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Article

Comparison of the Canadian and US Laws, Regulations, Policies, and Systems of Oversight for Animals in Research

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Abstract

The Canadian and United States' approaches to oversight of animals in research are both based on the "3Rs" principles outlined in Russell and Burch's classic text, *The Principles of Humane Experimental Technique*. Each country seeks to protect the welfare of animals, while permitting the legitimate goals of scientific research to be attained according to the legal principles, cultures, and strengths and constraints of their jurisprudential and societal traditions. Canada is one of the most decentralized federations in the world, and regulation of activities is based to a great extent on custom and practice. The United States is more hierarchical and, at least with respect to laws governing animal research, more centralized. Accordingly, the Canadian approach is rooted in the concepts of social contracts, with a greater emphasis on guidance and policy and less reliance on legislation. No federal (national) direct legislation of laboratory animal welfare exists, although the federal government uses its criminal and spending authorities to shape behavior. The central feature of the Canadian system is the Canadian Council on Animal Care, which was formed to support universities and government departments involved in animal-based science. Animal care committees play a central role in implementing the guidelines and policies in facilities that carry out animal research. The United States has enacted two federal (national) laws applicable to animals in research. The Animal Welfare Act is a more traditional, command-and-control law that gives authority to the US Department of Agriculture to promulgate regulations, inspect facilities, and enforce violations. The Health Research Extension Act, which amended the US Public Health Services (PHS) Act, applies to any activity conducted or supported by the PHS, including research efforts supported by the US National Institutes of Health. It is largely nonregulatory and establishes a system of assurances and policies that covered research facilities must follow. States play only a minor role in animal research protection. As in Canada, institutional animal care and use committees are tasked with self-regulation of activities that use animals for research.

Key words: Canadian Council on Animal Care; Animal Welfare Act; Health Research Extension Act; laboratory regulation; USDA; OLAW; APHIS

Introduction

The manner in which the United States and Canada provide oversight for animals in science is reflective of the difference in constitutions and governance in the two countries. Canada is one of the most decentralized federations in the world, and regulation of activities is based to a great extent on custom and practice. The United States is more hierarchical and, at least with respect to laws governing animal research, more

centralized. The US Constitution is a document of delegated authorities in which custom and practice play a smaller role. States, which hold the plenary power of the people, have delegated to the federal government certain authorities so that, among other things, interactions that cross state lines can proceed smoothly. The US Constitution contains provisions, including both an interstate commerce clause and supremacy clause, which establish federal law as the supreme law of the land. The US Congress has crafted a legislative system that allows for significant self-regulation of research facilities. Also, because of litigation in the United States as well as provisions found in state anti-cruelty laws, state animal anti-cruelty statutes are generally considered not to be applicable to research activities that are covered by the US Animal Welfare Act (AWA 2013) or the US Public Health Services Act (PHS 1944). By contrast, Canada has no federal legislation governing animal-based research. Under the division of powers in the Canadian Constitution, section 92 (13) and (16) (Government of Canada 1982), all matters to do with property and civil rights fall under provincial jurisdiction. Research falls under the realm of property, and the provinces have traditionally occupied this area. For this reason any attempt to create federal legislation for the oversight of animal-based research would be subject to constitutional challenge.

In both Canada and the United States, control of research activities involving animals can take two approaches; a formal or legislative approach or a nonlegislative approach. Both approaches are utilized, in different ways, to oversee the animal-based research of these countries.

In general, direct legislation and regulation provide the minimum requirements for oversight. Legislation is used to deliver sanctions retroactively, unless the legislative provisions are written in a permissive way. Legislation such as the Criminal Code in Canada (Government of Canada 1985) (Sections 444–447 of the Criminal Code, which broadly protects animals against cruelty in Canada) can only be effective in bringing sanctions after a prohibited act has been committed. In the United States, the AWA contains provisions that can be used to levy civil penalties against research laboratories that do not comply with the law.

Nonlegislative tools are also used extensively in both Canada and the United States. They can evolve much more rapidly and can set up frameworks of expectation for behavior that are captured in policies, guidelines, or licensing requirements. These tools are very useful in shaping activities and expectations, and convey the responsibilities of researchers who seek to use animals. The CCAC policy statement on ethics of animal investigation (CCAC 1989a) is an example of a proactive approach. It states: "The use of animals in research, teaching, and testing is acceptable ONLY if it promises to contribute to understanding of fundamental biological principles, or to the development of knowledge that can reasonably be expected to benefit humans or animals." Similarly, the US Guide for the Care and Use of Laboratory Animals states:

"The decision to use animals in research requires critical thought, judgment, and analysis. Using animals in research is a privilege granted by society to the research community with the expectation that such use will provide either significant new knowledge or lead to improvement in human and/or animal well-being [Citations omitted.] It is a trust that mandates responsible and humane care and use of these animals." (NRC 2011, p 4)

Although each country has established systems for the oversight of animal-based research that involve both legislative and nonlegislative frameworks, the approaches taken in the United States and in Canada to address the emerging public concerns about animal-based research are different. Here we have tried to provide an overview of these frameworks to illustrate how the two systems evolved quite distinctly while setting out to accomplish similar goals. Despite their differences, it is important to point out that the manner in which each system functions in practice likely would produce similar decision-making for similar facts.

Historical Background

In North America the first half of the twentieth century saw a rapid increase in animal-based research and testing. It is generally recognized that the First World War had involved so much human suffering that it stimulated the development of potential treatments, many of which were based on animal experimentation. During this period, public interest in benefits to be gained from animal experimentation outweighed the concerns about vivisection, which had emerged as a response to the public demonstrations of "experiments" in the late 19th century. Furthermore, the harmful experiments carried out on human subjects during the Second World War led to drafting of the Nuremberg Code at the time of the Nuremberg trials (Ghooi 2011) and the Declaration of Helsinki by the World Medical Association, first published 1964 (Carlson et al. 2004). Both the Nuremberg Code and the Declaration of Helsinki were interpreted to require that any experimentation involving humans should be based on previously carried out animal experimentation.

The further phenomenal growth of biomedical science in the 1950s and 1960s was countered by a growth in public disquiet about animal-based research. In the United States, the first large-scale animal activism involving animals in research began in the 1960s after an article published in Life magazine showed the conditions of dogs, some of which were purported to be stolen pets, at a facility that sold these dogs to research laboratories (Engber 2009). This article, and others like it, led to the passage of the US Animal Welfare Act. In Canada, there was not the same extent of animal activism; however, there was sufficient awareness of public concern about animal-based research that in 1961 the Committee on Animal Care of the Canadian Federation of Biological Societies prepared a one-page placard outlining "Guiding Principles for the Care of Experimental Animals" (CFBS 1961).

