

Establishing a Three Rs Programme at the Canadian Council on Animal Care

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Summary — The anniversary of the Fund for the Replacement of Animals in Medical Experiments (FRAME) provides an opportunity to celebrate the Charity's achievements over the past 40 years, and in particular, its contribution to the international acceptance of the Three Rs as the basis of an ethic for animal experimentation, and its role as a leader in the implementation of the Three Rs in the life sciences. The Canadian Council on Animal Care (CCAC) has based its work on the Three Rs, especially since the establishment of its fundamental *CCAC Policy Statement on the Ethics of Animal Investigation* (1989). Following recommendations from the evaluation of its programmes by external committees established by the national granting agencies, the CCAC recently launched a Three Rs Program. This programme will build on the work of FRAME and other similar Three Rs organisations, to further the promotion and implementation of the Three Rs in Canadian science.

Key words: *animal experimentation, CCAC, Canada, FRAME, Three Rs.*

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The Canadian Council on Animal Care

The Canadian Council on Animal Care (CCAC), Canada's oversight system for the use of animals in science, was established around the same time as FRAME, and celebrated its 40th anniversary last year. The CCAC has based its work on the Three Rs, especially since the establishment of its fundamental *CCAC policy statement on: the ethics of animal investigation* (1). As described in its mission statement, the CCAC acts "...in the interests of the people of Canada to ensure through programs of education, assessment and persuasion that the use of animals, where necessary, for research, teaching and testing employs optimal physical and psychological care according to acceptable scientific standards, and to promote an increased level of knowledge, awareness and sensitivity to relevant ethical principles" (2).

The CCAC delivers its mandate through interrelated programmes: the Assessment Program, the Education Training and Communications Program, the Guidelines Program (as described by Gauthier & Griffin [3]) and the more recently established Three Rs Program. Together, these programmes function as an evidence-based learning loop (as illustrated in Figure 1), permitting knowledge to be shared readily between the individual programmes, with a view to continuously improving the oversight of animals used in science.

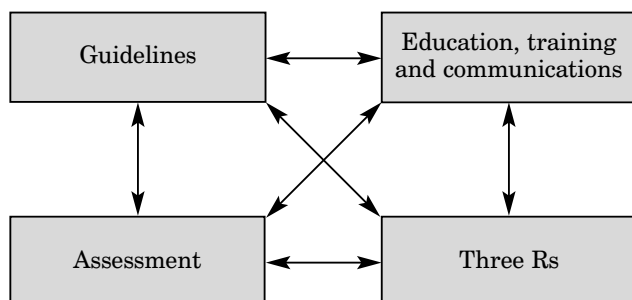
Typically, in other countries, programmes for assessment, education, guidelines development and the Three Rs, do not exist within the same organisation. This results in a considerable distance

between those setting the standards for animal care and use, and the agency or organisation responsible for the inspection, assessment or auditing of animal care and use within an institution. However, Canada is a country with a small population dispersed over a large geographical range, so, to conserve resources and to encourage information exchange, these programmes are closely integrated. Independence is achieved through distributed management and the involvement of many external expert volunteers.

Each of the CCAC programmes is peer-based, relying on the contributions of volunteer scientists, veterinarians, and community representatives. At the local level, the ethical review system relies on institutional animal care committees, designed to provide quality control by integrating the needs of scientists, animals and the community (4). At the national level, the CCAC provides quality assurance, by setting and ensuring the implementation of its national standards: its guidelines and policies for the care and use of animals in science.

The CCAC is financed primarily by Canada's two major granting agencies, the Canadian Institutes for Health Research (CIHR) and the Natural Sciences and Engineering Research Council (NSERC), and also by a system of cost recovery from government facilities and private institutions. The CCAC Council comprises 24 member organisations, whose representatives include scientists, veterinarians, educators, and delegates from industry and the animal welfare movement. Additional expertise, not available from Council, is achieved by the appointment of

Figure 1: The interrelated programmes of the CCAC



observers on Council and *ad hoc* members to any Standing Committee and subcommittee, as needed. Yearly, over 2000 volunteers across the country, including representatives of the public, participate in the four CCAC programmes and serve on over 220 institutional animal care committees.

