included in decision GMF99001. In summary, that discussion noted that antibiotics occur naturally in soil ecosystems and antibiotic resistance occurs in some soil micro-organisms. For example, the *nptII* gene, which confers resistance to kanamycin, is widespread in overseas environments and since it occurs in some strains of the bacterium *Escherichia coli*, which is very common in humans and animals, it is very likely to also be in New Zealand. Similarly, resistance to ampicillin is reported in some New Zealand soils, although the mechanisms for resistance have not been studied. There is little information available on the occurrence of antibiotic resistance in New Zealand, but the *aphIV* gene (which confers resistance to hygromycin) is also derived from *E. coli*, so that it is very likely to occur in the New Zealand environment. The Committee notes that antibiotic resistance genes have been introduced into New Zealand soils by a range of micro-organisms, such as *Rhizobium* bacteria.

Further proliferation of the antibiotic resistance genes would require they be transferred from cattle to soil micro-organisms as a result of HGT and be subject to a positive selective pressure. As discussed elsewhere in this decision, based upon experimental evidence the Committee considers that HGT from animals to micro-organisms may occur under some conditions, although at low frequency. The spread of resistance to antibiotics as a result of the proposed development is likely to require continuing contact with the relevant antibiotics at levels necessary to exert a selective pressure. This is unlikely to occur in the development.

Taking into account the above, the Committee concluded that the risk of increased levels of antibiotic resistance associated with the use of genes conferring resistance to antibiotics not regularly used in clinical or veterinary medicine is negligible when set against the existing occurrence of resistance to these antibiotics in the human and animal bacteria and/or in soil micro-organisms (clause 12 of the Methodology refers).

(ii) Consumption of products derived from genetically modified animals

Many submitters were concerned that adverse effects may result from consumption of products derived from the GM animals. Examples of possible adverse effects mentioned by submitters were allergens, toxins or new diseases.

The Committee notes the potential for genetic modification to produce allergens. While there may be uncertainty in the likelihood of unintended development of allergens, the Committee notes that main consideration will be exposure to any allergens. The most likely pathway for such allergens to affect humans is by direct contact or consumption of products derived from the animals. GM animals, or products derived from them, are not to be consumed (control 1.13) so the Committee considers that it is very unlikely for products from the GM animals (or surrogate mothers or recipient cows) to be consumed if the controls are adhered to. If GM cattle produced allergens in their hair, saliva, or other substances that workers may come in contact with, then adverse effects would be expected to be readily noted in individuals that come into contact with the GM animals. The effects would be local and probably treatable so that the magnitude of any adverse effects as a result of contact with allergens is expected to be minimal.

Many submitters were concerned that prion-like proteins could be inadvertently created due to the genetic modifications. The possibility of introducing an existing prion disease or creating a new prion disease applies to both the therapeutic protein and the gene function components of the application. However, the Committee concluded that the risk of a new prion disease forming was negligible because genes associated with prion-diseases are excluded from the approval (Annex 1) and pathogenic proteins that develop from mis-folding are generally well known, so genes coding for these can be excluded from the scope of any approval. The Committee was therefore satisfied that all material that could potentially cause a prion disease could be excluded.

The Committee also noted that the genetically modified animals, or products derived from them are not to be consumed. Consumption of infected animal products is the route of transmission of transmissible spongiform encephalopathies (TSEs) from animals to humans. Based on the mode of transmission of prions the Committee therefore considers that the potential for incidental transmission of prions by casual contact or through environmental pathways is very remote. The risk is thus considered to be negligible (clause 12 of the Methodology refers).

Although the application states that known toxins will not be used, there remains the possibility of new toxins being produced by recombination or unintended effects between proteins. Available information, based primarily on genetic modification of mice for many years, has not indicated the unintended development of new toxins by genetic modifications similar to the ones proposed in the application. The Committee is of the view that if any unknown mammalian toxins were produced the effects would be manifested in cattle first, and so very unlikely to pose a human health risk.

The likelihood of occurrence will be reduced to a very low level because of the impact of the controls that prevent any material from the genetically modified animals entering the food chain. The Committee's view is thus that both the magnitude and likelihood of any effects on human health will be low and the overall risk is negligible (clause 12 of the Methodology refers).

4.4 Unintended effects

Many submitters raised concerns about unintended effects. This issue involves the genetic modifications resulting in adverse effects on cattle either by disruption of other cattle genes or by new interactions between the transgenic protein and cattle proteins. The Committee notes that some unintended effects may also be potentially beneficial. (There were also submissions on the possibility of unintended adverse effects arising through HGT, unknown allergens and toxins, introduction of viral receptors with mammalian genes, and development of new viral diseases. These aspects are dealt with in sections 4.2 and 4.3)

The Committee notes the E&R report comments on p26 that adverse effects on the animals can be caused by higher or lower levels of expression of a gene than normal, expression in tissues where the gene is not normally expressed, disruption of other genes due to location of insertion, and unknown functions or interactions of the disrupted or introduced gene. (Much of this research has been done on mice and it was also acknowledged that many research projects involving genetically modified mice have been without reported unanticipated adverse effects.)

The Committee agreed with the E&R report that, “This application is for research purposes and ... unanticipated effects can be expected to occur in research to some degree. The likelihood of unanticipated effects will depend upon several factors, including the nature of the introduced genetic material, the location(s) of insertion, and the pattern and timing of expression of the foreign genetic material. The magnitude of adverse effects will also be dependent upon these factors”. The Committee notes that adverse effects may range from no observable adverse effect, to a range of morphological, physiological, or behavioural abnormalities, or in severe cases to the premature death of animals. Since such effects are very likely to be restricted to the modified animal, the magnitude of such adverse effects is considered to be minimal. However if new pathogens or diseases were to develop then, as discussed earlier, the magnitude of effect would be higher, depending upon the nature of the disease, the ability to control it, and the species affected.

The Committee has accepted the validity of generic applications per se, and that this application had sufficient (albeit with qualifications) information, to be considered. However, in regard to assessing the range and significance of unintended effects, the exclusion approach of this application means that there are uncertainties, which must be considered carefully.

The Committee paid particular attention to the possibility of unintended adverse effects from the elements listed under “Other Features” in section 5 of Appendix 1 of the application, noting that while the functions of the elements were identified the sources of them were not. The elements listed are not genes but elements that primarily affect gene transcription or protein maturation and so do not themselves produce proteins. Such elements are, therefore, very unlikely to produce products that have a toxic effect, although depending upon where the gene construct is integrated some may affect the expression of the sequence itself and adjacent cattle genes. The magnitude of any adverse effects resulting from such disruption will be dependent upon the nature of the disruption. The Committee considers that disruption of cellular pathways due to unintended effects of integration are likely to affect animal development, viability or welfare, so that the effects will be mainly on the animal and therefore of minimal effect on the environment or human health. However, possible effects on other organisms that come in contact with the cattle, such as biting arthropods, cannot be excluded.

Submitters had drawn attention to the Commoner⁶ article, which expressed concerns about the potential for adverse effects through alternative splicing mechanisms, and noted that the proposed modifications can include splice site signals. However, discussion in the E&R report challenging the major premises of Commoner’s article was accepted by the Committee, the evidence being that splicing is not random but is a process involving specific genetic signals and controls.

The Committee considers that, given the restrictions on the organism imposed in Annex 1 and controls 9.1 and 9.2, 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 cow and, as such, will be minor. A veterinarian will also be involved in monitoring the health and welfare of all animals in the trial, and to intercede if necessary. The risk is thus low. As a result of the organism restrictions, the level of uncertainty attaching to this conclusion has been reduced to an acceptable level (clause 12 of the Methodology refers).

4.5 Animal welfare issues

A number of animal welfare issues were raised at the hearing. The Committee acknowledges that there are possible adverse effects on animal welfare, and since actual modifications are not specified it is not possible for the Committee to evaluate in detail all of the possible risks to animal welfare. However, on the basis of previous genetic modifications in animals, some effects on the animal are considered likely. The significance of those effects is subject to considerable uncertainty in advance of the experiments being performed. The Committee notes that the loss of foetuses is high in transgenic animals.

⁶ Commoner B (2002). Unravelling the DNA myth. Harper’s Magazine. February.

The Committee considered that the magnitude of adverse effects on the animal will range from minimal if there are minor changes to morphology, behaviour, or physiology, to moderate if there is severe abnormality or suffering. Such adverse effects are considered to be local in that they affect the animal itself (or in some cases the surrogate mother), rather than affecting other animals or the environment.

The Committee was also presented with evidence that transgenic animals would be very well looked after. AgResearch acknowledged that it was in their best economic interests to make sure the cattle are in the best possible condition and therefore treated in the best possible manner. However the Committee also notes that once the animals are no longer of use they will be slaughtered.