Legislative, regulatory, and policy issues regarding animal-based research have been heavily influenced by a scholarly treatise published in the United Kingdom. From the 1940s onwards, the United Kingdom's Universities Federation for Animal Welfare had focussed on trying to improve the welfare of laboratory animals. On the advice of its founder, Major Charles Hume, and Nobel Laureate Sir Peter Medawar, the Universities Federation for Animal Welfare hired William Russell and Rex Burch in 1957 to explore means by which animal-based research could be conducted humanely. Their book *The Principles of Humane Experimental Technique* (Russell and Burch 1959) introduced and defined the concept of the 3Rs principles, which now form the basis for most international legislation and guidance concerning the ethical oversight of animal-based research, including the laws, regulations, and policies in North America (Hubrecht 2014).

Development Of Laws Regarding Laboratory Animal Research

Canada

In Canada, it was the research community itself that stimulated the development of a system to oversee animal-based

research. In 1964 the Canadian Medical Research Council asked the National Research Council of Canada (NRC[C]) to consider the issue of animals used in research. The NRC[C] formed a Special Committee on the Care of Experimental Animals to look into the use of experimental animals. The report of this Committee (National Research Council of Canada 1966) recommended the creation of a voluntary control program exercised by scientists in each institution that would be subject to peer judgment and committed to implementing the guiding principles of an independent advisory body. As a result in 1968 the Canadian Council on Animal Care (CCAC) was formed with the support of universities and government departments involved in animal-based science. The mandate of the CCAC is to act in the interest of the people of Canada to advance animal ethics and care by:

- "developing science-informed standards that incorporate expert opinion, the values of Canadians, and strategies to reduce the need for, and harm of, animals in science, while promoting their well-being
- encouraging the implementation of the highest standards of ethics and care for animals in science in collaboration with the animal care community and scientists across Canada
- providing assessment and certification programs that empower scientific institutions in achieving high standards of animal ethics and care
- providing education, training, and networking opportunities to support individuals, animal care committees (ACCs), and institutions in implementing CCAC guidelines and sharing best practices in the oversight of animal ethics and care in science". (http://www.ccac.ca).

The CCAC certifies individual institutions every 3 years based on the institutional compliance with CCAC policy statements and guidelines and other CCAC-recognized standards.

A CCAC Certificate of GAP—Good Animal Practice® is earned by institutions that:

- participate fully in the CCAC programs
- have been assessed by assessment panels composed of scientists, veterinarians, and community representatives
- have been found by the panel and by the CCAC Assessment and Certification Committee to have standards of animal ethics and care in animal-based science that satisfy the CCAC's guidelines and policy statements

United States

In the 1960s, the US Congress received more mail about animal care issues than about civil rights and the war in Vietnam combined (Kreger et al. 1998). As a result of this public pressure, and also the publication of investigative journalism in Life magazine mentioned above, the US Congress enacted the AWA in 1966 (Engber 2009). Additional provisions for research facilities were added to the AWA with the 1985 Improved Standards for Laboratory Animals Act amendment (https://awic.nal.usda.gov/legislative-history-animal-welfare-act/intro (last accessed 10 June 2016). These included the requirement for institutions to establish institutional animal care and use committees (IACUCs, discussed in detail below) to review animal-based proposed activities, which are often captured in research protocols, and for inspection of laboratory/animal facilities. A parallel law (the Health Research Extension Act; Public Law 99-158, November 20, 1985, codified at 42 USC §289d) was passed that same year (over a presidential veto) and was directed at facilities using animals in research that are funded by the US National Institutes of Health and Public Health Service. The AWA is administered by the US Department of Agriculture; the Health Research Extension Act is administered by the US Department of Health and Human Services. It is generally accepted that the US national laws are based on the principles of the 3Rs. However, an examination of the language of both the AWA and its regulations and the Health Research Extension Act reveal no explicit statutory or regulatory language that specifically addresses the 3Rs. Nevertheless, there is substantial evidence to support the statement that the 3Rs are incorporated into US laws, regulations, and policies. First, legislative history associated with the 1985 amendments to the AWA states that the amendments were intended to "reflect the importance of the 3Rs" (Congressional Record 1991). Second, the AWA regulations, especially §2.31, address the consideration of alternatives. Third, the PHS policy and US Principles include language that is supportive of the 3Rs principles (Bratcher and Reinhard 2015). Finally, the regulated community has acknowledged that the 3Rs are deeply ingrained in the AWA and laboratory animal practice. According to the group Speaking of Research, an advocacy organization that provides information about the importance of animal research in medical and veterinary science: "The 3Rs are implicit in the AWA and any scientist planning to use animals (except rats, mice, and birds, which are not included in the AWA) in their research must first demonstrate why there is no alternative; and that the number of animals used, and any suffering caused, will be kept to a minimum." (https://speakingofresearch.com/facts/animal-welfare-the-3rs/(last accessed 6 October 2016)).

Federal Legislation in Canada and The United States

Canada

A legal opinion obtained by the CCAC in 1998, Legislative Jurisdiction over Animals Used in Research, Teaching and Testing (Wilson 1998) and a study undertaken on behalf of Health Canada in 2000, The Protection of Animals Used for the Purpose of Xenotransplantation in Canada (Létourneau 2000), emphasized that the federal government cannot legislate to protect animals in science. According to the Constitution Act 1982 (Government of Canada 1982), the government of Canada cannot bring legislation if the provinces have already acted in the matter. However, there are three areas in which the federal government has taken action: criminal law power, health power, and spending power.

Criminal Code Canada

Sections 446 and 447 of the Criminal Code protect animals (not just research animals) from cruelty abuse and neglect (Government of Canada 1985). This section of the Criminal Code has been under review for several years. Despite many attempts to revise the Criminal Code in Canada, animals are still considered to be property in the current version (House of Commons 2005).

Health of Animals Act

The Health of Animals Act (Government of Canada 1990) and its regulations are focused primarily on Canadian livestock. The intent of the legislation is to protect livestock from infectious diseases that could endanger the health of the animals as well as people and could harm Canadian trade in livestock with other

countries. Under the Health of Animals Act, the Canadian Food Inspection Agency (CFIA) is responsible for testing, inspection, permit issuing, and quarantine activities for live animals (including research animals) imported to Canada.

Spending Power

While not, strictly speaking, legislative in nature, the federal government supports the humane treatment of animals through the use of its spending power. This enables the government to dictate the standards it expects for animal-based research.

Firstly, research grants awarded by the national granting councils are contingent on the home institution holding a CCAC Certificate of GAP-Good Animal Practice (Government of Canada 2015a). Secondly, where the government itself awards contracts for animal-based studies, clause A9015C of Public Works Standard Acquisition Clauses and Conditions Manual imposes conditions related to the care of research animals, including the requirement for the institution involved to hold a Certificate of GAP—Good Animal Practice (Government of Canada 2011).

United States

There are few, if any, criminal provisions under federal law that are directly applicable to research and testing involving animals. Neither the AWA or the Health Services Extension Act contains criminal provisions applicable to scientific research that is otherwise being carried out in accordance with these statutes and their regulations.

