Environmental Protection Authority
Te Mana Rauhī Taiao

New Zealand Government

Staff Advice Memorandum – Request for grounds for reassessment of ERMA200223

13 August 2021

Advice to the Decision-making Committee on APP204212: - request for grounds for reassessment of the AgResearch development in containment (including outdoor development) of genetically modified cows, goats and sheep

Application code:	APP204212
Application type and sub-type:	Section 62 determination of grounds for reassessment based on further information
Applicant:	GE Free New Zealand In Food and Environment Inc
Date further information received:	12 March 2021
Purpose of the Application:	To request a determination of grounds for reassessment of EPA approval ERMA200223

Background

1. This Staff Memorandum provides a summary and assessment of the application from GE Free New Zealand in Food and Environment Inc (GE Free NZ) regarding approval ERMA200223, granted to AgResearch on 15 April 2010.

2. The approval's stated purpose is: *"To develop in containment genetically modified goats, sheep and cows to produce human therapeutic proteins, or with altered levels of endogenous proteins for the study of gene function, milk composition and disease resistance."*

3. The approval allows the development in indoor containment of transgenic cattle, goats and sheep, as well as mice, human cell lines, and the bacterial species *Escherichia coli* (a commonly used laboratory organism used in the production of recombinant DNA). The approval further allows that aspects of the development work may be carried out with genetically modified animals held in outdoor containment. The research programme has been conducted for the last ten years on AgResearch's Ruakura campus, with ongoing animal ethics committee oversight.

4. The Environmental Risk Management Authority (ERMA) approval superseded earlier approvals to AgResearch for the outdoor development of genetically modified cattle dating back an additional ten years.

Legislative criteria for the determination of grounds for reassessment

5. Section 62(2) of the Hazardous Substances and New Organisms Act ("the HSNO Act") states:

> *Where any request has been made under subsection (1), the Authority may decide that grounds exist to reassess that substance or organism after taking into account that—*
>
> *(a) significant new information relating to the effects of the substance or the organism has become available; or*
>
> *(aa) a change in any controls under the Health and Safety at Work Act 2015; or*
>
> *(b) another substance with similar or improved beneficial effects and reduced adverse effects has become available; or*
>
> *(c) information showing a significant change of use, or a significant change in the quantity manufactured, imported, or developed has become available*.

6. Thus, while the Environmental Protection Authority (EPA) has a discretion to decide whether there are grounds for reassessment, it is essential that at least one of the factors in section 62(2)(a) to (c) exist, and it is mandatory to take into account that factor when deciding whether there are grounds for reassessment.

7. In this context, we consider that chronic non-compliance with the controls of the approval could constitute "a significant change of use" of the organisms developed under the ERMA200223 approval.

Assessment of this application (APP204212)

8. We note that the application submitted by GE Free NZ was submitted on its own letterhead, rather than an application form. Unlike applications for approval to import or release hazardous substances or new organisms, the request for a determination of grounds for reassessment (hereafter referred to as "request for Grounds") is not required to follow an approved form (sections 28(2) and 34(2) compared with s 62(1)). Therefore, we consider the application from GE Free NZ to be an appropriate request for Grounds.

9. As a result of not using an EPA application form, the application is organised such that there are some redundancies regarding topics of discussion between sections. We have undertaken this assessment according to the organisation of the application, and we have cross-referenced issues mentioned in the various sections of the application to assist in the committee's consideration of the application. Thus, the headings and sub-headings in this section mirror those of the application.

10. In addition, we add a final section not found in the document under the heading "*Animal welfare issues mentioned throughout the application".*

11. EPA Staff assessment of the claims of the application are provided as bullet points in response to the summary information in each paragraph.

Background information on ERMA200223 (p 2-5)

12. In this section, the applicant states that the ERMA200223 approval was granted to supersede AgResearch's previous approvals GMF98009 (field trial of transgenic cattle) and GMD02028 (development in containment of transgenic cattle). The applicant states that the reason that AgResearch submitted a new application to ERMA (now EPA), is because these two approvals were nearing their expiry dates.