Animal welfare is specifically regulated under the Animal Welfare Act (AWA) 1999, and the Animal Welfare Advisory Committee (AWAC) and National Animal Ethic Advisory Committee (NAEAC) guidelines issued by MAF. AgResearch holds a Code of Ethical Conduct (approved by MAF) that sets out the policies and procedures that are to be followed by the organisation. AgResearch also has the Ruakura Animal Ethics Committee (RAEC) that oversees animal welfare issues. Every project that involves the use of animals must be approved by the RAEC. This includes the humane slaughter of cattle that are no longer of use.

The applicant is required to comply with the Animal Welfare Act and to have the animals overseen by an experienced large animal veterinarian, who will have the power to determine a humane endpoint for any part of the experimental procedures in steps (e) and (f) (control 9.5). Under these circumstances the Committee is confident that animal welfare issues can be adequately dealt with by the RAEC.

The Committee notes that Ngā Kaihautū has recommended that information on cattle welfare be made available to the public and directly to Ngāti Wairere. The Committee has included a requirement for AgResearch to report on animal welfare issues in its final report (control 6.5). In addition, the control requiring ongoing liaison with Ngāti Wairere (control 9.4) will enable Ngāti Wairere to monitor all aspects of the development.

The Committee concluded that the animal welfare risks associated with this application are low, after taking into account the controls, the oversight of the RAEC, and the range in magnitude of the possible outcomes (clause 12 of the Methodology refers).

4.6 Risks to the relationship of Māori and their culture and traditions with their ancestral lands, water, sites waahi tapu, valued flora and fauna, and other taonga; risks to their economic, cultural and social wellbeing

Māori concerns need to be considered in the context of the specific requirements of section 6(d) and the more general requirements of section 5(b) of the Act.

Section 6(d) of the Act requires the Authority to take into account the relationship of Māori and their culture and traditions with their ancestral lands, water, sites, waahi tapu, valued flora and fauna, and other taonga. This application does not involve genes derived from native flora and fauna. The human genetic material used in the research is to be sourced from commercial gene banks from overseas. No human genetic material is to be sourced from New Zealand and the research does not specifically involve Māori genetic material (refer to AgResearch GMD 02028 application, page 8) and ERMA Evaluation & Review Report, page 44).

In considering the matters in sections 6(d) and 5(b), the Committee has given particular consideration to the views expressed by representatives of Ngāti Wairere, because they are the hapu with manawhenua over the proposed location of the research, and also the views of Ngā Kaihautū. They, and others, have objected to the application on traditional spiritual and cultural grounds. The Committee has also considered the views of the wider Māori community. These are set out in submissions on the application but the Committee is also aware of the very extensive material presented to, and considered by, the Royal Commission on Genetic Modification.

The Committee notes that for religious and moral reasons many Māori require that the motive and purposes for transgenic transfer needs to be identified and articulated thoroughly. The articulation of motive, purposes and reasons is known as establishing the kaupapa of a project. The kaupapa establishes the principles that will drive a project to its conclusion and beneficial outcomes. The kaupapa holds within it a traditional Māori belief that all things in creation, material and non-material, have from the moment of their creation a tinana, a tapu and mana, a hau, a mauri and a wairua. Within this view of life, there is no known traditional Māori religious objection to the insertion, for example, of one human gene into a cow. Historically, not only is transgenesis a relatively new science, it represents for Māori a new cultural practice, one for which there is no known tikanga.

According to Māori understanding of the conception of human life, the foetus is imbued with tapu (the sacred potentiality), hau (a life force), mana (its power and authority) and mauri (life itself, its nature). However, the wairua (the spiritual form) is bound to the new life form or organism (tinana) by the mauri. It is the combination of these elements, both spiritual and material, that constitutes what can be described as the ira tangata (the totality of human life).

Following is a line of reasoning on the spiritual and ethical considerations on intentions to insert a human gene in cattle (*Bos taurus*), according to traditional Māori thinking. The Committee recognises the difficulty in formulating a sound Māori religious case either for or against the science of transgenic transfer, specifically regarding the process of inserting a human gene into cattle. Tikanga Māori, rendered in this case as Māori religious ethics and values, may guide and inform a decision but they do not dictate a moral decision. It is within this wairua, this spirit and its spirituality, that we offer the following considerations. The Committee acknowledges that the following analysis is one way of looking at the issues, and that it may not be widely accepted at present.

According to a Māori worldview and understanding of life and its causation from the moment of conception or creation, all material and non-material things have the following constituent elements. A tinana, which is a body of physical form of its own or with which it is associated and imbued in the form is its tapu, its sacred potentiality. Closely associated with tapu is mana, which is its religious power and authority. Infused at conception is a hau, meaning its life force, its vitality containing its own set of qualities. Then it has its mauri, which is life itself or the life principle and is a force that interpenetrates all things to bind and knit them together acting as a bonding element to create a unity. In addition, it informs and guides its nature. Finally, the creation must have a wairua, which is its spiritual form and akin to a soul. The wairua is bound to the tinana by the mauri. The combination of these elements both spiritual and material constitutes for a human being the ira tangata, glossed as the totality of human life.

Scientists informed the Committee of the significant amount of genetic information that is shared by both humans and cattle and that it is not possible to say definitely what distinguishes the two.

At conception, the fertilised cell contains all of the genetic information it requires to become a functioning human (assuming that it is a viable). In a Māori religious view the human foetus contains a wairua, a mauri, a hau, tapu and mana, a tinana, and a full set of DNA. The mauri of the organism, therefore, permeates and binds together the totality of the organism. In traditional thought, however, each gene, which is a chemical and not an organism, would also have its own tinana, tapu, mana, mauri, hau and wairua, which would give each gene its distinctive function and purpose.

Mauri

Many Māori are concerned about the apparent mixing of the mauri of one organism with another through the transfer of genes. Yet, following traditional thought, the mauri of an organism is the exclusive property of that organism. It is indivisible and not transferable. The mauri is a quality of the totality of the organism and is not separable except at the death of the organism. It is imbued at creation and departs when it separates itself from the tinana thus releasing the wairua. The separation brings about the death of the organism. While the mauri can vary in strength and vitality over the course of life, it does not leave until death. When genetic material is extracted from an organism, it is thus removed without the mauri of the host organism. This is because a gene is a chemical that produces a protein not an organism. In other words, the only mauri present is the mauri of the particular sequence of bases, which constitute the gene. Each gene therefore contains its own mauri, the mauri of the gene, which allows it to exist and function. However, the gene does not have the mauri of the organism from which it is extracted.

The mauri of a human is to be a human — this is its nature. The mauri of a gene is to be a gene and produce a protein—this is how the gene expresses its nature. The mauri of a gene is not to be a human (or cow) and the mauri of a human (or cow) is not to be a gene, a protein, or any other kind of chemical. When the genetic material is extracted, it only has its own mauri, which is not the mauri of the human from which it derives because the totality of the human is not present in the individual gene. It thus follows that the gene does not introduce the mauri of the human into the cow.

When the human genetic material is implanted into another cell, which will in time become a cow (or any other organism), the mauri of the cell is still not that of the cow until the cell is viable. The cell has no 'cow' mauri unless it has everything it needs to become a cow, that is, a wairua, mauri, a hau, tapu and mana, a tinana, and a full set of DNA.

Although there does not appear to be a sound Māori religious objection to the process of genetic modification per se, there could well be religious and moral objections to the motive and purpose of particular applications of the technology, and these need to be identified and articulated thoroughly (i.e. understanding the kaupapa of the planned activity). In cases where no such objections exist, the appropriate way of dealing with the transplantation process is to conduct a suitable karakia, which is a form of ritual prayer, at the beginning of the process to extract the gene and then again at the end of the process. The karakia addresses the spiritual matters associated with issues of transgenic transfer, notably the potential clash of distinct intrinsic tapu. The material problems and risks associated with transgenic transfer can be dealt with by science. Provided the transfer is completed in accordance with the right motive and purpose, and with appropriate consultation and karakia, spiritual problems should not arise, and the risks are therefore considered to be low.

Whakapapa

The Committee considered the issue of whakapapa, which translates as genealogy. The view of two Maori submitters, Te Kotuku Whenua and Te Runanga o Ngai Tahu, was that aspects of genetic modification were incompatible with tikanga in particular the mixing of human genes with other species such as cattle as proposed in this application. According to this view, such contamination may lead to spiritual interference. The consequence of the mixing of genealogies is a perception of potential danger for humanity and the natural world.

