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Adopting alternative methods for regulatory testing in Canada

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Abstract
Advances in the understanding of basic biological mechanisms, and in technology, have led to the development of alternative methods that are not only founded on better science but that also incorporate the Three Rs to improve animal welfare. Despite the conclusive and scientifically rigorous international validation for many of these alternatives, the great majority are still not being used for regulatory testing. The opportunities to use scientific research to inform policy decisions require improved communication between stakeholders, and the coordination and harmonization of regulations (Schiffelers, 2005).

In Canada, the Canadian Council on Animal Care (CCAC) can be most effective by stimulating communication between stakeholders as a means to affect policy change. At the ICLAS/CCAC International Symposium on *Regulatory Testing and Animal Welfare*, held in Québec City, 2001, Gauthier (2002) proposed a framework to assist stakeholders to use scientific knowledge, as it evolves, to inform policy making for the implementation of alternative methods in regulatory testing. This framework comprises six elements which are now being examined by the CCAC, with a view of identifying impediments and opportunities for regulatory acceptance of data derived from alternative methods.

Keywords: regulatory testing, 3Rs, science policy

Introduction

Governments bear responsibility for ensuring that consumer products entering the marketplace are either safe for use or are appropriately labelled to convey the risk of their use. In Canada, there are laws to ensure that products receive the appropriate testing and that manufacturers are held responsible for the safety of their products. Some products, such as certain foods, pharmaceuticals and chemicals, require pre-market regulatory approval to ensure that the risk of adverse effects resulting from their use is sufficiently low for them to be considered "safe". This safety testing requires a large number of animals and often causes them considerable pain and distress.

While the Canadian public expects the government to protect them from unsafe products, the public supports animal use in science only when mechanisms are in place to minimize pain and distress (The Gallup Poll, 2007; Canadian Public Health Association, 2001; MORI, 2000). Public pressure and advances in science and technology have led to the development of alternative methods for testing that are based on better science and improve animal welfare. Despite validation studies, many of these alternatives are still not being accepted for testing by regulators. With the emergence of chemical management programs such as Europe's Registration, Evaluation, Authorisation and Restriction of Chemical Substances (REACH), the High Production Volume (HPV) Chemical Challenge in the United States, and Canada's own Chemicals Management Plan, there is pressure for regulators to accept data derived through alternative methods from industry to ensure safety data is produced in a timely, cost-effective and humane manner. For instance, Canada accepted a high throughput testing method, which did not require the use of animals, to ensure that chemicals with low priority[1] were not a risk for human health or the environment (Environment Canada, 2007).

To ensure that animals are not being used unnecessarily for testing and that the pain and distress that they experience is minimized, the Canadian public relies on the Canadian Council on Animal Care (CCAC) to work with stakeholders to implement Russell and Burch's principles of humane science (1959).

Canadian Council on Animal Care

The CCAC is the national peer review organization responsible for overseeing the care and use of animals involved in research, teaching and testing throughout Canada. The CCAC is comprised of 25 national member organizations (including the five federal regulatory departments and agencies) whose representatives include veterinarians, scientists, educators, delegates from industry and the animal welfare movement. The CCAC consists of three programs: guidelines, assessment, and education that are implemented with the help of volunteers, including the members of animal care committees at institutions across the nation. Through these three programs and on behalf of the people of Canada, the CCAC ensures that the use of animals for research, teaching and testing employs optimal physical and psychological care without compromising scientific integrity.

In Canada, where there can be no federal legislation to regulate animal use for scientific purposes due to the Constitutional division of power, the CCAC as the national quasi-regulatory body (CCAC standards are referenced in provincial regulations) has incorporated the Three Rs principles (Russell & Burch, 1959) into its fundamental *CCAC policy statement on: the ethics of animal investigation* (CCAC, 1989). The CCAC is also becoming internationally recognized as a Centre for the Three Rs in Canada.

In the past, the CCAC's activities have been focused primarily on promoting the Three Rs in research and teaching; in particular, refinement of housing and husbandry practices and the minimization of pain and distress in procedures, as demonstrated by its internationally recognized (Demers et al., 2006) publication the *CCAC guidelines on: choosing appropriate endpoints in experiments using animals for research teaching and testing* (1998). More recently, the CCAC has begun to get more involved in the area of regulatory testing. In 2001 the CCAC, in collaboration with the International Council for Laboratory Animal Science (ICLAS), hosted the *ICLAS/CCAC International Symposium on Regulatory Testing and Animal Welfare* in Québec City, which was attended by 168 representatives from regulatory agencies, industry, academia and the animal welfare movement from 22 countries. A number of recommendations emerged from this symposium to improve the implementation of the Three Rs in the area of regulatory testing. The 2006-2008 CCAC Fellowship in Animal Policy Development was offered in the area of regulatory testing and animal welfare in order to ascertain the extent to which the Symposium's recommendations have been implemented in Canada and abroad. The Fellowship is also aimed at an investigation of the obstacles and opportunities for further implementation of the Three Rs in this area.