    - The transfer of all cattle developed under approvals GMF98009 (ERMA 1999; ERMA 2001) and GMD02028 (ERMA 2002) to ERMA200223 (ERMA 2010) is noted in AgResearch's first "Annual" Report, submitted on 30 June 2010, approximately 8 weeks after the approval was granted (AgResearch 2010). Thus, despite both GMF98009 and GMD02028 remaining active approvals in 2010, neither was being used after ERMA200223 was granted.
    - Per Control 9.6 of the GMD02028 approval, the approval expired on 30 September 2012 (ERMA 2002). With the death of the last animal developed under it, the GMF98009 approval expired in June of 2019, per control 1.17 of the approval. This was noted in AgResearch's final report, filed on 30 June 2019, in compliance with Control 6.4 of GMF98009 (AgResearch 2019a).

13. Citing a 2008 pre-application letter from James Suttie of AgResearch to Susie Lees (not provided with the application), the applicant states that the purpose of the production of monoclonal antibodies in the milk of transgenic cows is for their potential use in the so-called "biosimilars" market.

    - We note "biosimilar" is defined as "a substance of biological origin (such as a globulin, vaccine, or hormone) that is used in the prevention or treatment of disease and is highly similar to a previously-approved proprietary biologic" (Merriam-Webster.com Medical Dictionary 2021). The definition further notes that "Biosimilars must be found to have no clinically significant difference to the previously-approved biologic and only vary in their clinically inactive components." Therefore, in the development of biosimilars, it is clearly understood that a similar substance is already available on the market, and the purpose of the development of biosimilars is to provide, for example, a competing drug, often at a lower cost than the existing drug.

14. The applicants then state (pp 2-3) that AgResearch's annual reports describe deformities, congenital problems and illnesses of the genetically modified animals. They go on to state that the surrogate cows have high abortion rates, and are themselves in poor health. They state that the genetically modified animals have a high rate of sterility, and they claim "only AI of previously created embryos can be brought to term." They finally state that there is no monitoring of the animals by the Ruakura Animal Ethics Committee (RAEC).

    - We note that somatic cell cloning of animals often results in poor survival rates of embryos and newborn animals. This issue is common to all laboratories around the world that undertake such research (Batchelder et al. 2017 and references therein; Matoba & Zhang 2018). Additionally, we note that ERMA200223 has been under the constant monitoring of the RAEC since its inception. Quarterly reports from the RAEC pertaining to the animals developed under ERMA200223 have been provided to EPA by AgResearch, over and above

the reporting requirements imposed by EPA in the approval in 2010. These points are discussed in greater detail in paragraphs 24 and 31.

Development Outdoors in Containment

15. The applicant states on p. 3 of its submission that the AgResearch approval has become an unapproved field test from its approval as an outdoor development approval. The applicant stated that the EPA referred to the AgResearch approval as a field test in an OIA response to the McGuinness Institute (p 3). The applicant discusses the difference between development outdoors, and a control from the now-expired approval GMF98009 stating that two generations of breeding was the limit for "proof of concept".

    - We note that the applicant is correct in its statement that the EPA referred to ERMA200223 as a "field test" in the aforementioned OIA response to the McGuinness Institute. However, this statement is simply an error on the part of EPA in its response letter, and the approval remains as an outdoor development approval, and not a field test of transgenic animals. Therefore, there is no breach of any controls, as the work continues as part of the approved outdoor development aspects of the approval.
    - In the context of section 62 of the HSNO Act, there is no "significant change of use" (per s62(2)(c)) of the genetically modified animals, and therefore we consider that s62(2)(c) has not been met in this application. We further consider that it is open to the committee to determine that **grounds do not exist** to reassess ERMA200223 on this basis.

Development Controls on Breeding

16. On pp 4-5, the applicant states that AgResearch is in breach of a number of controls of the GMD02028 approval, specifically regarding controls:

    a. on the number of generations of animal breeding that may be undertaken as proof of concept
    b. on the reporting of gene construct sequences and the characterisation of the genetic material therein to the Chief Executive of EPA prior to their first use
    c. on the notification to the Chief Executive of EPA of the intention to breed the genetically modified cattle.