The Committee recognises that there are many types of whakapapa such as the genealogy of creation and the genealogy of a human being. Whakapapa has logic and a structure that can be misunderstood and inadvertently misapplied. The key principle to understanding whakapapa is the idea of the laying of dimensions over each other. This idea is in the term 'papa', which is the act of laying one dimension over another. According to The Williams Maori Dictionary (1975:259) whakapapa is to place in layers, or, to lay one upon another. However, sometimes whakapapa is used in a European sense to refer to a family tree (see The Reed Dictionary of Modern Maori (1995:305). In this usage genealogy refers to a coming down from the top of the family tree but the appropriate Māori term is whakaheke, to come down from the top. The tree metaphor is the opposite to the meaning of the primary Māori idea of building layers from a base or foundation. Colloquially, it is stated that a person can 'whakapapa' to an ancestor or to God.

The whakapapa of human beings starts in a whanau and the union between a male and female who because of the union have children. This, according to tikanga is a level of 'papa'. To develop further the whakapapa requires the building of additional 'papa' or levels. It follows that to suggest the 'papa' is the result of placing a gene from one person into another is a misunderstanding of both the science and traditional Māori thought. The result of the transfer is still one person and is only an infinitesimal part of someone else.

The principle of whakapapa as foundations and layers leading to a higher level is elegantly expressed in the late Rev. Maori Marsden description of whakapapa. He says that the genealogy of creation "is quite specific and develops logically from the early stages of the root causes implanted within the cosmic space-time continuum of the void – abyss and nights in the primordial beginnings evolving into the highly specialised and variegated objects of the natural world. When each stage in this evolutionary process reached its high or 'Omega' point, the process took a leap forward to initiate a new stage and series." Genealogy he says is a tool for transmitting knowledge and pervades Māori culture. While it has functional purposes it is also an important symbolic mechanism used to depict, represent and illustrate a perceived reality. Whakapapa refers to genealogy ties and is a means of confirming membership and learning the history of the ancestors to whom a person has links.

Conclusion

The analysis set out above notwithstanding, the objections of Te Kotuku Whenua and others remain. They also remain despite the very extensive efforts by the applicant and in this decision, to ameliorate concerns through discussion and by imposing controls. The Committee especially notes that two very productive monitoring groups with Ngāti Wairere have been established, and are an ongoing forum for the discussion of measures to further ameliorate concerns. The Committee has included a control requiring the continuation of these monitoring groups (control 9.4)

However, a diversity of views exist amongst Māori as they do elsewhere. Hare Puke, a senior Kaumatua of Ngāti Wairere, takes a very much more open and supportive view of the research. This needs to be considered along with the view expressed by Te Kotuku Whenua Consultants.

Consideration must be given also to the existence of other work of a very similar nature, particularly at Ruakura, but also elsewhere. Māori, following a pragmatic tradition in this case, have found it possible to engage productively with the applicant, despite an existing and continuing source of spiritual concern.

The Committee's view is that the spiritually based concern of Te Kotuku Whenua Consultants and others is a matter that must be weighed in making a decision, in accordance with section 6(d) of the Act especially. McGechan J in his decision of 2 May 2001 in the High Court in regard to the appeal against GMF98009 says that "generalised reference to "taonga" include spiritual and cultural aspects, both as related to tangible taonga and in their own right."

The spiritual concerns are not amenable to an analysis of magnitude and likelihood, as set out in clause 12 of the methodology, as are biological and physical risks. As discussed above, the spiritual risks are, however, amenable to mitigation through ongoing dialogue and appropriate karakia, provided the motive and purpose of the research are identified and articulated.

The Committee concludes that, while the expressed concerns still remain, there are procedures in place between Ngāti Wairere and AgResearch to enable the dialogue to occur and appropriate cultural steps to be taken to avoid, as far as practical, the emergence of spiritual harm. Given this situation, the Committee's view is that risks attributable to the spiritual concerns are low.

4.7 Application of the principles of the Treaty of Waitangi

Section 8 of the Act requires the Committee to take account of the principles of the Treaty of Waitangi. In this context the Committee has been particularly conscious of the need for informed decision making, and to be sure that sufficient consultation has been undertaken in conjunction with other sources of information to provide for that outcome. The Committee recognises that AgResearch has an on-going dialogue with the two Ngāti Wairere groups and that this meets at least one key aspect of making the Treaty partnership a reality—i.e. the dialogue and its contribution to a developing relationship between a Crown agency and local tangata whenua. The Committee has also had regard to the principle of active protection and how it should apply in the context of the current application.

The Committee's view is that the consultation undertaken by the applicant, supplemented by the direct discussions between ERMA New Zealand and Ngā Kaihautū, on the one hand, and between ERMA New Zealand and representatives of the two Ngāti Wairere monitoring groups on the other, has been sufficient for the purposes of section 8 of the Act. It is emphasised again that relevant information is available from other sources, not just from consultation.

In this respect, the Committee does not agree with the suggestion from Ngā Kaihautū that further nationally based consultation is required before the application can be properly considered. However, the Committee does support the establishment of a wider forum and notes the applicant's willingness to engage more widely.

Ngā Kaihautū also recommended that a Māori mandated by the local tangata whenua be appointed to the Ag Research IBSC and the RAEC. The Committee has been advised by AgResearch that the IBSC already has a mandated Māori member, and that AgResearch expressed its willingness to appoint a further Māori member from outside the rohe. The Committee also notes that in AgResearch's legal submission in reply that AgResearch will explore the possibility of Māori scientist representation on the RAEC. The Committee is satisfied that AgResearch is taking practical steps along the road to partnership, in a manner consistent with the advice from Ngā Kaihautū.

In taking into account the need for active protection of whakapapa and mauri as taonga, the Committee notes that spiritual beliefs are different from tangible taonga, as they have come to be understood in the cases that have come before the Courts and the Waitangi Tribunal, and are not amenable to active protection in the same way as more tangible taonga. The term taonga was described in the Muriwhenua fishing report (Waitangi Tribunal report 1988, page 180) as *'the fisheries taonga, like other taonga, is a manifestation of a complex Māori physico-spiritual conception of life and life's forces. It contains economic benefits, but it is also a giver of personal identity, a symbol of social stability, and a source of emotional and spiritual strength.'* Additionally the findings of the High Court of New Zealand in the appeal against the decision GMF98009 of ERMA New Zealand the judge concluded that:

Overall I am satisfied the Parliamentary intention was that the reference in s6(d) to "other taonga" was to include intangible and spiritual taonga in accordance with usual concepts and in accordance with the Treaty.

The decisions of the Courts in the major Treaty cases refer to the Treaty as creating an enduring relationship of a fiduciary nature, and Māori interests which have been found to be subject to the government's obligation of active protection has included land, waters, economic resources such as fisheries and geothermal steam, and more recently the language itself. These are all physically or tangibly definable interests.

The Reports of the Waitangi Tribunal have similarly dealt with either historical claims in respect of land or other economic resources, and the consistency of Government legislation with the provisions of the Treaty, which give Māori rangātiratanga over such resources.

As far as the Committee could identify, none of the Treaty cases before the Courts, or the Waitangi Tribunal have addressed the nature of the Government's obligation to actively protect Māori spiritual beliefs, such as whakapapa and mauri, in contrast to tangible taonga with spiritual significance.

However, the Waitangi Tribunal in the Māori Language Report refer to the little known additional Article 4 of Te Tiriti o Waitangi, wherein Governor Hobson on February 6th 1840 at Waitangi agreed publically, in writing and orally in both Māori and English:

E mea ana te Kawana ko ngā whakapono katoa o Ingarani, o ngā Weteriana, o Roma, me te ritenga Māori hoki e tiakina ngatahitia e ia.

The Governor says that the several faiths (beliefs) of England, of the Wesleyans, of Rome, and also Māori customs shall alike be protected by him.

In considering the present application, the Committee concluded that active protection as sought by Ngāti Wairere and Ngā Kaihautū Tikanga Taiao would mean that the evaluation of and decisions on applications under the HSNO Act should be made according to the tenets of Māori spiritual beliefs, as these may be defined variously and from time to time.

The Committee concluded that the requirement to take into account the principles of the Treaty under section 8 does not extend this far.

This approach is consistent with the decisions in the major Treaty cases and in the only High Court decision in relation to the HSNO Act. For example, the Privy Council in the *Broadcasting Assets* case [1994] 1 NZLR 513, held:

‘Foremost amongst those ‘principles’ are the obligations which the Crown undertook of protecting and preserving Māori property, including the Māori language as part of taonga, in return for being recognised as the legitimate government of the whole nation by Māori. The Treaty refers to this obligation in the English text as amounting to a guarantee by the Crown. This emphasises the solemn nature of the Crown’s obligation. It does not however mean that the obligation is absolute and unqualified. This would be inconsistent with the Crown’s other responsibilities as the government of New Zealand and the relationship between Māori and the Crown. This relationship the Treaty envisages should be founded on reasonableness, mutual cooperation and trust. It is therefore accepted by both parties that the Crown in carrying out its obligations is not required in protecting taonga to go beyond taking such action as is reasonable in the prevailing circumstances.’