Most states have both civil and criminal provisions against animal cruelty. In two noteworthy cases arising out of the same set of facts, both a US federal court and a state court (Maryland) found that a scientific researcher was in violation of its state anti-cruelty laws and was convicted of violating Maryland's anti-cruelty act. On appeal, the Maryland Court of Appeals (the highest court in the state of Maryland) reversed the conviction, holding that Maryland's anti-cruelty statutes do not apply to an institution conducting medical research pursuant to a federal program (Taub 1983). The holding was substantially similar in a related federal case (International Primate Protection League 1986). As a result of these cases, and similar litigation, and because of specific statutory language in state anti-cruelty laws excluding scientific research (Reppy 2008), it would be very difficult to bring an action against a research facility or researcher in compliance with the US federal laws and regulations based on state anti-cruelty provisions.

In the US it is possible for the USDA to assess civil penalties under the AWA (see, for example, 7 USC §2149). Enforcement tools in the Health Research Extension Act seem more limited. This act does allow for the withdrawal of federal research funds in certain cases, but this provision is infrequently used.

Provincial/State Legislation in Canada and the United States

Canada

All Canadian provinces have some form of animal welfare legislation. Certain provinces have legislation or regulations pertinent to welfare as it relates to animal-based scientific activities within the province: Alberta, Manitoba, Ontario, Nova Scotia, Québec, and Prince Edward Island. Of the provinces listed, most make reference to compliance with CCAC standards in the regulations to their acts, details of which can be found on the CCAC website http://www.ccac.ca (last accessed July, 15, 2016). Ontario is different from the other provinces, in that it has a stand-alone Animals for Research Act (R.S.O 1990 c.a.22). This act requires research facilities to be registered and animal supply facilities to be licensed.

United States

In the United States, animals in research are regulated by the federal government under the AWA and Health Research Extension Act. The AWA requires the Secretary to "…cooperate with the officials of various States or political subdivisions thereof in carrying out the purposes of this chapter." This clause would appear to reserve to the states the authority to enact laws governing animal-based research (7 USC §2145(b)). However, to date, no state has enacted any such legislation and, in fact, many have largely sought to exempt federally regulated research facilities from state anti-cruelty laws (Reppy 2008).

The Use of Standards, Guidance Documents, and Policies

Canada

One of the first actions of the CCAC was to develop a set of standards for research animal ethics and care, based on the 1961 one-pager produced by Canadian Federation of Biological Societies (CFBS 1961). In 1968 the first edition of the CCAC Guide to the Care and Use of Experimental Animals was published. In 1993, the second edition was published (CCAC 1993), and subsequently, CCAC guidelines have been developed and continue to be developed and revised as smaller self-contained guidelines documents that can be updated more regularly (http://www.ccac.ca/en_/standards/guidelines (last accessed July 15, 2016)).

United States

The US Guide for the Care and Use of Laboratory Animals was first developed in 1963 (Zurlo et al. 1994, Appendix D). The guide has been updated frequently; its last update (8th edition) was in 2011 (NRC, 2011). The guide is used in the United States, and other places, as a floor to define minimal good laboratory practices and procedures. The guide is used in conjunction with sets of principles, such as the U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training (OLAW 2015) to establish acceptable practices in laboratories. The US Public Health Service Policy on Humane Care and Use of Laboratory Animals (OLAW 2015) also establishes that it is "the Policy of the Public Health Service (PHS) to require institutions to establish and maintain proper measures to ensure the appropriate care and use of all animals involved in research, research training, and biological testing activities (hereinafter referred to as "activities") conducted or supported by the PHS" (section I, Introduction). These supplement the federal laws and regulations discussed above.

In Canada, where there is no federal legislation pertaining to the oversight of animal-based science, reliance is placed on adherence to CCAC guidelines and policies, and these documents are therefore seen as providing the standards against which any charge of animal cruelty could be judged, whether at the federal level through the Criminal Code or the provincial level through the provincial animal welfare acts. In the United States, adherence to the US Guide is the manner in which the

legal provisions relating to laboratory animal care and use are implemented.

Performance versus Engineering Standards

In the United States, the standards for animal ethics and care are now mostly performance based, and in Canada there is a mix of performance and engineering standards. There has been an evolution over time, with the original CCAC Guide to the Care and Use of Experimental Animals and the US Guide for the Care and Use of Laboratory Animals being very much more prescriptive and providing "engineering standards," for example, in describing cage dimensions. The latest version of the US Guide for the Care and Use of Laboratory Animals (NRC 2011) is largely performance based. For example, the guide provides specific space requirements, and notes that specific space requirements are numbers (i.e., engineering standards). However, the guide goes on to explain that although the space requirements are numbers, they are used in a performance standards framework. In other words, these are not to be considered hard-and-fast rules. Professional judgment, advances in scientific understanding of housing needs, and other factors should be weighed in reaching performance-based goals (NRC 2011).

Scope of the Oversight of Animal-Based Research

Canada

The CCAC covers all vertebrates and cephalopods in animal-based science where the institutions are CCAC participants. The Ontario Animals for Research Act (R.S.O 1990, c.A.22), which covers all institutions in the province of Ontario carrying out animal-based scientific activities, extends to all nonhuman vertebrate animals. Some institutions in Canada are recipients of funding from the US NIH. For these institutions, the NIH accepts the CCAC Certificate of GAP-Good Animal Practice as assurance of the quality of animal care and use.

For the CCAC, participating institutions include all academic institutions, which are signatories to the federal granting Council's Agreement on the Administration of Agency Grants and Awards by Research Institutions (Government of Canada 2015a). Also included are government laboratories, both federal and provincial as well as private companies. Each science-based government department has a memorandum of understanding with the CCAC to ensure that their laboratories meet CCAC standards and that they hold a valid CCAC Certificate of GAP-Good Animal Practice. There is no legal or policy requirement for private sector companies to participate in the CCAC program. In theory, these companies could carry out animal-based research or testing without any oversight, except for inspection by provincial Societies for the Prevention of Cruelty to Animals, if there were grounds to suspect cruel treatment of the animals. However, most private companies do participate in the CCAC program and use the CCAC Certificate of GAP-Good Animal Practice as evidence of their corporate responsibility and commitment to animal ethics and care.

In Ontario, the Animals for Research Act (R.S.O 1990, c.A.22) applies to premises in the province carrying out animal-based research and includes premises for the collecting, assembling, or maintaining animals in connection with a research facility as well as supply facilities.

As far as the types of activities which are covered by the CCAC, these are outlined in the CCAC guidelines on: animal use protocol review (CCAC 1997a).

Animal-based studies fall into six main purposes described by the CCAC in the instructions document for completion of animal data reports (CCAC n.d.). These are referred to as Purposes of Animal Use (PAU).

> PAU 0: animals held in breeding colonies, or in holding protocols;
> PAU 1: studies of a fundamental nature ie, basic biomedical, biological or agricultural research;
> PAU 2: studies for medical purposes, include veterinary medicine related to human or animal disease, including applied research to develop therapies;
> PAU 3: studies for regulatory testing of products to protect humans, animals or the environment, including vaccine efficacy trials;
> PAU 4: studies for the development of products or appliances for human or veterinary medicine;
> PAU 5: education and training of individuals in post secondary institutions or facilities

The CCAC program does not extend to animals in primary or secondary education. In addition the CCAC program does not extend to animals that are being observed, provided that there is no impact on their normal behavior as a result of the presence of an observer. Nor does it extend to secondary use of animals or animal tissue (for example, fish obtained through commercial harvest or tissue obtained from slaughter houses, etc. [CCAC n.d.]).