    The applicant again states that ERMA200223 is now being treated as a field test, and not a development in outdoor containment approval. The applicant additionally states that AgResearch's purported failure to comply with these controls should be "considered as a major breach of controls".

    - We earlier noted (EPA response in paragraph 12 of this memo) that development of the animals under both GMF98009 and GMD02028 was being managed under ERMA200223 and its concomitant controls. Therefore, the controls under both these earlier approvals no longer applied to any of the genetically modified cattle developed/tested thereunder after the ERMA200223 approval was granted. Also as noted in paragraph 12, both of these earlier approvals have since expired, and the ERMA200223 approval supersedes both.
    - The controls in GMD02028 cited by the applicant are not found in ERMA200223, so there is no breach of the controls cited in the application.
    - Again, per s62(2)(c), there is no significant change in use (that is, an unauthorised use in breach of a control), and therefore we consider that it is open to the committee to determine that **grounds do not exist** to reassess ERMA200223 on this basis.

AgResearch 10-Year Report Concerns (pp 5-6)

17. The applicant states that the ERMA Decision-Making Committee considered that granting the ERMA200223 approval would provide benefits in the form of increased scientific knowledge and skills enhancement. The applicant further states that AgResearch does not provide details regarding the skills gained from the research. The applicant states that the facility is almost non-functional and there are ongoing staff shortages that lead to major and minor non-compliances. The applicant cited several statements from Ministry of Primary Industries (MPI) audit and verification reports in support of its claims.

    - We note that the MPI Audit reports cited by the applicant cover the Plant Facility, the small and large animal containment facilities, as well as PC1 laboratories. We examined the statements from the MPI reports quoted by the applicant, and we address them in turn below.
    - The applicant cites two statements from the MPI 01/03/2017 audit report, found in the AgResearch 2017 Annual Report (AgResearch 2017) regarding the facility's operating manager wishing to be replaced in the role and that AgResearch staff were facing increasing workloads and uncertainty in the workplace. We note that the Facility's operating manager was not the same person as the large animal facility manager, who continues in that role to the present day. No compliance issues under ERMA200223 were identified in this audit.
    - The applicant cites a statement from the MPI 24/08/2017 audit report found in the AgResearch 2018 Annual Report (AgResearch 2018) again noting that no replacement had been found for the facility's Operating Manager. Again, we note that this person is not the same person as the large animal facility manager. Again, the inspection noted no issues identified during the course of the audit.
    - The applicant cites a similar statement in the MPI 21/02/2018 audit report (AgResearch 2018). Again, the inspection noted no issues identified during the course of the audit.
    - The applicant cites a statement in the "Quality Assurance" section of the MPI 14/02/2019 Verification Report (AgResearch 2019b) that AgResearch was lacking in leadership for the management of the containment facility. We note that the report also states that "*Substantial compliance was observed with the controls of ERMA200223".*
    - Also from the 14/02/2019 Verification report, the applicant cites a statement that the operator is "*not in substantial compliance with regulatory requirements…".* This statement is found in the "Definitions" section of the Verification report, so it appears to be describing in part criteria for an "Unacceptable" rating to be given by an Inspector during an audit.
    - The applicant cites a major non-compliance noted by MPI in its 02/03/2020 Verification Report (AgResearch 2020a), in which a Facility tenant gained unauthorised access to the small animal containment facility. The Inspector noted that the incident was beyond the Facility Manager's control and "*potential containment risks were already well managed"*. We note that the unauthorised access did not pertain to the large animal facility managed under ERMA200223, and that compliance with the approval was verified by the inspector and found to be "Acceptable".
    - We note that the operating facility manager was replaced in 2019 (see paragraph 24), and more recent reports do not discuss issues regarding staff workload and uncertainty. We further note that during this time of stress and uncertainty, AgResearch was found to be in full compliance with the relevant controls of ERMA200223, as well as the relevant containment standards.
    - The facility is currently considered to be fully compliant with all requirements for ERMA200223 and the relevant containment standards. Therefore we consider that it is open

to the committee to determine that **grounds do not exist** to reassess ERMA200223 on this basis.