Basic conditions for the successful implementation of change in scientific practice

At the 2001 ICLAS/CCAC International Symposium on Regulatory Testing and Animal Welfare, Gauthier (2002) presented the *Principles and Guidelines for the Development of a Science-based Decision Making Process Facilitating the Implementation of the Three Rs by Governmental Regulators*. According to Gauthier, the basic conditions for the successful implementation of change in scientific practice relating to the use of animals for regulatory testing include:

- high quality science supporting the change;
- an understanding, recognition and implementation of the change by all stakeholders in a timely manner; and
- the involvement of all stakeholders (regulators, scientists, animal welfare organizations, the public and decision makers as users of science) in the communication of best practices.

These three conditions must be met in order to ensure a change in scientific practice. On their own, each condition may improve the possibility for change, but does not ensure it. For example, in the area of shellfish toxin testing, there is a desire by stakeholders to move away from the mouse bioassay as a means to detect the contamination of shellfish with marine biotoxins (David and Nicholson, 2004; Hess et al., 2006). However, no change in scientific and regulatory practices has occurred. The preliminary results of an investigation of the opportunities and obstacles to implementing the Three Rs in shellfish toxin testing in Canada conducted by the CCAC has revealed that this is probably not due to the quality of science supporting the change as the many alternative methods to the mouse bioassay are based on sound science (Quilliam, 2003a,b,c). One instrument-based method has even been validated in an international study and accepted by the AOAC[2] as an alternative to the mouse bioassay (Lawrence et al., 2005). Nor does the lack of change in scientific practice appear to be due to ignorance of the available alternatives or the problems with the existing method on the part of the stakeholders. As many of these alternatives were developed in Canada with the support of the Government of Canada, Canadian regulators are quite knowledgeable about the science of alternative methods for shellfish toxin testing. It appears that the main obstacle preventing a change in science policy may be due to a lack of communication between stakeholders (Guy and Griffin, 2008).

In Canada, there are three main stakeholders in

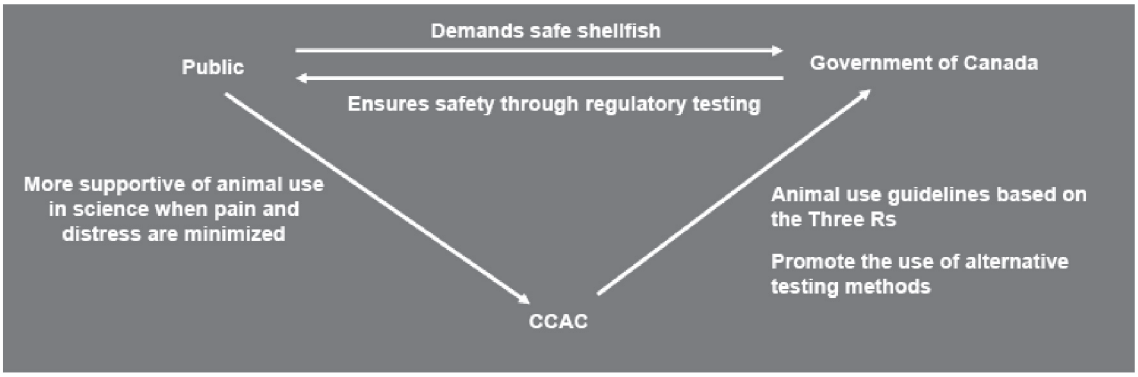

Fig. 1. Canadian Stakeholders in Shellfish Toxin Testing

the area of shellfish toxin testing: the public, the Government of Canada (government) and the CCAC (Figure 1). While the public demands safe shellfish, they do not support animal use for science when it causes pain and distress. The government ensures public safety by monitoring shellfish for toxins but uses a large number of animals and employs a testing method that has the ability to cause them considerable pain and distress. The CCAC has an obligation to the people of Canada to ensure that animals are not used unnecessarily and that pain and distress where they are used is minimized. To improve the communication between the public and the government, the CCAC can be most effective in facilitating change by working with the government, on behalf of the people of Canada, to find ways of implementing the Three Rs in its shellfish toxin testing program.

Improving communication between stakeholders was also identified as an opportunity to use science to inform policy in a study conducted by the Science Shop for Biology at Utrecht University that examined the opportunity and obstacles in implementing the Three Rs for regulatory testing in the Netherlands. In addition to improved communication between stakeholders, they found that the opportunities to use scientific research to inform policy decisions require the coordination and harmonization of regulations (Schiffelers et al., 2005).

Framework for the effective use of science advice to implement the three Rs

In addition to the basic conditions that must exist to ensure a change in scientific practice, Gauthier presented a framework for the effective use of science advice to implement the Three Rs in regulatory testing. This framework was based on a report prepared on behalf of the Council of Science and Technology Advisors (CSTA, 1999) to the Government of Canada and is made up of the following six principles: early identification, inclusiveness, sound science and sound science advice, uncertainty and risk, openness, and review. Even in isolation, these six principles have facilitated the effective use of science advice to implement the Three Rs in regulatory testing in Canada.