The High Court of New Zealand in the appeal against the decision GMF98009 of ERMA New Zealand concluded that the decision the Authority came to on the issue of active protection was sound:

“With that in mind the Authority and on good judicial authority, noted that the duty of active protection did not require Crown action beyond that which was reasonable in the prevailing circumstances. In the Authority’s view, treating the duty of active protection as a “determinant” - ie as prevailing over all other considerations - was unreasonable.”

In summary the Committee concludes that taking into account the need to provide active protection for Māori spiritual beliefs does not extend to accepting those beliefs as the determinant of whether the research proposed by the applicant should be approved.

4.8 Ethical issues

Although the Act does not directly identify ethical issues as matters to be considered, there is a presumption that they should be, both in the wording of section 5(b) and the definition of “environment” in section 2. In addition, the Royal Commission on Genetic Modification noted on page 24 and 38 of their report that sections 5, 6, and 8 of HSNO implies certain values that enable ethical decision-making.

Many submitters were of the view that the Committee should not consider this application until after the Bioethics Council is set up. However, the Committee has a requirement under the HSNO Act to consider valid applications. There is no provision for delaying decision-making to provide for factors such as the setting up of the Bioethics Council. Further, it is clear from the Royal Commission's report (p.40) that the Commission intended the Bioethics Council to develop guidelines at a policy level, while case-by-case assessment would still be carried out by ERMA.

The Committee notes that there are two strong, and opposing, bodies of ethical opinion in relation to this application:

- 1) that this research should be pursued because it may lead to possible benefits to human health and wellbeing without substantive harm to the environment or individuals; and
- 2) that it is ethically wrong to transfer genes from one species to another ie to cross the species barrier.

While section 5(b) of the Act requires cultural wellbeing to be recognised and provided for, this principle must be applied in respect of the whole of the community not just one part of it. The Committee acknowledges that there are concerns and anxiety over genetic modification: some are able to accept it should it occur in the laboratory but not accept it should it occur outside; others are concerned with the speed of the technology in the face of uncertainty; while others are in favour especially if specific benefits are identified.

Four specific ethical issues, unrelated to biophysical risks, were raised by submitters opposed to genetic modification:

- (i) use of companion animals for genetic modification experiments is unethical;
- (ii) concerns about the entry of cattle products containing human genes into the food chain
- (ii) that genetic modification is against the teachings of the Bible; and
- iii) animal welfare issues.

Animal welfare is discussed in section 4.5 of this decision. The other three ethical issues are considered below.

(i) Use of food producing animals for genetic modification experiments

Several submitters raised an ethical objection to using companion animals such as cattle as experimental tools, particularly in relation to experiments involving genetic modification. Individuals base their objection on the improper use of animals.

The Committee notes that over thousands of years, many societies have practiced cattle breeding, in the nature of experiments, seeking to increase the value of cattle to humans. In recent times the uppermost constraint on such breeding techniques has been the need to avoid cruelty to animals. As discussed in section 4.5, the development of genetically modified cows will be subject to the approval and oversight of the Ruakura Animal Ethics Committee which will ensure that any unnecessary pain and suffering is avoided.

While accepting that some individuals regard the use of cattle for genetic modification experiments as unethical, the Committee also recognises that as a society we have long bred cattle to produce meat and milk for human convenience. Given that the cattle's welfare will be managed by the RAEC, the Committee concludes that the ethical risks of using cattle as experimental tools are very low.

ii) Concerns about the entry of cattle products containing human genes into the food chain.

The Royal Commission on Genetic Modification in Chapter seven, page 161, paragraph 100 states that:

“If possible it would seem preferable to give priority to using animals not usually used for food as bioreactors in order to lessen the possibility of human health impacts and the associated anxiety over the potential for affecting food sources.”

The Royal Commission states a preference rather than a firm position, and it is unknown at this point whether it will find expression in legislation.

In the case of the current application an important consideration is that the work is for development, there is no intention of any genetically modified material finding its way into the food chain, and indeed controls are proposed to specifically prevent this. The Committee considers that any residual anxiety felt by those opposed to using food producing animals to produce biopharmaceuticals would be of a general character and not such as to suggest that it will lead to significant adverse effects. The risk is thus considered to be negligible (clause 12 of the Methodology refers).

(iii) Contravention of the teachings of the Bible

The Committee appreciates that many may object to genetic modification on spiritual or religious grounds. Individuals may have religious texts such as the Bible as a basis for their objections. This is reflected in some submissions.

The Committee also notes the evidence presented to the Royal Commission from the Catholic Bishops' Conference, stating (p. 23) that they ‘*did not see the technology of genetic modification in itself to be in conflict with ethical values. However ...there may be uses of genetic modification that are unethical or unwise*’. The Royal Commission also noted the strong Judaeo-Christian view that people have a responsibility to care for, or practise, stewardship of the environment.

It is the Committee's view that, given the organism restrictions, the proposed research is unlikely to contravene the responsibility to care for the environment, and that the pursuit of scientific knowledge that may have potential farming and health benefits, is ethically responsible and not an unethical use of genetic modification. Consequently, while accepting that some individuals regard genetic modification as a contravention of the Bible, the Committee does not regard this research as necessarily unethical from a Christian point of view.

4.9 Economic risks

The following economic risks were considered by the Committee:

- (i) impact on other cattle farming operations;
- (ii) broader effects on the agricultural sector; and
- (iii) impacts on tourism and our international image.

Many submitters were also concerned about the issue of liability. The Government is currently considering the issue of liability. However, it is not the role of the Committee to consider the adequacy of the current legal framework for attributing any liability that might arise from the development of genetically modified organisms. Rather the role is to identify and evaluate the relevant risks, costs and benefits - including taking into account the distributional effects of the costs and benefit over time, space and groups in the community. These matters are dealt with elsewhere in this decision.

(i) Impact on other cattle farming operations

Costs could be imposed if the cattle escaped and interbred with unmodified cattle, but even if the controls did not apply any effect would be localised and would be quickly detected.

The Committee is satisfied that the proposed containment would in any case, be adequate to contain the transgenic cattle and that escape from containment would be very unlikely. Both the magnitude and likelihood of adverse effects of cattle escaping on other farming in the area is thus very low, and this risk is considered to be negligible (clause 12).

As discussed in sections 4.2(i) and 4.2(iii), the Committee recognises risks arising from unintended creation of new viral reservoirs and new animal diseases, and potential transmission off-site by arthropods. The cost of such an outcome would most likely be borne by other cattle farmers, as well as AgResearch. The Committee acknowledged that this was an area of uncertainty, and has excluded from the material to be inserted into cattle all known animal viral receptors, all viral sequences except SV40, all bacterial sequences except from non-pathogenic *Escherichia coli*, and required all material inserted into cattle to be fully characterised (Annex 1 and controls 9.1 and 9.2). The Committee concluded, in section 4.2, that the risk of viral cell receptors and new diseases is low. Since the costs to farming arise as a direct consequence of the biophysical risk, the Committee considers that the expected cost associated with unintended creation of new viral reservoirs and new diseases is also low (clause 13 of the Methodology refers).

(ii) Broader effects on the agricultural sector

There were two types of submissions on this topic. One was that this research would be deleterious to our clean green image and the potential for organic farming. The other was that this type of research could be used in conjunction with organic farming. An Australian example was presented where the organic farmer preferred to grow his organic produce next to the genetically modified produce because less pesticide and herbicide was used on genetically modified produce than on non-genetically modified produce.

However, none of this evidence was considered to be very relevant to development work on cattle, given especially the very strict controls against any entry of material into the human food chain. The risk and cost is thus considered to be negligible (clauses 12 and 13 of the Methodology refers).

(iii) Tourism and international image

Some submitters claimed that this application would harm tourism and New Zealand's international image. At the hearing, other submitters noted that genetic modification in other places, notably Hawaii, has not harmed tourism.

There is no evidence that development work on genetically modified cattle will harm tourism or New Zealand's international image. The risk and cost is thus considered to be negligible (clauses 12 and 13 of the Methodology refers).

5. Assessment of the significant benefits associated with the application

The Committee is of the view that the benefits of this development would be primarily in the form of increased scientific knowledge and skills enhancement, regardless of the outcome of the project. It may also enhance New Zealand's reputation in the international science world.