Alternative similar substances are on the market (pp 6-7)

Human Follicle Stimulating Hormone (hFSH)

18. On page 6 of its submission, the applicant discusses compliance and ethics issues brought up by MPI regarding the expression of human follicle-stimulating hormone in cattle, which resulted in the unexpected deaths of two animals. It additionally discusses correspondence between Prof Sir Peter Gluckman and Hon Wayne Mapp (then Minister of Research, Science and Technology) regarding this work, regarding investigation of the matter by the Office of the Prime Minister's Science Advisory Committee (Watson and Beedle 2010) and discussion of similar substances already on the market.

    - We note that the issues discussed in this section were under AgResearch's earlier, now expired, GMD02028 approval. This work was not carried on under ERMA200223. Examination of the report from the Office of the Prime Minister's Science Advisory Committee cited in the current application shows that the unexpected cattle deaths that resulted from this experiment were investigated at the time. Therefore, there is no new information for the committee to consider regarding this point.
    - We consider that neither of the criteria in s62(2)(a) (significant new information), nor s62(2)(b) (consideration of similar substances) have been met. Therefore, we consider that it is open to the committee to determine that **grounds do not exist** to reassess ERMA200223 on this basis.

ERBITUX (Cetuximab)

19. On page 7 of its application, the applicant discusses the monoclonal antibody cetuximab, known commercially as Erbitux. Expression of cetuximab in the milk of goats is currently being studied by AgResearch under the ERMA200223 approval, as described in its 10-year report (AgResearch 2020b). The applicant states that the EPA failed to consider that there are already similar substances on the market in granting its approval.

    - We note that the approval is for transgenic animals and not for any substance, but regardless, we further note that in section 62(2)(b) of the HSNO Act, a criterion for finding grounds for reassessment is that another substance (in this case monoclonal antibodies) with similar or improved beneficial effects and reduced adverse effects has become available. However, as discussed in paragraph 13, the mAbs referred to by the applicant were already on the market at the time the ERMA200223 approval was granted, and the purpose of the current work is to produce a biosimilar drug that may be purified from milk, rather than from the more expensive process of tissue-cultured hybridoma cells.
    - Therefore, we consider that another substance has not become available. It is open to the committee to determine that there is no information relevant to the approval that the committee need consider as grounds for reassessment, and that **grounds do not exist** to reassess ERMA200223 on this basis.

20. The applicant discusses the expired approval GMD09016 for genetically modified goats that express genes encoding "proteins with potential biopharmaceutical applications (ERMA 2009).

The applicant further states that the goats developed under this approval should all have been euthanised no later than 2012, citing paragraph 3.4 of the (GMD09016) Decision document.

- We note that AgResearch applied for approval GMD090016, and also proposed a duration for the approval of a maximum of two years "*to allow AgResearch to meet contractual obligations until a separate publically notified application (ERMA200223, …) has been through the approval process".* Therefore, ERMA imposed additional controls:
  - 2.3: to limit the duration of new animal developments under the approval to 1.5 years
  - 2.4: to kill and dispose of all animals developed under the approval after two years, unless they are covered by another approval
  - 2.5: to limit the duration of the approval to two years.
- We note that ERMA200223 was decided and approved on 15 April 2010, four and a half months after GMD09016 was approved. Therefore, any goats developed under GMD09016 and subsequently held in containment under ERMA200223 were held in compliance with GMD09016 control 2.4. Therefore, there was no breach of any control in either GMD09016 or ERMA200223, and we consider that it would be open to the committee to determine that **grounds do not exist** to reassess ERMA200223 on this basis.