Early Identification

When the Canadian Environmental Protection Act was revised in 1995 (CEPA, 1995), new ecotoxicity testing was included which led to a dramatic increase in the use of fish for the safety testing of chemicals. Anticipating the need for guidance for the care and use of fish, the CCAC began to develop the *CCAC guidelines on: the use of fish in research, teaching and testing* (1999) before there was a high demand from stakeholders. Early identification of the need for guidance that ensures a high standard for animal care prompted the development of guidelines, grounded in the Three Rs, in a timely manner.

Inclusiveness

On December 8, 2006, the Government of Canada announced its plan to commit $300 million over four years to Canada's Chemical Management Plan (CCMP), a joint initiative between Health Canada and Environment Canada. To prevent the duplication of testing, the Government of Canada is encouraging the submission of existing data, in particular data generated for other chemical management programs, such as the HPV in the US and REACH in Europe. By accepting existing data from a variety of sources, the use of animals that would have otherwise been required for this program will be greatly reduced.

Sound Science and Sound Science Advice

The median lethal dose[3] or the LD_{50} was the universally required measure to determine the acute systemic toxicity of pharmaceuticals and chemicals before it was dropped in 1991 by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and in 2002 by the Organisation for Economic Co-operation and Development (OECD). The decision to eradicate the LD_{50} was based on the scientific advice of stakeholders that not only does this test use a large number of animals and

causes them a great deal of pain and distress, but that data derived from this test do not reflect the acute toxic properties of a compound, do not give sufficient information to categorize the compound and do not correlate well with different mechanisms of action of toxic agents. Based on sound science and sound science advice, this test was banned in favour of more humane alternatives.

Uncertainty & Risk

Under Section 73 of *CEPA 1999*, the Existing Substances Division of the Health Environment & Consumer Safety Branch of Health Canada conducted a priority setting exercise on the 22,400 existing chemicals on the Canadian *Domestic Substances List*[4] (DSL). As many of these older chemicals had never undergone a full environmental or health safety assessment, they were categorized to determine the extent of the safety testing required for risk management. Canada completed this scientific evaluation in September 2006. The result of this categorization was the finding that 4,300 substances on the DSL have incomplete toxicity data and therefore more testing is required.

Each substance was then categorized as either a high, moderate or low priority chemical. This prioritization exercise allowed for the communication of the degree and nature of scientific uncertainty to the regulators who could then make the appropriate risk management decisions for these chemicals in order to protect the public without requiring each manufacturer or importer to conduct a generic battery of *in vivo* tests, thus reducing the number of animals that might have otherwise been used for this project.

Openness & Review

The guidelines documents developed and published by the CCAC provide the solid base of standards needed for an effective Canadian system of surveillance of animal care and use in science. The unique peer-based process used to develop CCAC guidelines ensures that consensus on ethically sensitive issues is established jointly by animal users (including scientists working for governmental regulatory departments and agencies), animal care personnel, members of the animal welfare movement, and community representatives. In addition to including multiple stakeholders, the process is also very transparent. Furthermore, whenever the advancement of knowledge affects the science on which these guidance documents are based, the CCAC re-writes its guidelines to reflect best practices.

Conclusion

Improvements in the establishment of science policy in Canada is desirable to allow a mechanism through which scientific advancement, in particular in the area of the Three Rs, is regularly incorporated into regulations for regulatory testing. This change should promote best practices for animal use in regulatory testing while still protecting the public from unsafe products.

The CCAC plays a unique role in Canada as the national quasi-regulatory body responsible for overseeing the care and use of animals in science. As such, 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 who are requiring the use of data derived from animal-based tests for risk assessment purposes. The CCAC can, therefore, play an important role in bringing together the various stakeholders involved in regulatory testing to improve communication concerning actual data requirements (as per the third basic condition for the successful implementation of changes in scientific and regulatory practices outlined by Gauthier (2002)). In addition, in implementation of the sixth principle of the policy framework described above, the CCAC can also stimulate the review of past decisions/regulations in order to ensure that animals are not being used unnecessarily.

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Footnotes

[1] Under Canada's Chemical Management Plan, low priority chemicals are not persistent or bioaccumulative and do not present a great potential for human exposure.

[2] AOAC INTERNATIONAL is a not-for-profit scientific association committed to worldwide confidence in analytical results. AOAC Official Methods are accepted and recognized by regulatory agencies and organizations worldwide.

[3] The LD_{50} is the dose of a substance that would cause death in 50% of the animals in an experimental group. Death was the only endpoint and therefore, this test had the potential to cause considerable pain and distress.

[4] Chemicals in use in Canada between January 1, 1984 and December 31, 1986, at a quantity of greater than 100 kg per year, are considered to be "existing substances" and are listed on the *Domestic Substances List (DSL)*.