It is very likely that these benefits will occur (clauses 12 and 13 of the Methodology refer.) AgResearch is a reputable research institution and has invested considerable funds in this work. It would be unlikely to do so without some assurance of benefit. Because AgResearch is a CRI owned by the Government there is also some assurance that the benefits will accrue to New Zealand (clause 14 of the Methodology). In terms of clause 13(c) of the Methodology the immediate benefits will accrue to AgResearch itself, but its ownership indicates that a wider distribution of benefit will occur in the longer term. The benefits are likely to be both non-monetary and monetary (clause 13(a) of the Methodology).

However, there is considerable uncertainty in assessing the magnitude of the benefits (clause 13 of the Methodology). The Committee notes that AgResearch did not attempt to assess the magnitude of the benefits, stating that this research was aimed at ‘proof of concept’ and is not amenable to rigorous assessment of the magnitude of benefits. The Committee considers that the magnitude of benefits will range from minimal to moderate, depending on the success and significance of the research (clause 13(b) of the methodology refers).

In addition to the benefits associated with the research, the Committee considered that there may be some flow-on benefits associated with approval. As noted in section 2, the Committee identified the potential risk of loss of scientists and scientific expertise associated with not approving the application. In a similar vein, not approving this application could deter business investment in biotechnology. These benefits of approval, while uncertain, arise regardless of whether future applications are made and are therefore relevant for consideration. However, these benefits cannot be attributed uniquely to this application and have therefore been given a minimal weighting by the Committee.

6. Establishment of approach to risk

Clause 33 of the Methodology requires the Authority to have regard to the extent to which a set of risk characteristics exist when considering applications. The intention of this provision is to provide a route for determining how cautious or risk averse the Authority should be in weighing up risks and costs against benefits. Thus the Committee has considered whether:

- (a) exposure to the risk is involuntary;
- (b) the risk will persist over time;
- (c) the risk is subject to uncontrollable spread;
- (d) the potential adverse effects are irreversible; and
- (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 adverse effects.

The Committee’s views on the individual elements are as follows:

(a) and (c) The impact of effective containment is to make involuntary physical exposure unlikely and to prevent uncontrollable spread. However the committee also notes that Ngāti Wairere has no choice about the effects of spiritual/cultural exposure except in so far as conditions can be negotiated with AgResearch.

(b) This application is for a limited time period so risks to cattle should not persist over time. But risks from HGT, the escape of a bull, new viral diseases or unintended effects could potentially persist over time and spread beyond the containment site.

(d) The potential adverse effects are unlikely to be reversible in particular for cattle that are genetically modified. Similarly, risks from HGT and new viral diseases could potentially be irreversible.

(e) Genetic modification, and transgenic organisms in particular, are very controversial matters, but the extent to which the risks are known or understood by the general public is difficult to ascertain as are the possible measures for managing potential adverse effects.

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 by inclusion. Section 7 of the Act requires the Committee to take into account the need for caution where there is scientific or technical uncertainty about effects. This, coupled with part of the containment facility being outdoors, lead to serious questioning as to the ability to assess all potential beneficial and adverse effects.

After considering all of the factors set out above, it was thus decided to adopt a more risk averse approach than might normally be expected in an application for development in containment.

7. Alternative methods to achieve the research objectives

Section 44A(2)(b) of the Act requires the Committee to take into account any alternative method of achieving the research objective that has fewer adverse effects on the environment or human health and safety, than the proposed development. In this context the Committee had regard to material presented by the applicant, submitters, and in the E&R Report.

Possible alternatives considered, looking at the different objectives of the research, were:

- production of therapeutic proteins using fermentation (bacteria or mammalian cell lines), other mammals such as mice, plants, and recovery of proteins from unmodified tissues;
- establishing gene function using mice or rats.

Many submitters suggested that the research could be conducted using cell lines rather than whole animals, but they did not provide a detailed discussion of this. The applicant stated that cell culture systems may not properly express genes, or produce the correct active form of the protein, and results can differ if expression is compared between cell cultures and normal tissues. They also noted that tissue specific functions cannot be carried out in cell cultures. In response to questioning the applicant noted that plants have different post-transcriptional modification systems so plants may not produce animal proteins of the desired functionality. The spokesperson for the New Zealand Organisation for Rare Disorders also noted that supplies of therapeutic proteins from human tissues were usually insufficient to meet current or future demands. Production of proteins in small laboratory animals such as mice were also unlikely to be able to meet the demands for some of the proteins.

The Committee acknowledges that production of therapeutic proteins in the laboratory (such as use of fermentation or extraction from human tissues) could have fewer potential adverse effects on the environment, and would address many of the submitters concerns. However, the Committee's view is that investigation of the production of therapeutic proteins in the milk of cattle is a valid line of research, the applicant has demonstrable experience in this area, and that where large amounts of a specific protein product are required, then expression of the product in the milk of large mammals is likely to have technical and economic advantages over the use of cell cultures or other systems. As such the Committee does not consider that alternative methods could achieve the same outcome.

The applicant argued that it is impossible to study gene function related to cattle in other systems (such as laboratory mice or rats) because of differences in physiology and genomes. The Committee accepts the view that an understanding of gene function on cattle phenotype requires the modifications to be tested in cattle, so long as the traits being investigated are in relation to effects of phenotypes of particular relevance to cattle productivity or performance. The Committee's view was that while other methods might be applicable to meeting some elements of the objectives, work on genetically modified cattle was still required for meeting the objectives as a whole.

The Committee notes the concerns that animal cloning and genetic modification can have low success rates, but considers that further research may improve such techniques. The Committee's conclusion is that although alternative methods may be partially applicable to achieving the research objectives, there are no suitable alternatives with lesser potential adverse effects for meeting the applications research objectives. There are thus insufficient grounds under Section 44A(2)(b) to warrant declining the application.

8. Measures to reduce risk and uncertainty

Before evaluating and weighing the risks, costs and benefits, the Committee considered whether there were any measures that could be taken to reduce the identified areas of risk and uncertainty.

The Committee considered that the controls proposed in the application were inadequate to address the areas of risk, and the organism description in the application resulted in an unacceptably high level of uncertainty. At the hearing, the applicant was given a number of opportunities to refine the application. In their final response, AgResearch proposed certain limits on the organism description, which the Committee has considered. AgResearch stated that they would exclude sequences from known pathogens, all viral sequences except for the SV40 promoter and EBV origin of replication, known viral receptors, and that vector backbone sequences would not be introduced into the cattle genome. They also stated that the Tet on/off system for inducible gene expression would not now be used. The Committee is supportive of AgResearch's stated intention to undertake research to enable monitoring of insertion sites and characterisation of flanking sequences.

As discussed in section 3.6, the Committee has restricted the scope of the organism in a number of ways in order to reduce risk and uncertainty. These measures

- a) exclude all viral sequences other than SV40 and the EBV origin of replication;
- b) exclude from the vector insert all bacterial sequences other than reporter gene and marker genes, and their associated promoters, and multiple cloning sites derived from non-pathogenic strains of *E. coli* bacteria;
- c) exclude known animal (as well as human) viral receptors;
- d) exclude antibiotic resistance markers conferring resistance to antibiotics of clinical significance in veterinary or human medicine;
- e) exclude genes associated with the development of transmissible spongiform encephalopathies (prion diseases);
- f) limit donor DNA to genes relevant to the stated research objectives; and
- g) require characterisation and reporting of all genetic material in the vector insert.

In general, these restrictions are aimed at removing classes of risk associated with HGT, viral and prion diseases, and antibiotic resistance. The Committee made specific exceptions for the SV40 promoter, and EBV origin of replication, and for some sequences derived from non-pathogenic *E. coli* (such as reporter genes and selectable marker genes). The Committee considered that the exceptions for specified viral and bacterial sequences did not add to the risks (because the effects of these sequences are well known) and their inclusion will facilitate the research.

The Committee has also required on-site disposal of all surrogate mothers and recipient cows to avoid any escape of genetically modified material, and monitoring of micro-organisms at the disposal sites to detect any HGT. Should monitoring reveal any detectable HGT, the development and disposal of genetically modified cows is to cease immediately and AgResearch is to work with ERMA New Zealand to develop a remediation plan.

The Committee notes that Ngā Kaihautū also recommended exclusion of viral sequences and known transposable elements, and controls requiring characterisation, monitoring of disposal sites for HGT, and on-site disposal of surrogate mothers.

Finally, the Committee notes that information about the effects of genetic modification on the environment is a rapidly emerging area of knowledge. It is very likely that other information, relevant to the assessment of risks in this application, will emerge in the near future. The Committee was however, aware that proposed benefits of the research would require breeding of some cattle to obtain the desired genetic modifications, and that this would require more than the minimum of four years to produce an individual GM animal (the application notes on page 18 that developing a line will span a period of 3 to 4 years with breeding and milking in years 3 and 4). The applicant indicated that production of cattle homozygous for a particular trait would involve selective breeding of GM animals and requested an approval for 10 years.