21. On p 8, the applicant states that section 40 of the HSNO Act requires that applicants for genetic modification development approvals submit information to the EPA Chief Executive on experimental procedures, biological material, expression of foreign nuclear [sic] acid material, and the effects of the organism on the environment. The applicant states that AgResearch has committed a major non-compliance, apparently implying that they submitted no information to the Chief Executive.
    - We note that while section 40 requires the submission of information to EPA stated by GE Free NZ (as well as the identification of the host organism), there is no requirement in the HSNO Act to submit this information to the Chief Executive. Instead, s 40 requires that any person intending to import, develop, or field test any new organism in containment must apply to the EPA before doing so, and that the application shall be in an EPA-approved form.
    - AgResearch complied with these requirements in the application form it submitted for ERMA200223 (AgResearch 2009). That information was considered, deemed to meet the information requirements in section 40, and an EPA Decision-Making Committee decided to issue the ERMA200223 approval with controls in 2010 in accordance with section 45 of the HSNO Act. Therefore, we consider that it would be open to the committee to determine that **grounds do not exist** to reassess ERMA200223 on this basis.

22. Similarly, the applicant also states on p. 8 that AgResearch did not submit any genetic information via application(s) under section 67A of the HSNO Act on a number of developments it is undertaking.
    - We note that the scope of ERMA200223 was intentionally broad to allow a wide range of activities under the approval. The stated purpose of the approval[1] is: "To develop in containment genetically modified goats, sheep and cows to produce human therapeutic proteins, or with altered levels of endogenous proteins for the study of gene function, milk composition and disease resistance."

[1]Page 1 of the ERMA200223 decision document

- Similarly, the description of approved genetic modifications in Appendix 1 of the ERMA200223 decision is for "coding, non-coding and/or regulatory regions, antisense sequences or other RNA interference-inducing sequences of eukaryotic, viral and/or prokaryotic genetic material donors associated with human therapeutics, milk protein composition, gene function or disease resistance."
- The approval allows for a wide range of donor genetic material to be used in the work, including insect, human (excluding sequences derived from Māori), mouse, cow, goat, sheep, deer and more than 100 other mammalian species, fish, African clawed frog, plants, fungi, bacteria, protozoa, and viruses.
- We note further that no commercial rationale is required for any research activity to be undertaken under ERMA200223. However, AgResearch describes its rationale for its experimental work using these genes in its 10-year report, submitted in compliance with Control 12 of the approval (AgResearch 2020b). Five of the 10 projects described by AgResearch in its 10-year report involve alterations of milk composition, and the other five projects involved gene function studies involved in germline development, kidney development, decreased mortality in somatic cell nuclear transplantation cloning, sex selection in animal breeding, and adaptation of animals to hotter climates.
- We therefore consider that the activities undertaken by the applicants and described above are all within the scope of the ERMA200223 approval. Thus they did not require amendments under section 67A of the HSNO Act to be undertaken. Consequently, we consider that it would be open to the committee to determine that **grounds do not exist** to reassess ERMA200223 on this basis.

Animal Welfare Concerns

23. The applicant states on p 8 that the work under ERMA200223 is being undertaken in the absence of any oversight by the RAEC. The applicants cited an OIA Response letter to GE Free NZ that stated that the RAEC reports are provided directly to the EPA, and not the National Animal Ethics Advisory Committee (NAEAC), nor the National Animal Welfare Advisory Committee (NAWAC).

    - We note that both the NAEAC and the NAWAC are committees established under the Animal Welfare Act 1999, and are administered by MPI. The RAEC was itself established under the Animal Welfare Act (ERMA20223 decision, paragraph 1.1.6). Furthermore, every Annual Report provided to EPA by AgResearch contains the quarterly RAEC reports, so the claim by the applicants that there is no ethics committee oversight is incorrect.
    - We further note that the provision of these reports and the MPI audit reports go above and beyond the ERMA200223 controls, which specify no requirement for the provision of such reports to the EPA. Neither is reporting to the NAEAC nor the NAWAC a requirement of the approval. The fact that AgResearch provides these reports to the EPA in excess to its reporting requirements under the approval speak to its efforts to be as transparent as possible in its reporting on its activities under the ERMA200223 approval. Therefore, we consider that it would be open to the committee to determine that **grounds do not exist** to reassess ERMA200223 on this basis.