United States

In the United States, the AWA defines an "animal" as:

"any live or dead dog, cat, nonhuman primate, guinea pig, hamster, rabbit, or any other warm-blooded animal, which is being used, or is intended for use for research, teaching, testing, experimentation, or exhibition purposes, or as a pet." (quoting 9 CFR §1.1). This definition has been controversial because it excludes "birds, rats of the genus Rattus, and mice or the genus Mus bred for use in research." (AWA, (1990); quoting 7 U.S.C. 2132(g))

The Health Research Extension Act (PL-99-158 1985) defines an animal as "[a]ny live, vertebrate animal used or intended for use in research, research training, experimentation, or biological testing or for related purposes" (Article III.A. of the Public Health Service Policy on Humane Care and Use of Animals [OLAW 2015]). In other words, it does not exclude rats, mice, and birds bred for use in research.

The US Guide defines the term "laboratory animal" as "any vertebrate animal (i.e., traditional laboratory animals, agricultural animals, wildlife, and aquatic species) produced for or used in research, testing, or teaching" (NRC 2011). This definition is not intended to limit the applicability of the guide; later chapters note that the principles set forth can be applied to invertebrate creatures (NRC 2011, see chapter 3).

The implications of the differences in the framework for oversight result in somewhat different approaches employed at the institutional level, for internal oversight of animal-based research, in order to provide external accountability. In Canada, assessment visits ensure that CCAC guidelines and policies are implemented in institutional animal ethics and care programs as recognized by the issuance of a Certificate of Good Animal Practice (CCAC 2016); however, because the visits are formative, there is strong encouragement and support for institutions to

improve standards of animal-based ethics and care. In the United States, the Health Extension Act requires approval of an Assurance by the Public Health Service prior to commencement of any animal activities, and this Assurance must be renewed every 5 years, with an annual report to the Office of Laboratory Animal Welfare. The United States approach tends to be more focused on meeting the requirements and continuance of the assurance.

Key Features of the Systems of Laws, Policies, and Regulations in Canada and the United States

In the sections that follow, we set out key features of the systems that control animal use in research. These are based on the components identified by the World Organisation for Animal Health (OIE) as regulatory requirements for a national system to oversee animal-based research (OIE 2016).

In both Canada and the United States, considerable responsibility is placed on the local ACC (Canada) or IACUC (US).

Canada

Institutions that hold a CCAC Certificate of GAP-Good Animal Practice® are required to establish an ACC according to the CCAC Policy Statement on Terms of Reference for Animal Care Committees (CCAC 2006). The composition of ACCs should include scientists or teachers involved in animal-based research or teaching, veterinarian(s) responsible for caring for the institution's animals, scientists not involved in any animal-based research or teaching, one or more community representatives, technical staff representative, students (where appropriate), and the ACC coordinator who provides the administrative support.

ACCs are responsible for protocol review and approval and follow-up (post approval monitoring). In addition, ACCs are responsible for working with their institution's administration to ensure that appropriate facilities are being used and are well maintained and managed and that veterinary and animal care services, continuing education and training programs, and occupational health and safety and crisis management programs are all in place.

United States

The establishment of IACUCs was one of the central tenets of the 1985 amendments to the AWA and the Health Research Extension Act. The IACUC provisions of these two laws are very similar. Under the AWA (7 USC §§2143(b) and (c)) each research facility must have at least one IACUC. The IACUC members must be appointed by the chief executive officer of the facility and must have at least three members who can (1) assess the animal care, treatment, and practice needs of the facility, and (2) represent society's concerns regarding the welfare of the animals used at the facility. The IACUC must have at least one veterinarian (who holds a doctor of veterinary medicine) and at least one member who is not affiliated with the facility. If the IACUC has more than three members, not more than three can be from the same administrative unit within the facility.

Under the Health Research Extension Act, IACUCs are required to have three members. The PHS policy requires five members, including (1) a veterinarian with training in laboratory animal science, (2) a researcher who is experienced in using animals, (3) a nonscientist member (e.g., clergy, lawyer), and (4) a person who is not affiliated with the institution, except as an IACUC member (IV.A.3 of Public Health Service Policy on Humane Care and Use of Laboratory Animals). Section IV.A.1. of this Public Health Service Policy also specifies that these IACUCs must follow the guide as a basis for developing and implementing their program.

Authorization of Proposed Animal Activities

Canada

In Canada, authorization of proposed animal-based activities (or protocols) is the responsibility of the local (institutional) ACC. The CCAC provides guidance on the level of invasiveness of protocols (CCAC 1991) to indicate which studies require review and to categorize the studies so that the animals can be properly monitored and cared for, and so that the numbers of animals and the potential pain and distress experienced is reported to the CCAC in a consistent fashion for inclusion in the annual animal data report.

In providing for the authorization of protocols, the CCAC policy for senior administrators responsible for animal ethics and care programs (CCAC 2008) describes the institutional officials' responsibility to (1) put mechanisms in place to ensure that the proposed animal-based work has merit; and (2) ensure that one (or more) appropriately composed and structured and well-functioning ACC(s) is (are) in place for the institution, according to the most recent version of the CCAC policy statement on: terms of reference for animal care committees (CCAC 2006) and that this (these) committee(s) is (are) provided with sufficient, qualified human resources to function appropriately and effectively and ensure compliance with all relevant standards.

There are currently five distinct categories of invasiveness ranging from A (the lease severe) to E (the most severe):

A—invertebrates or live isolates (no capacity to experience pain and distress)
B—little or no discomfort or stress
C—minor stress or pain of short duration
D—moderate to severe distress or discomfort
E—severe pain near, at, or above the pain tolerance threshold of unanesthetized conscious animals

In reviewing the protocols, the CCAC guidelines on: animal use protocol review (CCAC 1997a) provides a list of the elements that ACC should consider.

The CCAC policy statement on terms of reference for animal care committees (CCAC 2006) also requires ACCs to ensure that those carrying out the procedures are listed on the animal-based protocols and are competent (CCAC guidelines on: training for personnel working with animals; CCAC 2015).

United States

Both the AWA as well as the Health Research Extension Act require the local IACUCs to review animal-based activities, including research proposals. Under the AWA, it is the responsibility of the IACUC to review those components of the activity that address the care and use of animals and decide whether the activity conforms to the AWA's laws and regulations (9 CFR§2.31 (d)). The specific requirements are set out in detail in the AWA regulations and are very similar to the CCAC review requirements. They include review of (1) procedures to

minimize pain and distress, (2) the consideration of alternatives, (3) assurances that the procedure is not duplicative, (4) the use of analgesics and anesthetics when necessary, and (5) appropriate living conditions and medical care for the animals (9 CFR §2.31 (d)(1)(i—xi)). The Health Research Extension Act requires that each institution that receives funds to be used for animal research provide an assurance to the Director of the NIH that the institution provides appropriate animal care and treatment, which includes the use of analgesics and anesthetics when necessary and appropriate veterinary care (42 USC §289d (c)).

