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Facilitation of an international approach for data sharing and acquisition in relation to genetically-engineered animals

Gilly Griffin and Clément Gauthier

Canadian Council on Animal Care

Corresponding author: Gilly Griffin
Canadian Council on Animal Care
1510-130 Albert Street, Ottawa, ON, Canada K1P 5G4
Phone: (1)-613-238-4031 ex. 25, ggriffin@ccac.ca

Abstract
In 1997, the Canadian Council on Animal Care (CCAC) published CCAC *guidelines on*: *transgenic animals.* Because this was recognized to be a rapidly evolving field, a commitment was made to revise the guidelines within a few years. CCAC is now working on draft *guidelines on: genetically-engineered animals*. This paper outlines some of the changes that are being proposed in the new guidelines; in particular, the need for detailed information on the characteristics of the animals, in order to improve the well-being of the animals and to meet the scientific goals of the studies for which they have been created.

Internationally, several groups are currently working on guidelines in this area. This paper also considers recommendations for information collection and sharing of information that are being proposed by other jurisdictions, including the mouse passport, with a view to facilitating international agreement on data acquisition and sharing of characteristics of genetically-engineered animals. The passport would also be a useful tool for national surveillance bodies to undertake the concerted efforts needed to address current inefficiencies in the creation and care of genetically engineered-animals, if an escalation in number and unnecessary suffering is to be avoided.

Keywords: Canadian Council on Animal Care, genetically-engineered animals, international harmonization, data sharing, 3Rs

Introduction

The escalation in the generation and use of genetically-engineered animal lines in the past twenty years has raised concerns for national authorities responsible for overseeing the ethical use of animals in science. National systems of oversight are based on the principles of the Three Rs, replacement, reduction and refinement. Implementation of these principles in respect to genetically-engineered animals is particularly challenging due to the considerable numbers of animals involved in the generation of a new animal line, and in the potential for pain and distress due to the uncertainty of the effects of the modification on the phenotype of the animal.

Various national authorities have prepared guidelines documents in order to implement the principles of the Three Rs more effectively in relation to the generation of genetically-engineered animals. The Canadian Council on Animal Care (CCAC) first published *CCAC guidelines on: transgenic animals* in 1997 and is currently working on *CCAC guidelines on: genetically engineered animals*. In preparing this document, the CCAC examined guidelines that were either published or under development by other national authorities, as a means of international harmonization. Harmonization of guidelines relating to genetically engineered animals is important because of the considerable extent of the international transfer of these animals between laboratories.

This paper examines the recommendations that are evolving internationally as guidelines, and considers how these might be harmonized to ensure that data and animals can be shared between countries, with a view to improving the implementation of the Three Rs in this area.

Canadian Council on Animal Care

The Canadian Council on Animal Care (CCAC) is the national organization with the responsibility for overseeing the care and use of animals in Canadian science. Through the overarching *CCAC policy statement on the ethics of animal experimentation* (CCAC, 1989), the CCAC has incorporated adherence to the Three Rs of Russell and Burch (1959) as the fundamental ethical basis for the oversight of animals used for scientific purposes in Canada.

The CCAC delivers its mandate through three interrelated programs: the Assessment Program, the Education Training and Communications Program, and the Guidelines Program (Gauthier & Griffin 2005). These programs function as an evidence-based learning loop, permitting knowledge to be shared readily between programs to continuously improve the oversight system overall. These three programs are fundamental to CCAC's ethical review system which is designed to operate as quality control at the local institutional level by integrating the needs of scientists, animals and the community through institutional animal care committees (ACCs) (CCAC, 2006), and to operate as quality assurance at the national level by setting and ensuring the implementation of its national standards, that is its guidelines and policies for the care and use of animals in science.

CCAC Guidelines Program

The CCAC is a peer-based organization involving scientists, veterinarians and other animal care personnel, animal welfare organizations' representatives and community representatives at all levels of its operation. Guidelines are developed by subcommittees of experts, peer-reviewed nationally and internationally by additional pools of experts, and subject to a widespread review involving constituents of the CCAC system and any parties likely to be affected by the guidelines, including the general public (Griffin & Gauthier, 2005). CCAC guidelines are developed first and foremost to be suitable for use in the Canadian animal use oversight system, which is more decentralized than many other national mechanisms of animal use oversight in science. More specifically, guidelines are developed to meet the needs of the CCAC Assessment Program; current and emerging issues for the Canadian research community; and in response to advances in laboratory animal care. The guidelines documents are tailored to provide a mechanism for the implementation of best practices at the local (institutional) level, and so provide key recommendations, in the form of guidelines statements, with justification balancing sound scientific evidence and expert opinion, as well as suitable references to both published and grey (non-peer reviewed) literature.