In their study of models for the protection of humans and animals, Schuppli and McDonald (5), concluded that the CCAC approach has several advantages for Canada:

- it is a Canadian model of governance that works across both federal/provincial and public/private jurisdictions;
- it is moderately independent from research and sponsor interests;
- it monitors and assesses the effectiveness of the system and compliance with standards;
- it collects and publishes information about the effectiveness of the system as well as research trends; and
- it has a national education programme.

They noted that these features result in the ability of the CCAC system to provide adequate quality assurance for the use of animals in science, whilst being relatively more transparent and accountable than the other models they considered.

Briefly, the Assessment Program ensures that institutions are adhering to CCAC guidelines and policies (through assessment visits to institutions using animals for scientific purposes, to assess their animal care and use, including the functioning of the institutional animal care committee). The Assessment Program also provides feedback on the findings from assessment visits, which is then applied in the development of guidelines and educational materials. In turn, the Guidelines Program develops guidelines based on: needs iden-

tified within the scientific community; advances in laboratory animal care and procedures carried out on animals; and the requirements of the Assessment Program. These guidelines are then implemented through the Assessment Program and also through the Education, Training and Communications Program.

Establishment of the CCAC Three Rs Program

The work of the CCAC itself, as a recipient of public funds, is reviewed by an external granting agency evaluation committee, on a tri-annual basis. Recommendations made by recent evaluation committees to increase activities in relation to the Three Rs, and in particular in the area of *replacement*, led the CCAC to establish its fourth programme in 2008, the Three Rs Program

The work of the CCAC is rooted in the principles of humane science — *reduction, refinement and replacement* (6). In the past, the CCAC's activities have been focused primarily on promoting the Three Rs in research and teaching. Of the Three Rs, refinement of housing and husbandry practices, and the minimisation of pain and distress in procedures, were the main focus, as demonstrated by its internationally recognised (7) publication, the *CCAC guidelines on: choosing appropriate endpoints in experiments using animals for research, teaching and testing* (2, 7).

The CCAC formally launched its Three Rs Program with two primary aims: promoting the Three Rs, through communication of CCAC's ethics of animal experimentation, the maintenance of an up-to-date Three Rs microsite on the CCAC website, and, the consolidation of the CCAC's role as Canada's National Centre for the Three Rs; and, supporting the implementation of the Three Rs in all areas relating to the use of animals in science, covered by the CCAC.

Promoting the Three Rs

The Three Rs as an ethic of animal experimentation

When FRAME was established as a charity in 1969, it was already 10 years after the publication of *The Principles of Humane Experimental Technique*, by Russell and Burch (6). Balls *et al.* (8) have described the evolution of the Three Rs, pointing to the fact that Russell and Burch's book had little obvious impact on thinking or practice in the early years after its publication. Although it is uncertain whether Dorothy Hegarty was aware of their book, she founded FRAME specifically to

advance the humanitarian and scientific benefits that would result from the replacement of animal experiments by other methods.

FRAME went on to play a significant role in shaping the *Animals (Scientific Procedures) Act 1986*, and throughout the 1980s, new laws were enacted in various other parts of the world, which not only recognised Russell and Burch's concept, but placed legal and moral obligations on all concerned to seek to replace, reduce and/or refine laboratory animal experimentation wherever possible. This included an *ethical code for animal experimentation*, a set of International Guiding Principles for Biomedical Research Involving Animals published by the World Health Organisation for the Council of International Organisations of Medical Sciences (CIOMS; 9).