Non Compliance of controls set down in the decision of ERMA200223 (pp 9-13)

Control 4.

24. The applicant cites a number of AgResearch facility non-compliances in their application, and state that the AgResearch Facility suffers from chronic non-compliance issues in breach of Control 4 of the approval. The applicant states that the non-compliances constitute "major non-conformity" and a "system failure" calling into question AgResearch's credibility in the operation of the facility.
    - We again note that the MPI Audit reports cited by the applicant cover the Plant Facility the small and large animal containment facilities, as well as PC1 laboratories. Despite claims by the applicants regarding chronic non-compliance at the facility, we note that the non-compliances are generally minor, and pertain to laboratories and facilities other than the large animal facility.
    - The 06/08/2018 audit non-compliance was noted as "minor" (AgResearch 2018, p 24), and the overall inspection findings were summarised as "Overall good operator control was demonstrated. Sampled records were up to date for animal treatments, transfer approvals, animal counts and training." (AgResearch 2018, p 23).
    - The non-compliance in the 14/02/2019 verification report was part of an audit of three facilities. The particular non-compliance under consideration was in the PC1-level South Wing 101 rooms and the Dairy Science Room 1, and not the PC2-level large animal containment facility (AgResearch 2019b).
    - The non-compliances the 28/08/2019 audit report cited by the applicant were in the context of the Inspector's summary statement "*Good compliance was noted for animal containment (small and large).*", as well as the first audit with a new facility manager (AgResearch 2020a). The first non-compliance, to do with transfers, pertained to a tenant of the AgResearch Ruakura facility, and not the large animal facility (AgResearch 2020a, p 24). The second non-compliance pertained to the transfer of genetically modified organisms without a transfer approval from MPI. However, the relevant EPA approval cited by the Inspector under which the GMO was being held was APP201858 (APP201857 is for non-GMO new organisms), and not ERMA200223 (AgResearch 2020a, p 25). The third non-compliance was rated as "Minor", and pertained to laboratory facilities, and not the large animal containment facility. The fourth non-compliance cited by the applicant again pertained to laboratories and was rated as "Minor".
    - The non-compliances in the 02/03/2020 audit report cited by the applicant pertained to "*hygiene not maintained to an acceptable level*", which again was in laboratories, and not in the large animal containment facility. As with two of the non-compliances in the 28/08/19 report, the non-compliance was rated as "Minor". The second non-compliance in this report cited by the applicant pertained to plant research laboratories, and not any animal facilities. Once again, the non-compliance was rated as "Minor".
    - We wish to stress that compliance with the controls of any EPA approval and the relevant containment standards is an important issue, but various minor non-compliances found during the audits in question are not atypical in the operation of a large containment facility such as the Ruakura site, and all non-compliances were resolved to the satisfaction of the MPI Inspector within the assigned time frames.
    - The two non-compliances pertaining to unauthorised transfers did not involve organisms developed under ERMA200223, and are also outside the controls of any EPA approval for

containment within a laboratory. We further note that they pertained to failures to obtain proper authorisation from MPI, rather than any breach of containment. The AgResearch containment facility was given an "Acceptable" rating in its February 2021 audit, which is the most recent information on compliance held by EPA. Therefore, we consider that it would be open to the committee to determine that **grounds do not exist** to reassess ERMA200223 on this basis.

Control 5.

25. The applicant states that AgResearch breached Control 5 requiring the use of animals to graze in the space between the facility's double-perimeter fences to be of a different species than the animals held within the paddock. The applicant cites the AgResearch 2020 Annual Report stating that five non-transgenic steers were moved out of the facility during the reporting period.

    - We note that Control 10 of the approval allows conventional (that is, not genetically modified) animals to be moved out of the facility, provided that that the animals have not been used as surrogates, and they are tested twice to ensure that they are not pregnant. Given that the animals in question were steers (that is, neutered bulls) and therefore could not possibly become pregnant, both criteria were readily met. Therefore, we consider that it would be open to the committee to determine that **grounds do not exist** to reassess ERMA200223 on this basis.