Both during the development of guidelines and post-development, the CCAC Guidelines Program engages in international harmonization initiatives. During the development of guidelines, these initiatives are targeted towards making best use of other guidelines documents, either recently developed, or in development. Post-guidelines development, CCAC has worked to ensure that its guidelines are suitable to be recognized internationally. See for example Demers et al (2006) in relation with the *CCAC guidelines on: choosing an appropriate endpoint in experiments using animals for research, teaching and testing* (CCAC, 1998).

International harmonization

The increasing globalization of science has emphasized the need for international harmonization of standards due to the broad implications for international collaboration between scientists. In addition, harmonization of standards is needed to improve global acceptance of research data and to facilitate international trade (Gauthier & Griffin, 2005). For this reason, international harmonization is one of the priorities of the CCAC Guidelines Program.

The CCAC Guidelines Program considers that it is important to remain connected to ongoing guidelines development initiatives elsewhere, as a pre-emptive means of ensuring Canadian guidelines are in-line with other international documents. It is also an efficient means of using international expertise. For example, a recent initiative to update CCAC guidelines on euthanasia used the international reference documents adopted by the International Council for Laboratory Animal Science (ICLAS; Demers et al, 2006). It also drew on more recent initiatives to address the issue of carbon dioxide as a euthanasia agent (the Newcastle consensus meeting on carbon dioxide; Hawkins et al, 2006); and the problem of euthanasia of neonatal animals (Artwohl et al, 2005).

While international guidelines are most useful as reference documents, it is important that they be suitable for use within the particular national context. In Canada, the local, institutional ACC is given the exclusive responsibility to provide an ethical review of animal use protocols. Therefore, CCAC guidelines documents must provide the tools for them to do so. This requires crafting clear guidelines statements, with an explanation of the basis for that statement, and reference to the scientific evidence, grey literature, or expert opinion that has been used as a basis for the guideline. This enables ACCs to communicate effectively with the principal investigators, and is transparent for all parties concerned. This need to ensure that sufficient information is provided to support the CCAC's devolved system means that where international guidance documents are adopted for use by CCAC (instead of undertaking the de novo development of a CCAC guidelines document), considerable work is needed to ensure that the guidelines work well within the Canadian oversight system.

Recent international exercises in harmonization of guidelines documents have proven to be complicated by differences in national oversight systems. However, it is likely that the most useful approach

to international harmonization is to recognize that guidelines cannot be standardized across nations, due to the differences in the various oversight mechanisms in place. In recognition of cultural differences, and to leave flexibility to nations to operate their particular systems, international agreement on a set of shared principles, with recognition of documents that are of sufficient calibre to be used by other countries without guidelines already in place, is an effective and respectful approach (Demers et al 2006).

International guidelines concerning the care and use of genetically-engineered, -modified, -altered animals[1]

As already discussed, during the development of a CCAC guidelines document, an environmental scan is conducted to determine where similar guidance is under development elsewhere, whether this is suitable for use by CCAC, and whether some degree of international harmonization is possible. During the period of development of the *CCAC guidelines on: genetically-engineered animals*, the following guidance documents were also in evolution:

- Guidelines for the generation, breeding, care and use of genetically modified and cloned animals for scientific purposes (Australia – Animal Welfare Committee, National Health and Medical Research Council, 2007);
- FELASA Guidelines for the production and nomenclature of transgenic rodents (Rülicke et al, 2007);
- Assessing the welfare of genetically altered mice – Report of the Working Group on genetically altered mice (Wells et al, 2005); and
- Phenotyping of genetically-engineered mice (Wasson, 2006).