The view of the Committee is that a seven and a half year approval is reasonable to enable development of GM cattle. A ten year approval was not supported because the committee considered that the non-specific nature of the application required additional caution. A shorter period of approval was also considered but rejected because technical difficulties can slow the development of GM cattle and so potential scientific benefits may not be able to be realised in a shorter approval period.

It is up to AgResearch to determine how best to focus its research efforts within this period. Section 1 of this Decision discusses restrictions on breeding necessary to ensure the development does not include field testing. Nothing in this approval prevents AgResearch from making another application to develop a specific line over a longer time period.

The Committee is satisfied that the above restrictions adequately deal with the risks and uncertainties created by the very broad organism description in the application. While the Committee accepts that HSNO does not preclude generic applications, and that this application met the legal minimums in terms of information requirements, we do not believe it is in the best interests of applicants to make generic applications that force the decision-making Committee to make broad exclusions to deal with classes of risk. It would be preferable for generic applications to specify in more detail what is excluded from the application, and to provide sound reasons for seeking flexibility.

9. Overall evaluation and weighing up of risks, costs and benefits and the overall adequacy of containment

The overall evaluation of risks, costs and benefits set out below was carried out having regard to clause 22 and 34 of the Methodology and in accordance with the tests in clause 27 of the Methodology and sections 45 and 45A of the Act. Clause 27 was appropriate because the combined risks were considered to be not negligible.

Clause 34 of the Methodology sets out the approaches available to the Authority in evaluating the combined impact of risks, costs and benefits. It was not possible to use common units of measurement, whether monetary or non-monetary. However, it was possible to identify dominant risks ie those having a dominant influence over 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 impact of the organism restrictions in Annex 1 and the impact of containment and other controls set out in Annex 2. These include:

- risks to public health including those arising from antibiotic resistance and the consumption of products from the genetically modified cattle;
- biological and physical risks to the environment and human health from the possible escape of the genetically modified cattle.

In relation to ethical risks, the Committee considers that the risks to animal welfare are non-negligible. The Committee recognises the high level of public concern over the appropriateness of genetic modification as a technology and the modification of food-producing animals in particular. However, the Committee does not consider that such ethical concerns are overriding in the circumstances of this application. . There are potentially non-negligible risks to the environment that are not related to the ability of the cattle to escape. These risks include unintended insertion of viral cell receptors and creation of new viral reservoirs, and adverse effects arising as a result of HGT.

This application has been characterised by the cumulative effect of uncertainty resulting from the broad scope of the organism description. The Committee was initially limited in its ability to fully assess risks because of the lack of specificity of a number of the elements that could be involved in the genetic modification process, and lack of evidence regarding absence or presence of potential adverse effects. This constraint has been overcome to a satisfactory extent by restricting the scope of the approved organism, requiring monitoring of micro-organisms, and limiting the period of approval to 7 ½ years.

In relation to Maori spiritual risks, the Committee concludes that, while the expressed concerns of Te Kotuku Whenua and others still remain, there are established and ongoing procedures in place between Ngāti Wairere and the applicant that ensures dialogue occurs and appropriate cultural steps are taken to avoid, as far as practical, the emergence of spiritual harm. Given the expressed commitment of AgResearch and Ngāti Wairere to ongoing dialogue, the Committee regards the spiritual risk to be low.

With these controls in place, the combined non-negligible risks referred to above are considered to be low, even after taking account of uncertainty (clause 12 of the Methodology refers).

As assessed in section 5 of the decision the benefits of the application 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, (clause 13(b) of the methodology refers).

The issue then is whether, given the organism restrictions and the containment and controls proposed, the benefits outweigh the non-negligible risks and costs, i.e. environmental risks that are not related to the ability of the cattle to escape, risks to animal welfare, and Māori cultural and spiritual concerns. The Committee's view is that the benefits do outweigh these costs and risks, although this is very much a matter of judgement, given the difficulty of quantifying risks, costs and benefits, and the impact of uncertainty.

The Authority was satisfied that the containment regime would be adequate to contain the organisms, both generally in accordance with section 45(a)(iii) and specifically in accordance with section 45A(2)(a).

Decision

1. Pursuant to section 45(1)(a)(i) of the Act the Committee is satisfied that this application is for one of the purposes specified in section 39(1) of the Act, being section 39(1)(a), and that the scope and content of the application is acceptable for an application with this purpose. Notwithstanding the generic nature of the organism description in the application, the Committee is also satisfied that the application contains sufficient information on the organism to enable the application to be validly considered.

2. To ensure that work covered by this decision is implemented as a development, controls on breeding are imposed. These are intended to ensure that the applicant does not increase, beyond that necessary for development, the number of animals of a particular construct through breeding.
3. 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 Annex 1, and is this organism description to which this decision applies.
4. Pursuant to section 44A(2)(b) of the Act, the Committee is satisfied that, having considered alternative methods for achieving the research objectives, there are no practical alternatives with demonstrably fewer adverse effects.
5. The committee is satisfied that the proposed containment regime together with the additional controls imposed will adequately contain the organisms as required by section 45(1)(a)(iii) of the Act and that the controls satisfy the requirements of section 45A(2)(a), to ensure that after the end of the development, the organisms and any heritable material from the organisms are removed or destroyed.
6. 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 and clause 27 of the Methodology and has relied in particular on the following criteria in the Act:
 - Section 5(b) – to achieve the purpose of the Act and to recognise and provide for the maintenance and enhancement of the capacity of people and communities to provide for their own economic, social, and cultural wellbeing and for the reasonably foreseeable needs of future generations;
 - Section 6 and in particular s.6(c) (public health) and 6(d) (the relationship of Māori and their culture and traditions with their ancestral lands ... and other taonga) and (e) (the economic and related benefits to be derived from the use of the new organism);
 - Section 7 – dealing with scientific and technical uncertainty; and
 - Section 8 – the principles of the Treaty of Waitangi.
7. The Committee also had regard for the whole of the Methodology and in particular the following clauses:
 - Clause 9(b) [equivalent of s.5(b)] and 9(c) [equivalent of s.6];
 - clause 10 [equivalent of ss.36 and 37];
 - clause 12 – evaluation of assessment of risks;
 - clause 13 – evaluation of assessment of costs and benefits;

- clause 21 – the decision accords with the requirements of the Act and regulations;
 - clause 22(1) – the evaluation of risks, costs and benefits – relevant considerations;
 - clause 24 – the use of recognised risk identification, assessment, evaluation and management techniques;
 - clause 25 – the evaluation of risks;
 - clause 27 – risks and costs are outweighed by benefits;
 - clause 29 (a) - determination of materiality and significance of scientific uncertainty;
 - clause 32 – dealing with uncertainty;
 - clause 33 – risk characteristics; and
 - clause 34 – the aggregation and comparison of risks, costs and benefits..
8. Approval is thus given for the development of genetically modified cattle that conform with the organism description in Annex 1, and subject to the controls set out in Annex 2.
- 9 The development of the cattle under this approval may be carried out using embryos developed by way of steps (a) to (e) of the experimental method described in the application, or by using embryos developed by way of *in vitro* or *in vivo* fertilisation using sperm of *Bos taurus* that conform with the organism description or by artificial insemination using sperm of *Bos taurus* that conform with the organism description.

Dr Lindie Nelson (Deputy Chair)
Special Committee of the Authority

Date Signed: 30 September 2002

Amendments:

16 November 2005; Decision amended to clarify that this Approval allows the development of cattle from previously developed sperm or embryos from transgenic animals and the use of artificial insemination, *in vitro* and *in vivo* fertilisation to generate live offspring. This clarification is made through the following changes:

1. Decision amended by inserting clause 9, on page 50;
2. Control 1.1: Amended by inserting the words “or *in vitro* fertilisation if it occurs in New Zealand” after the words “Steps (a) to (d) as specified in the application.”
3. Control 1.3: Amended by inserting the words “and artificial insemination or embryo transfer or *in vivo* fertilisation” after the words “Steps (e) and (f), as specified in the application.”
4. Controls 1.6 and 1.8: Amended by inserting the words “mothers or” before the words “surrogate mothers.”
5. Control 9.2: Amended by inserting the words “artificial insemination or transfer of embryos or” before the words “nuclear transplantation.”

16 November 2005; Decision amended to allow the use of a selectable marker gene coding for puromycin resistance derived from the bacterium *Streptomyces alboniger*. The organism description is amended by inserting the words “for a selectable marker gene for resistance to puromycin derived from *Streptomyces alboniger* and selectable marker genes derived from” after the word “except” in the specification of selectable marker genes in Annex 1 on page 53.