The AWA regulations define "painful procedure" as any procedure done on an animal that, if done on humans, would cause more than momentary or slight pain or distress (9 CFR §1.1). Facilities are required to prepare an annual report that contains information about pain and distress. According the the AWA regulations (9 CFR §2.36), all facilities must assure that each principal investigator has considered alternatives to painful procedure, and that any exceptions to standards and regulations under the AWA (such as the failure to alleviate pain and distress) are fully explained by the investigator and approved by the IACUC, and a summary of all exceptions attached to the report. The USDA's "Policy 11" (available at https://www.nal.usda.gov/sites/default/files/Policy11_0.pdf, last accessed 15 July 2016) expands upon the AWA law and regulations. Facilities are required to report to the USDA by category the number of animals used that (1) are subject to only minimal, or no, pain and distress (category C); (2) are subject to more than minimal pain and distress, but such pain and distress is alleviated with appropriate drugs (category D); (3) are subject to more than minimal pain and distress that is not alleviated (category E). Studies that report animals in category E are required to provide detailed scientific justification to the IACUC and must be explained in a separate attachment to the annual report (Brown and Gibson 2009).

Principle V of the US Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training requires that procedures that create more than momentary or slight pain or distress should be performed with appropriate analgesia or pain killers. The Public Health Service Policy on Humane Care and Use of Laboratory Animals makes it the responsibility of IACUCs to minimize or eliminate pain and distress, consistent with the provisions of the policy and the Guide for the Care and Use of Laboratory Animals (see IV). A detailed discussion regarding pain and distress evaluation and management is contained in chapter 4 of the guide (NRC 2011).

Ethical Evaluation

Canada

As part of the authorization of protocols, ACCs are expected to carry out an ethical evaluation of the proposed study based on the CCAC guidelines on: animal use protocol review (CCAC 1997a). As described above, before an ACC can review a protocol, there must be evidence of scientific, pedagogical, or regulatory merit. This may be provided by the peer review of a granting agency; however, where this does not exist, the ACC must have an independent peer review mechanism incorporating appropriate expertise to establish scientific merit. Similarly, for animal-based teaching, the pedagogical merit of the teaching protocol should have been evaluated independently. For animal-based testing, the ACC should assure itself that the study has been planned according to the most current regulatory requirements acceptable to the relevant regulatory agency.

For ACCs to make sound decisions on the ethical acceptability of an animal-based study, the CCAC expects animal-based protocols to include the following components:

- the project title and descriptive procedures
- name of the principal investigator and all personnel who will be handling the animals, along with their training qualifications
- department affiliation
- proposed start and end dates; funding sources
- an indication of scientific or pedagogical merit, or regulatory requirement
- lay summary
- indication of the use of hazardous materials, with institutional approvals
- category of invasiveness
- evidence of addressing the Three Rs
- description and time course of procedures
- description of endpoints
- description of capture, etc. (for field studies)
- method of euthanasia
- ultimate fate of the animals
- other relevant information (e.g., previous studies)

Decisions on the acceptability of a protocol are generally taken by consensus of the ACC members.

The Ontario Animals for Research Act also requires that ACCs within a registered research facility coordinate and review:

- the activities and procedures relating to the care of the animals
- the standards of care and facilities for animals
- the training and qualifications of personnel that are engaged in the care of animals
- procedures for the prevention of unnecessary pain, including the use of anesthetics and analgesics

United States

Neither the AWA nor the Health Research Extension Act require that IACUCs carry out an ethical review of any animal-based activity, including research protocols, or project. The AWA regulations state that IACUCs should focus on the parts of the activities that cover animal care and use, and the Health Research Extension Act contains similar language but refers to proposed research projects (9 CFR §2.31 (d)(1) and 42 USC 289d (b)(3)). The guide includes statements about the ethical duties of researchers who use animals, and the ethics underlying certain decisions, such as use of analgesics, pain killers, and anesthesia (NRC 2011).

Review of Experimental Procedures

Canada

Before any experimental procedure is carried out, it must be approved by an ACC protocol, according to the CCAC guidelines on: animal use protocol review (CCAC 1997a). The CCAC's overarching policy statement on the ethics of animal investigation (CCAC 1989a) requires that the possibility for the use of nonanimal models has been taken into consideration in planning the protocol, that the appropriate number of animals will be used,

and that any potential pain and/or distress will be minimized as far as possible, thus implementing the principles of the Three Rs.

Animal protocols are assigned a category of invasiveness at the time of protocol approval based on the potential pain and distress to be experienced by the animals. This assignment is prospective and is based on the worst case scenario. So, for example, in a dose-response study, many of the animals receiving low doses of a compound would not experience any pain or distress, despite the protocol being rated at a high level of invasiveness.

United States

All activities or proposed research projects that involve animals (as that term is defined in each individual statute) require review and approval by an IACUC.

The AWA regulations (9 CFR §§2.31(c) and (d)) set out in detail the function and review responsibilities of IACUCs. The AWA law and regulations focus IACUC activities on "those components … related to the care and use of animals and determine that the proposed activities are in accordance with" the AWA regulations, unless an acceptable justification is provided in writing (CFR §2.31(d)(1)). These IACUCs must evaluate activities to make sure that:

- procedures will avoid or minimize discomfort, distress, and pain
- the principal investigator has considered alternatives (and provided a written narrative description of the methods and sources) to procedures that could cause more than momentary or slight pain or distress
- procedures will not unnecessarily duplicate previous experiments
- procedures that could cause more than momentary pain are performed with appropriate drugs to relieve this pain, unless withholding these drugs is justified for scientific reasons
- the attending veterinarian is consulted
- housing and living conditions are species appropriate
- medical care is available and appropriate

In addition, if surgery is to be performed, appropriate preoperative, operative, and postoperative care (in accordance with good veterinary practice) must be provided. For animals that experience severe or chronic pain, the proposal must provide that the animals will be painlessly euthanized at the end of the procedure or, if appropriate, during the procedure. Certain changes in a protocol that significantly impact animal welfare after the research has begun must also be reported to, and approved by, an IACUC. In some situations, the IACUC can adopt policies to allow a veterinarian to change the methods of euthanasia without additional IACUC review, as long as such changes are compliant with the AVMA Guidelines (http://grants.nih.gov/grants/olaw/significant_changes.htm (last accessed 6 October 2016).

The Health Research Extension Act (42 USC §289d(b)) requires that all facilities establish IACUCs that receive funding from the Public Health Service (which includes the NIH) to carry out research in animals. These IACUCs must assure compliance with the NIH guidelines.

In practice, it appears that institutions that must comply with both the AWA and Health Research Extension Act (and those institutions seeking accreditation from the AAALAC International) do not create separate IACUCs for each law. Instead, a facility will create one (or more) IACUCs that meet the statutory and regulatory requirements of both laws (Borkowski et al. 1997).