In Canada, the publication of the *CCAC policy statement on: the ethics of animal investigation* (1) defined the Three Rs for the CCAC, and continues to provide the principles for the conduct of animal-based science in Canada, in the following terms: "*Animals should be used only if the researcher's best efforts to find an alternative have failed. A continuing sharing of knowledge, review of the literature, and adherence to the Russell-Burch "3R" tenet of "Replacement, Reduction and Refinement" are also requisites. Those using animals should employ the most humane methods on the smallest number of appropriate animals required to obtain valid information.*"

The use of the Three Rs to guide the conduct of animal-based science has stood the test of time. Nonetheless, because of the rapidly changing face of science, it behoves all organisations involved in the promotion of the Three Rs to continually reassess and reinterpret the Three Rs, and to ensure that the ethical framework is understood by all the players (see, for example, 10).

Developments in science have also led to new challenges to the implementation of the Three Rs. The most notable of these is the rapid increase in the use of genetically-modified animals, described by Schuppli *et al.* (11) and Ormandy *et al.* (12). From the beginning of the introduction of techniques permitting the manipulation of the genomes of animals, FRAME has not shied away from considering the value and relevance of genetically altered mouse models of human disease (see, for example, 13), and in doing so, has provided other organisations with a well-considered basis for the further elaboration of their policies around the creation and use of genetically-engineered animals. While recognising the potential to develop animal models of greater relevance to human disease, FRAME also pointed out that this would, at least in the short term, lead to an increase in the numbers of animals.

The establishment of its new Three Rs Program will now provide the CCAC with the opportunity to

re-examine this fundamental ethic of animal experimentation, and to address some of the limitations associated with use of the Three Rs in the oversight of animal-based science. These limitations, summarised by Fenwick and Griffin (14), include:

- the underlying premise that the scientific use of animals is acceptable, as long as the criteria of the Three Rs have been met;
- the lack of provision for special considerations for certain species;
- conflicts between *reduction* and *refinement*, particularly when using newer scientific techniques; and
- conflicts between with the goals of the Three Rs and the goals of certain types of research, for example, agricultural or wildlife research.

The CCAC's Three Rs microsite

FRAME has long been in the business of providing up-to-date information to a broad audience, reaching out to the scientific community through its peer-reviewed journal, *Alternatives to Laboratory Animals (ATLA)*, to the public and politicians through its newsletter, *FRAME News*, and to schools through the provision of balanced information concerning the use of animals and alternatives in the life science, via its *Focus on FRAME* leaflets. Of course, as the world moved into the electronic age, FRAME also developed its own website (<http://www.frame.org.uk>), which has undergone several redesigns since its launch.

Taking its cue from FRAME's emphasis on communication, one of the first things that the CCAC Three Rs Program was able to accomplish, was the launch of a Three Rs microsite (<http://www.ccac.ca/en/alternatives/index.html>). Tailored specifically to Canadian investigators and animal care committee members, the microsite communicates best practices and new Three Rs information that is progressive, and that may go beyond what is currently required by CCAC guidelines. Similarly, the Three Rs Search Guide section of the microsite, aims to assist investigators to find Three Rs-related information prior to submitting their protocols for ethical review.

The CCAC as Canada's National Centre for the Three Rs

The idea of national centres for the Three Rs is new, despite the existence of centres such as FRAME, which have performed this role for many

years. According to Altweb (<http://altweb.jhsph.edu/3rscenters.htm>), there are currently some 30 such organisations across the globe. Although there is overlap between the mandates of some of the centres, it is evident that they each have their special focus. Together, they have the potential to have a huge impact worldwide, as they should be able to feed and nurture each other, based on their particular specialities. It is into this fold that the CCAC has recently been added. While the CCAC is unlikely to be able to provide funding for research on the Three Rs, it will be able to draw on research funded by other Three Rs centres, and, with time, will be able to contribute its unique tools for use by others. For example, the CCAC seeks first to find alternatives for procedures where animals experience the most pain and distress, an approach recommended by Smyth (15), and therefore has become more involved recently in the area of regulatory testing. This was initiated in 2001, when the joint *International Council for Laboratory Animal Science/CCAC Symposium on Regulatory Testing and Animal Welfare* was held in Québec City, leading to studies of particular areas of regulatory testing by CCAC research fellows (16). In addition, the *8th World Congress on Alternatives and Animal Use in the Life Sciences*, to be hosted by the CCAC in Montréal on 21–26 August 2011, will provide a focus on the involvement of the public in the oversight of animal use, an area where the CCAC has much useful experience to share.