CCAC guidelines on: genetically-engineered animals

In 1997, faced with an increasing number of protocols involving the creation and use of genetically-engineered animals, the CCAC published the *CCAC guidelines on: transgenic animals* (CCAC, 1997). In the ensuing years the number of genetically-engineered animals used internationally has risen steeply (see Comber & Griffin, 2007; Zhao et al, 2007; and Ormandy et al, 2008). Although at the present time, the CCAC does not record the numbers of genetically-engineered animals separately from non-engineered animals in its annual animal use survey, we have reason to believe that numbers have grown substantially in Canada as elsewhere (Griffin, Dansereau & Gauthier, 2008). In the UK, where genetically modified animals are enumerated, the numbers have quadrupled since 1995 (Home Office, 2007).

At the time of publication of the *CCAC guidelines on: transgenic animals* (CCAC,1997), it was recognized that the use of genetically-engineered animals was a particularly rapidly changing area, and that revised guidance would be required within a few years. Consequently, CCAC has been monitoring the challenges faced by investigators and animal care staff in this area and is in the process of developing new guidance.

Issues to be addressed

As a fore-runner to the revision of the *CCAC guidelines on: transgenic animals* (1997), the CCAC offered a fellowship in animal policy development to a young scientist/bioethicist, (Ms Julie Comber), who during the course of 2003-2005, prepared a number of discussion papers that formed the basis for the first draft of the new guidelines document.

From her analysis of the published literature and from the first hand experience of short stages in animal care facilities and laboratories involved with the care and use of genetically-engineered animals, the following areas were identified by Ms Comber as particular issues where CCAC would need to develop guidance:

- choice of animal model (genetically engineered or not);
- efficiency of the method chosen to generate the animals;
- genotyping using the least invasive methods
- assessment of the welfare of newly generated animal lines;
- training both of animal users, and of animal care staff required to carry out welfare assessments;
- breeding colony management;
- reporting of animal use; and
- information transfer.

These issues have been discussed briefly elsewhere (Griffin & Gauthier, 2008). In this paper we have focused on assessment of the welfare of newly generated animal lines and information transfer as the key elements to facilitate data sharing.

Assessment of the welfare of newly generated animal lines

The new CCAC guidelines on genetically engineered animals will require investigators to carry out a welfare assessment of their newly generated lines. Although animal care facilities do monitor the animals within their care, for genetically-engineered animals this is of particular importance, because the potential random insertion of the genetic material or recombination of genes can cause unexpected and unintended consequences. The more rapidly these can be ascertained, the more rapidly appropriate measures can be put in place, to minimize pain,

distress or discomfort for the animals. Currently, the CCAC guidelines require any protocol involving the generation of genetically-engineered animal to be assigned to severe category of invasiveness (Griffin, Dansereau & Gauthier, 2008), as a precautionary step until the welfare implications of the phenotype are understood.

Within the CCAC *guidelines on: genetically-engineered animals* (in preparation), the following recommendations are currently under discussion, that:

- newly generated genetically-engineered animals should undergo a welfare assessment;
- welfare assessments should be more rigorous if welfare problems are observed; and
- strategies should be developed to mitigate any welfare problems**.**

These recommendations are likely to have an impact on animal care facilities as they will of necessity require additional time to be spent by animal care technicians in carrying out detailed observations of the animals. The CCAC guidelines on: genetically-engineered animals will provide some assistance in this regard by providing a generic welfare assessment check list that can be tailored to suit individual institutions and used as an aide memoire when examining the animals. It should also assist in providing detailed information on the welfare status of the animals, which would be of particular importance if the animals were to be transferred between institutions.

Other jurisdictions have made similar recommendations concerning the welfare assessment of newly generated animal lines, namely:

- "Make and analyze routine observations in order to detect deviations from norms of health and well-being" (Australia – NHMRC, 2007);
- "It is essential to gather all available information on the strain… so that high welfare standards are maintained" (FELASA -- Rülicke et al, 2007);
- " Structured welfare assessments should be carried out for newly bred and maintained lines, and lines that are newly introduced" (Wells et al, 2005); and
- "Clinical surveillance and assessment of phenotype…An effective means to address potential animal welfare issues in newly created lines" (Brown & Murray, 2006, quoting Dennis, 2002).

It is encouraging that internationally, requirements are similar to ensure that the welfare of the animals is monitored. Provided that this information is properly recorded, this also means that detailed data sheets about the characteristics of each strain can be maintained and used to provide the best housing and husbandry conditions that are suitable for the animals' needs.