Assurance of Training and Competency

Canada

In Canada, the CCAC guidelines on: training of personnel working with animals (CCAC 2015) makes it a requirement for all personnel from institutions participating in the CCAC program and who are involved in animal-based studies to be trained in the principles of animal ethics and care. These personnel (including investigators, graduate students, postdoctoral fellows, research staff, study directors, animal health professionals, animal care committee members, and institutional officials) have different educational and training needs. To meet these needs, the CCAC offers a variety of educational and reference materials or makes materials available through external links. These include a training syllabus, training modules, workshops, and web-based seminars.

For those involved in the conduct of animal-based studies (rather than the care of the animals), that is, investigators, graduate students, postdoctoral fellows, research staff, study directors, etc., the CCAC provides access to training modules to support the recommended syllabus for an institutional animal user training program. Institutions can choose whether to use these training modules as part of the theoretical training. However, institutions are expected to provide practical hands-on training as appropriate to ensure that personnel are competent to carry out animal-based procedures required for their studies. The CCAC guidelines focus on the establishment of competency. Institutions are expected to have a system in place to establish, assess, and maintain records of competency for those working with animals: investigators, graduate students, postdoctoral fellows, research staff, and study directors.

United States

Both the AWA and Health Research Extension Act require that the animal researcher, and any staff handling or responsible for animals, are trained to perform their duties. It is the responsibility of the facility and institution to provide this training and to make sure that personnel are instructed properly. Under the AWA, training must include instruction about humane methods of animal maintenance and experimentation, the basic needs of each species being used, proper use of analgesics and anesthetics, and several other areas. The Health Research Extension Act requires that institutions have appropriate training available as part of the assurance it provides to the NIH (9 CFR §2.32 and 42 USC 289d (c)(1)(B)). The guide stresses training, too, and provides considerable detail about the nature and type of training that is required (NRC 2011, p 15–17).

Provision of Veterinary Care

Canada

The CCAC requires institutions in its program to provide adequate veterinary care for all animals maintained within the institution. The Canadian Association for Laboratory Animal Medicine/L'association canadienne de la médecine des animaux de laboratoire (CALAM/ACMAL) Standards of Veterinary Care (CALAM 2007) are the national standards recognized by the CCAC. The CALAM/ACMAL Standards include the CALAM/ACMAL Position on Standards of Veterinary Care, which states

that "a veterinarian with authority and responsibility for supporting an institutional animal care and use program must be involved in all issues and activities that relate in any way to animal care and use."

As, in general, veterinarians are liable for the use of pharmaceuticals dispensed for veterinary care, the CALAM/ACMAL standards emphasize that the veterinarian should be part of the research team, particularly where they have prescribed pharmaceuticals for the use of investigators and/or when medical or surgical procedures are involved. Although the CCAC encourages veterinarians to maintain licensing under the relevant provincial veterinary acts, this is not currently a CCAC requirement.

The Ontario Animals for Research Act (R.S.O 1990, c.A.22) states that "the Lieutenant Governor in Council may make regulations…classifying research facilities, requiring the operators of any class of research facility to provide for the services of a veterinarian in connection with the care of animals in the research facility and prescribing the terms and conditions on which such services shall be provided in respect to any such class." At present, regulations in respect of veterinary services have yet to be made.

United States

The AWA as well as the guide stress veterinary care as a central tenet of animal research programs. The AWA regulations (9 CFR §2.33) require that every research facility have an attending veterinarian and furthermore that the attending veterinarian has the authority to ensure appropriate care and oversee animal care and use. The attending veterinarian must be a voting member of the IACUC. While the Health Research Extension Act does not specifically discuss veterinary care, the Public Health Service Policy on Humane Care and Use of Laboratory Animals requires that institutions comply with the guide as part of their assurance to the NIH. The guide stresses the role of the attending veterinarian in animal care and use programs (NRC 2011, chapter 2) and endorses the American College of Laboratory Animal Medicine's "Guidelines for Adequate Veterinary Care" (ACLAM n.d.).

Source of Animals

Canada

The CCAC guidelines on: procurement of animals used in science (CCAC 2007) describes the expected conditions for the acquisition of animals destined for animal-based studies. Institutions are encouraged to obtain animals from reputable suppliers, in preference to breeding in-house, to minimize the number of animals. They are also encouraged to visit suppliers where possible to provide quality assurance of the suppliers' processes and practices. Reputable suppliers should be able to provide detailed information about the health status of the animals.

In Ontario, it is illegal under the Animals for Research Act (R.S.O 1990, c.A.22) to obtain animals for research, teaching, or testing from pet stores, unless a person wishes to purchase or otherwise acquire an animal for use in a research facility and the animals is not of a type that may be readily purchased or otherwise acquired under the act by reason of its species or strain or by reason of any specific disease or condition desired of the animal.

Similarly, where possible, institutions are expected to purchase purpose—bred animals. However, for some activities, for example, training veterinary technicians and veterinary students or where a particular size or breed of animal is required, nonpurpose-bred animals may be acquired.

United States

Under the AWA, obtaining animals for research is tightly regulated. The AWA makes it unlawful for any animal to be sold or transferred in commerce unless the dealer has a license issued by the USDA (7 USC §§ 2133 and 2134). To obtain a license, a dealer must meet stringent standards of humane care, handling, and treatment, including requirements for:

- animal handling, housing, feeding, ventilation, sanitation, and watering
- separation by species, when deemed necessary by the USDA
- exercise for dogs and psychological well-being of primates (7 USC §2143(a))

In addition, dealers must keep records about animal sales (7 USC §2140(a)). The USDA has promulgated detailed regulations for licensure. These regulations can be found at 9 CFR Subchapter A, Part 2.

For laboratory animals, dealers are divided into two classes. Class A dealers produce animals that are specifically bred for research. These purpose-bred animals are mostly rodents, which include hamsters, guinea pigs, and rats and mice (for which no licence is required). Class B dealers sell "random source" animals—those that have not been purpose bred for research. These animals come from the general population, such as individual owners, hobby breeders, pounds, and shelters (NRC 2009). The USDA regulations contain specific requirements that cover how class B dealers can acquire live, random-source dogs and cats (9 CFR §§2.132 & 2.133). Both types of dealers are subject to licensure by the USDA and must comply with strict licensing standards.

The majority of animals used in research facilities are obtained from class A dealers. As of 2007-2008, only a very small percent of research animals were obtained from class B dealers. In 2012 the NIH stopped funding research on random-source cats and in 2014 funding was stopped for research on random-source dogs, based on the recommendations of the National Academies report (NRC 2009).

Disposition of Animals

Canada

Reuse of animals is within the Canadian system, as described in the CCAC guidelines on: procurement of animals used in science (CCAC 2007). Whether within an institution, or transferring between institutions, the transportation must comply with the CFIA Health of Animals Regulations, and any relevant provincial acts and regulations (http://ccac.ca/en_/training/niaut/stream/cs-guidelines for a list of the relevant provincial acts). Documentation should accompany the animal detailing the original source and the history of the animal (e.g., conditioning, housing, nutrition, previous studies, etc.). Where animals are being transferred between facilities a health certificate should be provided. In general, animals are not permitted to be involved in a second study if they have been subjected to invasive procedures.