Chair

Date

Dr Kieran Elborough

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: 22 August 2007

Dr Kieran Elborough

Chair

December 2007, Decision amended to allow for the use of LoxP sites derived from the bacteriophage P1 and a polyadenylation signal derived from Simian Virus 40. The Organism description is amended by inserting the words LoxP sites (minus the sequence encoding the Cre protein) derived from the bacteriophage P1 and a polyadenylation signal derived from Simian Virus 40 after the word *E. coli* in the specification of features associated with the insertion or removal of foreign genetic material in Annex 1 on page 53.

Date: 14 December 2007

Dr Kieran Elborough

Chair

March 2010

Decision amended to extend the approval period from 7.5 to 10 years. The wording in control 9.6 was updated.

Date: 11 March 2010

Dr Kieran Elborough

Chair

Annex 1. Description of the approved organism

Host organism

The host organism is *Bos taurus* Linnaeus 1758 (cattle; Family Bovidae) cells, embryos and whole animals genetically modified with material of the following type. The modifications shall meet the requirements of Category A or B experiments as described in the HSNO (Low-Risk Genetic Modification) Regulations 1998.

Vectors

The vector consists of two components – (i) the vector “backbone” which shall not be introduced into the cattle genome, and (ii) the vector insert that will be introduced into the cattle genome. All components of the vector shall be characterised such that the DNA has been sequenced and there is an understanding of their function and, if relevant, the potential gene products.

(i) Vector Backbone

The vector backbone shall only contain any or all of the following elements:

- **Promoter**, operator, regulatory element binding and enhancer sequences derived from non-pathogenic bacteria
- **Selectable marker genes** that confer an ability to:
 - Be resistant against antibiotics that are not clinically significant, (that is are not used in human medicine)
 - Deactivate metabolic inhibitors
 - Deactivate vertebrate toxins⁷
 - Deactivate other selective drugs
- **Origins of replication:**
 - Col E1 or pUC origins of replication derived from plasmids sourced from non-pathogenic strains of *Escherichia coli*
 - Bacteriophage f1 origin of replication
 - Epstein-Barr virus (EBV) origin of replication (Ori P)

(ii) Vector Insert

The vector insert shall only contain any or all of the following elements:

- **Promoter**, operator, regulatory element binding and enhancer sequences derived from yeast or mammals, or the SV40 promoter. Promoters normally associated with the permitted reporter or selectable marker genes derived from *E. coli* described below may also be used with those genes.

⁷ Vertebrate toxins are considered to be those that have, or are suspected to have, a measurable LD₅₀ value for any vertebrate species of less than 100 micrograms/kg body weight

- **Reporter genes** (genes encoding easily assayed proteins) that are not derived from bacteria (except non-pathogenic strains of *E. coli*) or viruses and do not produce proteins that are pathogenic or toxic in vertebrates (have an LD₅₀ less than 100 micrograms/kg body weight).
- **Selectable marker genes** that are not derived from viruses or bacteria (except for a selectable marker gene for resistance to puromycin derived from *Streptomyces alboniger* and selectable marker genes derived from non-pathogenic strains of *E. coli*) and confer an ability to:
 - Be resistant against antibiotics that are not clinically significant in veterinary or human medicine. Genes providing resistance to beta-lactam antibiotics shall not be used.
 - Deactivate metabolic inhibitors
 - Deactivate vertebrate toxins
 - Synthesise green fluorescent protein
 - Deactivate other selective drugs

With the exception of antibiotic resistance genes the marker genes shall not be likely to provide identifiable selective advantages to micro-organisms in the environment

Other features associated with insertion or removal of foreign genetic material or with gene or protein expression Sequences not derived from bacteria or viruses (with the exception of multiple cloning sites derived from non-pathogenic strains of *E. coli*, LoxP sites (minus the sequence encoding the Cre protein) derived from the bacteriophage P1 and a polyadenylation signal derived from Simian Virus 40), limited to the following:

- Multiple cloning sites
 - Polyadenylation signals
 - Splice sites
 - Transcriptional activators
 - Transcriptional responsive elements
 - Transcriptional terminator sequences
 - 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.
 - Insulator elements
- **Donor DNA:** The donor gene DNA will be sourced from humans (provided that the human donor DNA shall not come from Māori), mice (*Mus musculus*), cattle (*Bos taurus*), sheep (*Ovis aries*), deer (*Cervus elaphus*), or goats (*Capra hircus*). The genes will be one gene (or two genes for immunoglobulins) from the donor organisms specified and be cDNA or genomic DNA. Sequences shall be limited to genes associated with the production of therapeutic proteins in milk or study of cattle gene function.

The donor DNA shall not include:

- Known⁸ vertebrate toxins
- Sequences that will produce particles able to infect humans, animals or plants
- Known human or animal virus receptor genes
- Known genes of allergens
- Transposons, transposable or mobile elements, genes for transposases, retrovirus long terminal repeat sequences (LTRs)
- Known genes associated with the development of transmissible spongiform encephalopathies.

⁸ Known means that there is published material in the peer-reviewed scientific literature indicating that the material is or may be associated with the trait

Annex 2 Controls

This annex contains three types of controls:

1. *Third schedule controls.* Under s45(2)(a) containment approvals must contain controls to address the matters detailed in Part I of the Third Schedule of the Act. The third schedule controls comprise controls 1.1 to 7.2.
2. *Mandatory controls.* Under s45A(2)(a) of the HSNO Act, an approval must include controls to ensure that, after the end of the development or field test, heritable material is removed or destroyed. The mandatory controls comprise control 8.1(a) and (b).
3. *Other controls.* Under section 45(2)(b) additional controls may be imposed to give effect to the Act. Other controls comprise controls 9.1 to 9.6.

This approval is subject to the controls specified below.

1. **To limit the likelihood of any accidental release of any organism or any viable genetic material⁹:**
 - 1.1 Steps (a) to (d) as specified in the application, or *in vitro* fertilisation if it occurs in New Zealand, shall be carried out in an indoor containment facility approved by the Ministry of Agriculture and Forestry (MAF) under the Biosecurity Act 1993, in accordance with the MAF/ERMA Standard 154.03.02¹⁰ *Containment Standard for Micro-organisms* at Physical Containment level 1 (PC1).
 - 1.2 The operation and management of the indoor containment facility shall be in accordance with MAF/ERMA Standard 154.03.02¹⁰ *Containment Standard for Micro-organisms*.
 - 1.3 Steps (e) and (f), as specified in the application, and artificial insemination or embryo transfer or *in vivo* fertilisation shall be carried out in an outdoor containment facility¹¹ approved by the Ministry of Agriculture and Forestry (MAF) under the Biosecurity Act 1993, in accordance with the MAF/ERMA New Zealand Animal Health and Welfare Standard 154.03.06¹⁰: *Containment Standard for Field Testing Farm Animals*.

⁹ Viable Genetic Material is biological material that can be resuscitated to grow into tissues or organisms. It can be defined to mean biological material capable of growth even though resuscitation procedures may be required, eg when organisms or parts thereof are sublethally damaged by being frozen, dried, heated, or affected by chemical.

¹⁰ Any reference to this standard in these controls refers to any subsequent version approved or endorsed by ERMA New Zealand

¹¹ The *outdoor containment facility* refers to the area where the genetically modified cattle are to be maintained, and that is registered by MAF under the Biosecurity Act 1993 as a *containment facility*.

- 1.4 The operation and management of the outdoor containment facility shall be in accordance with MAF/ERMA Standard 154.03.06¹⁰: *Containment Standard for Field Testing Farm Animals*.
- 1.5 The outdoor containment facility shall be enclosed by double 2 metre high perimeter fences constructed in accordance with the requirements of the standard specified in control 1.4. The inner perimeter fence shall be electronically monitored and alarmed (in order that the location of any breach of containment is detected immediately), stock-proof, and capable of preventing entry and escape of cattle.
- 1.6 No genetically modified cattle, mothers or surrogate mothers (cows carrying GM foetuses to full term or near to full term), or recipient cows (cows that implant a GM embryo but subsequently lose the foetus) are permitted to leave the outdoor containment facility except in accordance with the requirements of the standard listed in control 1.4. All such animals shall be returned to the outdoor containment facility.
- 1.7 The number of genetically modified male calves shall be kept to a minimum. All genetically modified male calves shall be destroyed after semen has been collected, and disposed of in accordance with control 1.9.
- 1.8 All genetically modified cattle, mothers or surrogate mothers, recipient cows, and non-transgenic calves¹² associated with this approval, no longer required for the development shall be destroyed, and disposed of in accordance with control 1.9. Surrogate mothers and recipient cows are defined by pregnancy to the stage of demonstrable placentation at, or before, the 35 day scan, whether or not they carry the calf to term. Conventional cattle that do not implant a GM embryo can be disposed of off-site.
- 1.9 Disposal shall be by burial in unlined offal pits. Offal pits are to be located within the outdoor containment facility and shall be positioned to minimise leaching to groundwater. The applicant shall consult with Ngāti Wairere with respect to developing culturally appropriate mechanisms and protocols for disposal, which add to and are consistent with the rest of this control.
- 1.10 In the event of mortality of genetically modified cattle in the containment facilities, carcasses shall be immediately removed to prevent access by scavengers and the carcasses disposed of in accordance with control 1.9.
- 1.11 Milking of genetically modified cattle shall be performed within the outdoor containment facility and the milk shall be transported, in secure containers to prevent spill, to the indoor containment facility (approved under control 1.1) for evaluation. A log of the quantity of milk obtained and its fate shall be maintained and recorded in a register.