Implementation of the Three Rs

The work of the CCAC Three Rs Program, directed toward supporting the implementation of the Three Rs in research, teaching and testing, will take more time to evolve, and will need to rely heavily on the studies funded and carried out by other Three Rs Centres. The work of the FRAME Alternatives Laboratory (FAL) is particularly valuable, as this provides the basic science on which more-applied research and, subsequently, policy can be built. Although, back in the 1980s, it would have been hard to believe that the development, validation and regulatory acceptance of alternative methods could possibly take so long, it is nonetheless rewarding to see methods originating in the FAL are now being used for regulatory purposes.

As the national quasi-regulatory body responsible for overseeing the care and use of animals in science, the CCAC has the ability to speak, not only to those carrying out tests to submit data to regulatory agencies, but also directly to the regulatory agencies requiring the use of data derived from animal-based tests (17). At the *International Council for Laboratory Animal Science/CCAC Symposium on Regulatory Testing and Animal Welfare* mentioned above, three basic conditions

for the successful implementation of change in scientific practice relating to the use of animals for regulatory testing were described: a) high quality science supporting the change; b) an understanding, recognition and implementation of the change by all stakeholders in a timely manner; and c) the involvement of all stakeholders in the communication of best practices (18). These three conditions, and an accompanying series of six principles, provide the framework for the effective use of science advice to implement the Three Rs, and have been subsequently used by CCAC as the basis for an investigation of the opportunities and obstacles to implement the Three Rs in shellfish toxin testing in Canada (16).

CCAC Fellowship Program

Over its 40-year history, FRAME has provided a fertile ground for the training of young scientists. The opportunity to work at FRAME provided not only hands-on laboratory work, but also the possibility of being involved in the development of policy.

There is little formal training in Canada (or elsewhere) for scientists in policy development. With this in mind, the CCAC established a fellowship programme in animal policy development, offering its first fellowship in 2004. This programme has proved to be quite successful in exposing young scientists to ethical issues and working with them to develop potential policy solutions or outcomes.

The first fellow, Julie Comber, was responsible for providing a first draft of a revision of *CCAC guidelines on: transgenic animals* (19), drawn from her examination of some of the ethical issues with respect to genetically-engineered mice (see, for example, 20). The second fellow, Allison Guy, completed an interview-based study on the opportunities and obstacles to the implementation of the Three Rs in shellfish testing (16). A comprehensive analysis of the complete dataset resulted in recommendations for Canadian regulators on the minor steps needed to refine the pre-column High Performance Liquid Chromatography method, an instrument-based method to detect toxins responsible for paralytic shellfish poisoning developed by Health Canada (21), and make it a reliable *replacement* alternative to the currently used mouse bioassay, which requires 36,000 mice per year in Canada alone.

Conclusions

The new CCAC Three Rs Program has much to learn from the well-established Three Rs centres around the world. Of these 30 centres, FRAME must rank as one of the most mature, having con-

tributed to the evolving field of research ethics and the Three Rs for the past 40 years. In celebrating this achievement, the CCAC Three Rs Program looks to FRAME to continue its cutting-edge work.

As a charity, independent from research funding organisations and from the national oversight of animal use in science, FRAME can run further ahead with its research and policy suggestions. The CCAC Three Rs Program, while sitting closely to those working with animals in science, is not in a position to be able to test newly-minted ideas until they have been subject to various levels of evaluation. Therefore, the CCAC Three Rs Program will benefit enormously from organisations like FRAME, from which it can draw ideas and information that can be further crafted, developed and reviewed for subsequent implementation.

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