Control 8

26. The applicant states that embryo transfers from the laboratory to recipient animals after treatment with replication-defective viral vectors "is cause for serious concern for the spread of GM material outside of containment" in light of the non-compliances it listed regarding Control 4.

    - We note that the applicant has not stated that Control 8 has actually been breached. As regards the claims of "continuing non-compliance issues (2017-2020)", we established that the non-compliances by and large were minor and not in relation to ERMA200223 (see discussion under heading "Control 4"). Therefore, we consider that it would be open to the committee to determine that **grounds do not exist** to reassess ERMA200223 on this basis.

Control 11

27. The applicant claims that AgResearch consistently (in the last four years) submits its reports to EPA late, and that the 2019 report is missing from the EPA website. The applicant also states that the 10-year report was not published on the EPA website until November 2020.

    - We note that AgResearch submits a draft report to EPA annually on 30 June, as required by Control 11 of the approval. The report is in draft form to allow EPA to examine it for any potential errors, as well as to allow time for the 2nd quarter RAEC report (provided for public examination in good faith over and above the requirements of Control 11) to be completed and added to the Annual Report.
    - We further point out that there is no set time by which EPA must publish the annual reports on its website.
    - The statement that the 2019 report had not been published on the EPA website is incorrect. We wish to point out that the EPA publishes the ERMA200223 reports at two different locations on its website. The first is under the ERMA200223 approval number (https://www.epa.govt.nz/database-search/hsno-application-register/view/ERMA200223), and

the second is on our "Monitoring and Reporting" page(s) (https://www.epa.govt.nz/resources-and-publications/monitoring-and-reporting?tag=70&start=10). In examining this statement, we found that the 2019 Annual report was published on the Monitoring and Reporting page, and not on the ERMA200223 page. We have now corrected this oversight.

- The statement regarding the 10-year report pertains to the wording of Control 12 of ERMA200223, which states that the report is intended to assist the EPA Chief Executive in deciding whether or not to request a determination of grounds for reassessment.

  The report was submitted on time by AgResearch, examined by EPA, and minor corrections were made by AgResearch at EPA's request. EPA Staff then prepared an assessment and recommendation for the Chief Executive to assist in deciding whether to request an application for Grounds (Environmental Protection Authority 2021).

  As the 10-year report and the assessment discussed commercially sensitive information, redactions of both were required, which necessitated consultation with AgResearch and their commercial client. Once these processes were complete, the AgResearch (2020b) report was published.

  Again, we note that Control 12 had no set time by which EPA was required to publish the report. Therefore, we consider that it would be open to the committee to determine that **grounds do not exist** to reassess ERMA200223 on this basis.

Control 12.

28. The applicant's claims regarding Control 12 on the 10-year report again state that the development approval has become a field test, and that AgResearch is in breach of controls that were imposed on now-expired approvals.

    - These points were addressed in paragraph 15 of this document.

Control 13.

29. The applicant states that AgResearch is not engaging with Māori because the Iwi Liaison Committee required under Control 13 has not met in many years.

    - Based on the information we reviewed in the AgResearch Annual Reports and its 10-year report, the iwi liaison committee has not met because the Ngati Wairere hapū has yet to designate its committee members. Despite this difficulty, AgResearch described many activities in its 10-year report that are aimed at informing and engaging iwi and Māori industry groups, with an intention to form a standing iwi committee for consultation and constructive engagement. Therefore, we consider that it would be open to the committee to determine that **grounds do not exist** to reassess ERMA200223 on this basis.

Animal welfare issues mentioned throughout the application

30. The applicant discusses congenital birth defects and health issues in calves and kids resulting from the work on somatic cell cloning throughout the document. The applicant also cites poor health of the transgenic animals throughout its application.