¹² Non-transgenic calves are animals with no foreign genetic material in their genome, but which have transgenic animals in their line of breeding.

1.12 All milk, skim milk, and cream shall either be disposed of by an effluent treatment digester or incineration within the indoor facility, or by spraying onto pasture within the outdoor containment facility following treatment in order to destroy any cells present in the milk; or be removed into secure containment in accordance with the MAF/ERMA New Zealand Standard 154.03.02¹⁰ *Containment Facilities for Micro-organisms*.

1.13 No part or product of genetically modified cows, surrogate mothers or recipient cows (as defined in control 1.8), or non-transgenic calves¹³ shall be ingested by any person at any time.

1.14 Any cattle with signs of any exotic disease, including transmissible spongiform encephalopathies, shall be reported to MAF via the Exotic Disease and Pest Emergency Hotline. Disposal of animals will be according to MAF direction..

2. To exclude unauthorised people from the facility:

2.1 The applicant shall comply with the requirements contained in the standards listed in controls 1.2 and 1.4 relating to identification of entrances, numbers of, and access to entrances, and security requirements for the entrances and the facilities.

2.2 At all times only persons authorised by the Operator or the Manager of the containment facilities shall have access to the containment facilities.

3. To exclude other organisms from the facility and to control undesirable and unwanted organisms within the facility:

3.1 The applicant shall comply with the requirements contained in the standards listed in controls 1.2 and 1.4 relating to exclusion of other organisms from the facilities and the control of undesirable and unwanted organisms within the facilities.

4. To prevent unintended release of the organism by experimenters working with the organism:

4.1 The applicant shall comply with the requirements contained in the standards listed in controls 1.2 and 1.4 relating to the prevention of unintended release of genetically modified cattle, cells or embryos by experimenters working with the organisms.

4.2 The maximum number of cattle¹¹ housed in the outdoor containment facility shall not exceed the capacity of the containment facility as approved under control 1.3 and any requirements of the Ruakura Animal Ethics Committee.

¹³ Including all genetically modified and non-genetically modified cattle

4.3 All conventional cattle within the facility shall be double tagged (ie by two different ear tags). All genetically modified cattle shall be individually identified by an ear tag for visible identification and also implanted with a subcutaneous electronic microchip for individual electronic identification. In the event that subcutaneous microchips cannot be implanted until cattle reach a certain age, cattle shall have two different types of ear tags in place at all times to allow for immediate identification.

5. To control the effects of any accidental release or escape of an organism:

5.1 If a breach of containment occurs, the facility operator must ensure that the MAF Inspector responsible for supervision of the facility has received notification of the breach within 24 hours.

5.2 In case of unintended or accidental release or escape of genetically modified cattle, the applicant shall recover the escaped cattle and return them to the outdoor containment facility. If there has been any possibility of mating occurring, steps shall be taken to abort any possible resulting pregnancies, and the foetuses and mothers disposed of in accordance with control 1.9.

6. Inspection and monitoring requirements for containment facilities:

6.1 The Authority or its authorised agent or properly authorised enforcement officers, may inspect the containment facilities at any reasonable time.

6.2 The Manager responsible for maintaining genetically modified cattle in the outdoor containment facility, shall report immediately to ERMA New Zealand and the facility Supervisor (at least within 24 hours) on any event that is likely to be in the public interest, eg unexpected mortality in genetically modified cattle, a breach in security, or presence of TSE.

6.3 The applicant shall maintain a register with records of identity and fate of all cattle in the development.

6.4 Micro-organisms shall be tested for the presence of the introduced genetic modifications at the disposal sites. If HGT is detected, genetic modification and disposal of cattle shall be immediately halted and the Chief Executive of ERMA New Zealand informed. A remediation plan to manage the impact of the HGT event shall be developed in consultation with the Chief Executive of ERMA New Zealand.

6.5 The applicant shall provide a comprehensive report to ERMA New Zealand in each December on the progress in the development of genetically modified cattle, including an inventory, with particular reference to the topics listed in section 4.13 of the MAF Biosecurity Authority Standard 154.03.06¹⁰. This report shall also include:

- a) information on animal welfare issues including any reports to the RAEC in relation to this development;
- b) information on progress in relation to investigations of HGT; and

- c) a summary of any unforeseen positive or negative effects to the environment, public health, Māori culture, or the economy or society resulting from the research.
- 6.6 The applicant shall provide a final report to ERMA New Zealand, within six months of the end of the project or the end of the approval period (whichever is sooner). The report shall include:
- a) the results of the monitoring under control 6.4;
 - b) any reports of the RAEC in relation to this development;
 - c) whether there have been any unforeseen positive or negative effects to the environment, public health, Māori culture and the economy or society resulting from the research; and
 - d) whether the controls imposed have been practicable and/or effective in their control purpose.

7. Qualifications required of the persons responsible for implementing those controls:

- 7.1 The applicant shall inform all personnel involved in the production and development of genetically modified cattle of the controls imposed in this decision.
- 7.2 The applicant shall notify the supervisor and ERMA New Zealand if there are any changes in ownership of the property housing the containment facilities in which the organisms under this approval are maintained.

8. To ensure that, after the end of the development, heritable material is removed or destroyed:

- 8.1 In the event that operations involving genetically modified cattle cease, and in any case at the end of the approval period:
- a) all genetically modified cattle, surrogate mothers and recipient cows (as defined in control 1.8) shall be destroyed and disposed of in accordance with control 1.9, unless a further HSNO approval has been obtained; and
 - b) all heritable material (including semen and ova) derived from genetically modified cattle shall be removed into secure containment or destroyed on-site in accordance with the requirements in control 1.2.

9. Additional controls imposed by the Committee:

- 9.1 Sequences from the vector backbone shall not be integrated into the bovine genome.
- 9.2 Before artificial insemination or transfer of embryos or nuclear transplantation, all genetic material in the insert vector shall be characterised (that is, the DNA has been sequenced and there is an understanding of the potential gene products and their function) and the details of the genetic material (including source) and

each construct shall be provided to the Chief Executive of ERMA New Zealand.

- 9.3 Breeding shall be limited to the minimum necessary to complete development. In the case of genetically modified cattle developed to study gene function and gene performance, no breeding of animals is authorised, except where necessary to develop homozygous transgenic cattle. In the case of cattle modified to express therapeutic proteins in milk, genetically modified cattle may be bred, where necessary a) to produce one subsequent generation to investigate stability of inheritance or b) to produce two subsequent generations to develop homozygous transgenic cattle. Prior to any breeding of transgenic cattle, the Chief Executive of ERMA New Zealand shall be advised of the intention to breed and the reasons for the breeding.
- 9.4 The applicant shall facilitate the continued cooperation of the existing monitoring groups with Ngāti Wairere (Ahi Ka and Te Kotuku Whenua), to enable Ngāti Wairere representatives to monitor the implementation and progress of the development, and to develop culturally appropriate mechanisms and protocols, as required. AgResearch shall advise the Chief Executive of ERMA New Zealand if either of these groups are disbanded or cease to operate satisfactorily.
- 9.5 The production and maintenance of genetically modified cattle in the outdoor containment facility shall be in accordance with the relevant sections and regulations of the Animal Welfare Act 1999, the Animal Welfare Advisory Committee (AWAC) and National Animal Ethics Advisory Committee (NAEAC) guidelines administered by MAF, and the Ruakura Animal Ethics Committee (RAEC). The husbandry of the animals shall be overseen by an experienced large animal veterinarian, who shall have the power to determine a humane endpoint for any part of the experimental procedures in steps (e) and (f) (ie generating live offspring from cultured embryos and checking gene stability through reproduction).
- 9.6 The approval is for a period of ten years from the date of the signed decision.

Annex 3. Qualitative scales for describing effects

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 or very low	Not impossible, but only occurring in exceptional circumstances
Unlikely or low	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	Negligible	Very low to Negligible	Low	Medium	High
Unlikely	Very low to Negligible	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