Information pack (passport)

Genetically-engineered animals are frequently transferred between institutions, and often between institutions in different countries. The requirement to develop information sheets in association with the genetically-engineered lines is being recommended as a means of providing detailed information, not only for the animal care facilities in the institution where the animals were generated, but also for institutions that will subsequently acquire the animal line. This should facilitate the care of those animals, in particular by animal care staff new to the genetically-engineered line of interest.

The information sheets should describe the characteristics and requirements for maintaining the particular genetically-engineered animal strain. In particular, information collated in the packs should include:

- information on the phenotype;
- indices of potential animal welfare concern;
- special requirements in terms of behavioral needs, feed, sensitivity to temperature, etc.;
- special conditions for husbandry; and
- mitigation strategies for pain and/or distress.

Similar initiatives are in place elsewhere to ensure that as much information as possible about the animals is transferred to the laboratory receiving them, namely:

- "A phenotype report should accompany animals whenever they are transferred between laboratories (number of animals affected, nature and time of onset of adverse effects, means of alleviating distress)" (Australia – NHMRC, 2007);
- "Data sheet or pointer to web-page should be sent in advance to the receiving laboratory, and a copy should accompany the animals" (FELASA – Rülicke et al, 2007);
- "Information pertaining to husbandry, welfare issues, breeding recommendations and expected phenotype should be disseminated when mice are transferred between establishments (passport template)" (UK – Wells et al, 2005);
- "Before obtaining an established line, it is important to gather as much information as possible… to determine special requirements to maintain the health and well-being of the animals" (US – Brown & Murray, 2006).

Although different jurisdictions place the onus on different parties to provide or obtain detailed

information concerning the health and welfare of the genetically-engineered animal strain, the end result is the same – facilities where the animals are developed will need to carry out detailed assessments of the animals that they generate, register the details in suitable records, and ensure that the relevant information is transferred with the animals.

Sharing information

In developing the *CCAC guidelines on: genetically-engineered animals*, the following guideline was prepared by the subcommittee:

> "Investigators should only generate a new genetically-engineered line if there is no existing line available that can answer the research question (Guideline 3 in *CCAC guidelines on: genetically-engineered animals*"(in preparation)).

The implementation of this guideline requires that information about genetically-engineered animal lines is readily available to research scientists. Internationally, there have been recommendations made to encourage the establishment of data banks where this information can be shared, namely:

- "Publication of information on the existence and characterization of a new genetically modified strain is essential to avoid duplication elsewhere" (Australia – NHMRC, 2007);
- "All characterized mutant strains should be stored as frozen germ cells/embryos in central repositories for use within the wider scientific community" (FELASA – Rülicke et al, 2007); and
- "A database should be developed on which the welfare implications of the use of all strains of genetically modified animals available to research are recorded" (UK – Animal Procedures Committee, 2001).

These three recommendations encompass different aspects of data sharing, all of which are important, in addressing the Three Rs (Reduction, Replacement and Refinement – Russell & Burch, 1959), the fundamental basis for the oversight of animal use in science worldwide. Knowledge of the existence of a genetically-engineered strain, and the ability to obtain it from a central repository should have an impact on Reduction, by limiting the number of animals currently used in generating genetically-engineered animals. The procedures involved in the generation of genetically-engineered animals can also involve considerable pain and distress for the animals, which would be obviated if an animal line already in existence is used. In addition, knowledge of the welfare implications of particular modifications should help to minimize pain and distress for the animals once a line is acquired by an investigator.

Conclusion

In conclusion, international harmonization of the care and use of genetically-engineered animals is needed in order to ensure that the internationally recognized principles of the Three Rs are applied to this rapidly advancing field. The fact that embryos, sperm and the animals themselves are being transported around the world, crossing borders between national systems of oversight, requires a willingness to share information. In doing so, closer attention to the animals should result in higher quality scientific data and improved welfare of the animals themselves.

In order for this to occur, there is a need for the implementation of guidelines at a national level to require careful welfare assessment of any newly generated line. It will also require as much information as possible about the genotype, phenotype and consequences of the genetic modification to the animal to be shared with any investigator interested in using the genetically-engineered strain in question, and with the institutional animal facilities where the animals are to be housed and cared for. Finally, it will also require the publication of this type of information, its collation in databases, and central repositories easily accessible to investigators where genetically-engineered lines can be stored for future use.

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Footnote

[1] Different jurisdictions use different terms to refer to animals that are products of biotechnological intervention. Genetically-engineered, genetically- modified and genetically-altered are the most common terms used.