Setting Free/Rehoming

During the preparation of an animal-based protocol, investigators are required to indicate the intention for the disposition of

the animals at the end of the study. In general, rehoming of laboratory animals is not encouraged; however, some Canadian institutions have rehoming programs in place, particularly for cats and dogs.

United States

The provisions regarding animal reuse in the United States are similar to the provisions applied in Canada. Facility IACUCs are most likely to be confronted with questions about animal reuse. Generally, for humane reasons, reuse of animals is not favored, especially if an animal has undergone invasive surgery or procedures (NRC 2011, p 5). State laws allowing for adoption programs for dogs and cats used in research have been enacted in California (see Bill number AB 147, amending section 66017.7of the Education Code), Nevada (Bill number SB 261). Several other states are either considering such laws or have passed similar measures.

Euthanasia

Canada

The CCAC guidelines on: euthanasia of animals used in science (CCAC 2010) provide the general principles for euthanasia. These are based on the recommendations made by the International Council for Laboratory Animal Science Working Group on Harmonization (Demers et al. 2006) and the two international reference documents on euthanasia recommended by International Council for Laboratory Animal Science: the American Veterinary Medical Association (AVMA) Guidelines on Euthanasia (American Veterinary Medical Association 2007) and Recommendations for Euthanasia of Experimental Animals Part 1 and Part 2 (Close et al. 1996, 1997), with some modifications to fit the Canadian context. An overview of acceptable methods of euthanasia as well as conditionally acceptable methods is included. These latter methods require approval by the ACC to ensure that they comply with the general principles. Additional information on the impact of research data is available on the website, as often the method to be used is dictated by the particular goal of the study.

The Ontario Animals for Research Act (R.S.O 1990, c.A.22) has specific provisions for euthanasia in regulation 24 "Research Facilities and Supply Facilities," requiring personnel to be trained in the procedures to be used; that the death of the animal occurs without unnecessary pain, delay, or discomfort; and that other animals in the facility are not endangered or disturbed. Only methods of euthanasia listed in the regulations may be used; however, some of the methods listed in the Ontario Act are no longer considered to be acceptable by the CCAC (e.g., the use of chloral hydrate).

United States

Both the AWA and Health Research Extension Act address euthanasia and require that it be humane and without pain (except in special circumstances; see 9 CFR §1.1 and §2.31(d)(ix)). Exceptions can be made for scientific reasons and approved by the IACUC, but these should be justified by the investigator in writing. Recommendations of the AVMA (AVMA 2013) should be followed. The AWA regulations define euthanasia as "the humane destruction of an animals accomplished by a method that produces rapid unconsciousness and subsequent death without evidence of pain or distress" (9 CFR §1.1).

The Health Research Extension Act requires the NIH to establish guidelines on the appropriate methods of euthanasia. (42 USC §289(d)(a)2(A)). The Public Health Service Policy on Humane Care and Use of Laboratory Animals also requires that animals that would experience unrelieved severe or chronic pain or distress must be painlessly killed at the end of the procedure or, if appropriate, during the procedure (C.1.c).

Transportation

Canada

The CFIA is responsible for the humane transportation of animals in Canada under the Health of Animals Act (Government of Canada 1990). This act requires the provision of food, water, rest, protection from adverse weather, use of proper containers and transport vehicles, and segregation of incompatible animals. The act, which is primarily focused on livestock, requires that livestock, poultry, animal embryos, and animal semen exported from Canada be accompanied by a health certificate provided by a CFIA inspector. The CFIA is also responsible under the act for testing, inspection, permit issuing, and quarantine activities for live animals imported to Canada. Guidelines for transportation of animals covered by the CCAC program can be found in the CCAC guidelines on: procurement of animals used in science (CCAC 2007). The transportation section of this guideline document is based on recommendations made by the US NRC Guidelines for the Humane Transportation of Research Animals (NRC 2006) and the UK Laboratory Animal Science Association Guidance on the Transport of laboratory Animals (Swallow et al. 2005). As these documents are focused on animals typically housed in vivaria, there are also recommendations regarding the transportation of farm animals and of fish to be found in the CCAC guidelines on: the care and use of farm animals in research, teaching, and testing (CCAC 2009) and the CCAC guidelines on: the care and use of fish in research, teaching, and testing (CCAC 2005), respectively.

The Ontario Animals for Research Act (R.S.O 1990, c.A.22) also includes regulations specific to transportation of animals destined for research. The regulations refer to the transportation vehicles, primary containers for the animals, feed, water, length of transportation, and requirements for personnel to accompany the animals and to receive the animals at their destination.

United States

Transportation of laboratory animals is subject to control by several US federal and state agencies. As explained in the guide:

"Transportation of animals is governed by a number of US regulatory agencies and international bodies. The Animal Welfare Regulations (USDA 1985) set standards for interstate and export/import transportation of regulated species; the International Air Transport Association (IATA) updates the Live Animals Regulations annually and IATA member airlines and many countries agree to comply with these regulations to ensure the safe and humane transport of animals by air (IATA 2016). The Centers for Disease Control and Prevention and USDA enforce regulations to prevent the introduction, transmission, or spread of communicable diseases and regulate the importation of any animal or animal product capable of carrying a zoonotic disease. The US Fish and Wildlife

Service regulates importation/exportation of wild vertebrate and invertebrate animals and their tissues. As the national authority arm of the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES), the US Fish and Wildlife Service also regulates movement of CITES-listed species that are captive bred, including nonhuman primates (DOI 2007)" (NRC 2011, p 117).

A complete description of the laws and regulations relating to transportation is beyond the scope of this article. In this section, we focus on the transportation requirements of the AWA and Health Research Extension Act and its related policies and principles.

The AWA requires that the USDA promulgate regulations that govern the transportation and humane care and handling of animals. The regulations must assure the humane treatment of the animals during transportation. See 7 USC §2143(a)(4). These regulations, found at 9 CFR Part 3, cover handling, care, treatment, and transportation of animals on a species-by-species basis. The Health Research Extension Act does not directly address transportation. However, the US Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training require that institutions assure that the transportation of animals complies with the AWA and other applicable federal laws (Principle I). Chapter 4 of the Guide contains further recommendations about transporting animals (NRC 2011).

Physical Facility, Animal Husbandry, and Environment

Canada

The basic requirements for a laboratory animal facility are included in the CCAC guidelines on: laboratory animal facilities—characteristics, design, and development (CCAC 2003). Where there are specific requirements for certain species, these are included in the species-specific guidelines. In particular, requirements for the facilities for farm animals and for fish are included in the relevant guidelines, recognizing that requirements for facilities focused on agricultural or aquaculture research can be quite different from facilities where fundamental biological or biomedical research is conducted.

Where either animal or human pathogens are involved in the research activities, the Public Health Agency of Canada in collaboration with the Canadian Food Inspection Agency has developed and maintains the Canadian Biosafety Standards (Government of Canada 2015a, 2015b) and Canadian Biosafety Handbook (Government of Canada 2016). The standards and handbook assist in compliance with the Public Health Agency of Canada Act (Canada 2006) by providing current standards and guidelines for the design, construction, and operation of facilities in which pathogens or toxins are handled or stored.