    - As noted in the Summary and Analysis File Note to the EPA Chief Executive of AgResearch's ERMA200223 10-year report (Environmental Protection Authority 2021), AgResearch reported 1-year survival rates of transgenic animals ranging from 9% to 57%. Such a range of

survival rates is not inconsistent with animal cloning work carried out in other laboratories around the world (Batchelder et al. 2017 and references therein; Matoba & Zhang 2018). Therefore, AgResearch's findings are consistent with worldwide best practice laboratories. Additionally, AgResearch has undertaken work to improve survival rates of transgenic animals with its research project entitled "Improved bovine cell reprograming by epigenetic modulators", as discussed in the 10-year report (AgResearch 2020b).

- Of the animals developed under the approval that survive longer than a year, animal health is good, any animal infirmities are treated promptly, and reported to the Ruakura Animal Ethics Committee (RAEC). Animals with health problems that cannot be successfully treated are euthanised, also as noted in the on-farm and RAEC reports provided in full with each of AgResearch's annual reports (see the application register at https://www.epa.govt.nz/database-search/hsno-application-register/view/ERMA200223).

Conclusion

31. We have carefully examined and considered the information provided by the applicant in its request for a determination of grounds for reassessment of ERMA200223. In addition, we thoroughly examined the information cited by the applicant in the AgResearch Annual Reports as well as its 10-year report. This examination and consideration leads us to conclude that:

    - AgResearch continues to operate under a development in outdoor containment approval, and ERMA200223 has not become a field test.

    - Statements pertaining to breaches of controls on breeding of animals under a development approval are not based on controls in ERMA200223, but rather in superseded (and now expired) earlier approvals.

    - The applicant's claims that the large animal facility is moribund and poorly managed lack foundation, as AgResearch was found to be fully compliant with ERMA200223 during a period of managerial uncertainty. The most recent MPI reports that state that the facility is compliant and well managed.

    - The applicant's claims about the research not needing to be undertaken due to similar substances being on the market either pertain to work carried out under earlier approvals that is not being conducted under ERMA200223, or to substances that may be used in the biosimilars market. Additionally, we note that the approval is for transgenic animals and not for any substance.

    - Any work on development of goats undertaken in approval GMD09016 that was transferred to ERMA200223 was done legally in accordance with controls in GMD09016.

    - Statements pertaining to breaches of controls regarding the provision of information on genetic sequences and constructs to the Chief Executive of EPA are either based on controls in superseded and expired earlier approvals, or a misinterpretation of section 40 of the HSNO Act.

    - The research under the approval is progressing as intended under full oversight and supervision of the RAEC for the last 10 years. Animal genetic modification work leads to low survival rates of animals, but this is a consistent finding with laboratories engaged with animal

genetic modification and cloning around the world. These were issues that were well understood when ERMA200223 was approved. Animals that survive are well maintained, and cared for to a high standard.

- AgResearch is fully compliant with the controls imposed under the approval, including those specifically discussed by the applicant.

- AgResearch is acting in good faith to establish a partnership with mana whenua hapū and iwi, which is ongoing. In the meantime, AgResearch has undertaken a wide range of activities to engage with and inform Māori of its research and its implications for Māori, consistent with the intent of section 6(d) of the HSNO Act.

32. Based on the above conclusions, we consider that:
    - no new information relating to the effects of the organisms has become available, therefore significant new information under s 62(2)(a) cannot have not become available
    - information on alternate substances becoming available since the approval was granted has not been provided by the applicant, and as such another substance with similar or improved benefits and reduced adverse effects under s 62(2)(b) has not become available
    - the controls of the approval have been met such that a significant change of use, under s 62(2)(c), has not occurred.
33. In addition, no information on the quantity of transgenic animals developed has been provided by the applicant such that we consider that there has not been a significant change in the quantity developed as required for s 62(2)(c). The 2017 changes to the Health and Safety at Work Act controls relate to hazardous substances and are therefore not consider relevant to this application.

Recommendation

Based on the conclusions above, WE recommend that there is **no significant new information** relating to the effects of the organisms, their use or the other factors in section 62(2) of the HSNO Act that justifies a determination of grounds for reassessment of ERMA200223.

‘signed’

Principal Scientist, New Organisms

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