The general principles for husbandry of animals maintained in laboratory animal facilities are included in the CCAC guidelines on husbandry (in preparation). Details concerning the husbandry of different types of animals are included in the genus-specific guidelines. The CCAC guidelines focus primarily on meeting the physical and psychological needs of the animals, which is required by the CCAC policy statement on: the social and behavioral needs of experimental animals (CCAC 1989b). There never has been a strong focus on enclosure dimensions, so where cage sizes are included they are seen as minimum performance-based requirements, with the expectation that institutions will strive to improve the housing conditions for the animals in their care. Institutions are encouraged to enhance the animals' environment, not just through increasing available space, but also by opportunities to stimulate their physical and mental capacities. This reflects the CCAC's general approach to the development of guidelines. The guidelines are intended to provide the framework for the implementation of good animal practices, which encourage evidence-based refinements to animal care as well as to animal-based procedures.

General requirements for husbandry are also included in the Ontario Animals for Research Act (R.S.O 1990, c.A.22)

United States

The AWA requires that animals used in research must be housed, treated, and maintained in ways that promote humane care and treatment (7 USC §2131 and 42 USC 289d (a)). The AWA regulations, especially 9 CFR Part 3, contain detailed species-by-species standards regarding housing facilities, exercise requirements, enclosures, environmental enhancement, and space requirements. Chapter 3 of the guide also provides significant detail about housing needs, and covers both terrestrial and aquatic animals (NRC 2011).

Facility Inspection

Canada

The CCAC carries out assessments of institutions generally every 3 years. Because the CCAC program is peer-based, CCAC assessment visits are by assessment panels which include a scientist and a veterinarian with expertise in the scientific areas covered by the institution and a community representative. The assessment panels are accompanied by a CCAC associate director of assessment (http://www.ccac.ca/en_/assessment, (last accessed July 11, 2016).

When conducting a visit, the structure and resources of the animal ethics and care program, the composition, functioning and effectiveness of the ACC, and the appropriateness of animal care and animal-based practices are all assessed as well as all relevant animal facilities. As part of the preassessment documentation, the institution to be assessed must include reports of their (6-monthly) site visits to the animal facilities within their institution.

The Ontario for Research Act (R.S.O 1990, c.A.22) requires all research premises to be licensed, and inspections are carried out by the Ontario Ministry for Food and Rural Affairs inspector unannounced.

United States

In the United States, inspections of facilities covered under the AWA are carried out by US Department of Agriculture inspectors. These inspectors conduct field investigations and prepare reports, which document items of noncompliance that are then examined by the USDA's Animal and Plant Health Inspection Service (APHIS). If APHIS determines that there has been an instance of noncompliance, it can take a number steps to ensure the Act is enforced (https://www.aphis.usda.gov/aphis/ourfocus/business-services/ies (last accessed 29 June 2016). Both the AWA and the Health Research Extension Act require that the local IACUCs carry out an inspection at least once every 6 months. In addition, under both the AWA and the Health Research Extension Act, each facility must make

available the annual report to APHIS and to the Office of Laboratory Animal Welfare (OLAW) at the NIH. Under the AWA, each facility is required to submit an annual report that must include assurances that (1) the facility followed professionally accepted standards governing the care, use, and treatment of animals; (2) each PI has considered alternatives to painful procedures; and (3) the facility is adhering to the AWA and its regulations. Additional reporting requirements regarding pain and distress are also required (9 CFR §2.36). The IACUC must also report semiannually to the institutional official about any deviations from the AWA law and regulations, and distinguish major from minor deficiencies (9 CFR §2.31). Under the Health Research Extension Act, IACUCs must report to OLAW any serious or continuing noncompliance with the Public Health Service Policy on Humane Care and Use of Animals, any serious deviation from the provisions of the guide, or any suspension of an activity by an IACUC (Public Health Service Policy on Humane Care and Use of Animals, section IV.F., [OLAW, 2015]).

Conclusions

Both Canadian and US approaches to ensure laboratory animal welfare seek to implement the 3Rs principles that were first postulated by Russell and Burch in 1959. It is clear, however, that the path toward 3Rs implementation differs in each nation. In reviewing the laws, regulations, policies, and guidelines that underlie the oversight of animals in Canada and the United States, we have identified some of the key differences and similarities in each approach. The evolution of each system is likely a reflection of the cultural differences between the two countries. The United States has developed a more hierarchical and centralized legal framework, largely as a result of its Constitution, public pressure, and its tradition of federalism. Nonlegislative tools, such as the Guide for the Care and Use of Laboratory Animals, can be useful in implementing the some of the requirements of the US federal laws.

In Canada, with its decentralized federation and smaller population base, the concept of social contracts has resulted in less reliance on legislation and a greater emphasis on nonlegislative tools such as regulations, policies, guidelines, and funding requirements. Both the Canadian and US approaches depend to a considerable extent on assertive facility self-regulation. Because the fields of laboratory animal research and laboratory animal welfare can change rapidly, flexibility at a facility level provides an advantage in that it allows for the more rapid integration of evolving science than traditional "command and control" regulation and legislation. However, at least in the United States, this flexibility has been critiqued on several grounds. First, it has been pointed out that IACUCS are often insular and that it can be very difficult, and sometimes impossible, to determine how they operate. Second, critics have alleged that enforcement of the AWA is hampered by a number of factors, including the broad discretion given to IACUCs and failure to provide standing for citizens to bring lawsuits (Swanson 2002). Third, it has been noted that the AWA does not offer protection for rats, mice and birds bred for research purposes, because the definition of "animal" does not cover them. Accordingly, the AWA is not applicable to the majority of animals used in research.

In Canada, only the province of Ontario has enacted legislation in relation to animals in research, the animal welfare acts in some of the other provinces also refer to compliance with CCAC guidelines and policies within the regulations to the act. Therefore, in theory, failure to comply with these commonly accepted standards could lead to cruelty charges being laid. In the US, state anti-cruelty laws have not been used successfully to prosecute animal research facilities that are in compliance with federal laws and regulations.

In the United States, the two major federal laws that are applicable to animals in research are the AWA and the Health Research Extension Act. Of the two, the AWA is a more traditional administrative law under which the USDA has promulgated regulations applying to research facilities, animal dealers, transportation, and a host of other related activities. The Health Research Extension Act relies on a series of policies for implementation, especially the Public Health Service Policy on Humane Care and Use of Laboratory Animals and the US Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training. The Guide for the Care and Use of Laboratory Animals (NRC 2011) functions as the basic "playbook" for more detailed advice and the structuring of animal care and welfare programs at institutions. A number of other policies and guidance documents, especially those adopted by the US Department of Health, National Institutes of Health, play an important role in US animal research control.

In Canada, where there is no federal legislation, the CCAC guidelines and policies provide the standards which institutions and their personnel involved in animal-based science must conduct themselves. In both the United States and Canada, failure to meet acceptable standards can result in loss of federal research funding, and additionally in the United States can also lead to other sanctions under the AWA and other federal laws.

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