

U.S. perspective on the "consideration of alternatives" regulatory requirement

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Abstract

In the United States, the requirement to consider alternatives to painful and distressful procedures was made law by Congress in the 1985 amendments to the Animal Welfare Act. This session will present the historical perspective on development and intent of this law.

The regulation interpreting the law was finalized in 1989. Correspondence, policies and worksheets have been written to provide additional clarification regarding regulatory compliance expectancies, and examples of these will be provided.

Lastly, this session will present a review on the methods used in the U.S. to promote consideration, acceptance and use of alternatives.

Keywords: laboratory animals, alternatives, regulations

Introduction: History

The Laboratory Animal Welfare Act was enacted in 1966 in response to public concern regarding the acquisition of animals used in research laboratories. It initially covered only six species (dogs, cats, nonhuman primates, guinea pigs, hamsters and rabbits) and it focused on identification and recordkeeping requirements.

The name was later broadened to the "Animal Welfare Act" after amendments in 1970 and 1976 brought commercial carriers and exhibitors under regulation. It was amended again in 1985 in response to public concern regarding the care and treatment of animals used in research, experimentation, teaching and testing. Several incidents in the early 1980s, including the "Silver Spring" monkeys and the head trauma experiments at the University of Pennsylvania, made headlines and garnered the attention of Congress. Especially evident was the public's desire to minimize pain and distress inflicted upon animals used in research (Kulpa-Eddy, 2005). While Congress recognized that the use of animals is instrumental in certain research and education for advancing knowledge, they also recognized that measures which help meet the public concern for laboratory animal care and treatment are important (US Public Law, 1985).

These measures include the requirement that

researchers consider alternatives to any procedure likely to cause pain to, or distress in, an experimental animal. Congress established an information service at the National Agricultural Library to provide such information on improved methods of animal experimentation. It was also hoped this information would lead to an end to the much wasteful duplication that seemed to be occurring in animal research (US House Hearings, 1984).

The term "alternative" was not defined in the Animal Welfare Act, but the concept of the "3 Rs" (replacement, refinement, reduction) was evident in hearings held on the matter and also in the text of the 1985 amendments. Hearings before the US House of Representatives in 1981 opened with a statement from Rep. Walgren who said "This hearing is not simply on the question of how animals are treated and cared for by scientists. We are exploring the more difficult question of when and under what circumstances the use of live animals is justified." He identified several questions to which Congress sought answers and concluded by saying "I believe that everyone, scientists and nonscientists alike, should have the same goals in mind. The first of these goals is to reduce as much as possible the number of animals used in research and testing by placing emphasis on alternatives to animal use, and secondly, by giving more thought to the limited circumstances when the

use of animals may be justified. And third, we need to make sure that the proper conditions for their treatment and care exist when animals must, under those circumstances, be used." (US House Hearings, 1981).

In fact, much was made of scientific advances occurring at the time that seemed to predict that animals would soon no longer be needed. For example, Congressman Roe stated during the 1981 hearings that "The Ames test takes from 48 to 72 hours and costs a few hundred dollars, whereas a similar animal test takes 2 to 3 years and costs at least \$150,000. The Ames test disclosed the chemical dangers in the fire retardant fabric Tris more than a year before the U.S. Consumer Products Safety Commission ordered the removal of 20 million children's sleeping garments from the market on the basis of animal tests." (US House Hearings, 1981). Examples such as computer simulations, cell cultures, and bacterial and other non-animal models certainly focused on replacement. Refinement was represented by an interest in the use of anesthetics, analgesics and tranquilizing drugs, or euthanasia when animals are experiencing severe or chronic pain or distress that could not be relieved. Biomathematical modeling was recognized as a potential means to reduce the number of animals required for particular studies by sharpening the focus of research plans.

Materials and methods: Regulatory intent

The law of the Animal Welfare Act was subsequently incorporated into the regulations, which outline the intent and expectancies for compliance with the law.

The first expectancy in the regulations is that potentially painful/distressful procedures be recognized as such. Identification of painful or distressful procedures continues to be problematic as demonstrated in this example of a recent citation from October 2006 which indicates that the research facility did not fully recognize the potential outcome (distress, discomfort) of the procedure to be used (caloric restriction). "The protocol does not discuss methods that will prevent or reduce the associated distress and/or discomfort associated with the decrease in caloric intake (nutritional requirements) and the associated weight loss of the animals on study." Other examples from recent inspections include prolonged restraint and cardiac catheterization procedures that were conducted without a documented consideration of alternatives.

One of the resources available to research facilities on this topic is Animal Care's Policy 11, compiled in 1997 from correspondence originally written in 1990 and 1991 (USDA, 1997). Policy 11 includes the definition of a painful procedure: "any procedure that would reasonably be expected to cause more

than slight or momentary pain and/or distress in a human being to which that procedure is applied." It provides examples of potentially painful (ocular and skin irritancy testing) and distressful (food/water deprivation, noxious stimuli) procedures. Another resource is the 1992 Institute of Laboratory Animal Resources "Report on the Recognition and Alleviation of Pain and Distress in Laboratory Animals", which is currently under review and being updated (ILAR, 1992). An excellent internet resource is the "Pain and Distress" webpage of the USDA National Agricultural Library' Animal Welfare Information Center (USDA, 2007).

The second expectancy in the regulations is that the researcher will conduct a "good faith" effort to look for replacement, reduction and refinement methods. The regulations require the principal investigator to provide a written narrative description of the methods and sources used to determine that alternatives were not available. This example of a recent citation from December 2006 indicates the research facility did not understand what constitutes a proper database search: "An internet search engine was used to do the literature search, which yielded no relevant results. Also, the trade name and not the chemical name were used in the search." Other examples from recent inspection reports include the lack of key words associated with the procedures that may cause pain (nephrectomy, splenectomy and thoracic lobectomy) or the use of a search strategy that is too specific (the use of "cystic fibrosis animal model alternatives" as the only phrase for a database search does not address finding alternatives for the surgical procedures or anesthetic methodology).

Animal Care's Policy 12, updated in 2000 and based on correspondence originally written in 1992, provides guidance on the requirement to provide a written narrative of the consideration of alternatives to painful and distressful procedures. (USDA, 2000). It includes examples of what is meant by an "alternative" as well as the components of an adequate written narrative. A very detailed worksheet has been developed by AWIC to assist researchers in this endeavor (USDA, 2007). The Altweb internet site contains a self-tutorial "step-by-step" approach to an alternatives search (Johns Hopkins, 2007).

The third expectancy in the regulations is that after a proper search has been conducted, and the alternatives considered, they will be incorporated, where appropriate, into the research protocol. If no replacement is suitable for the research purposes, the principal investigator must provide a rationale for using live animals. In order to ensure reduction has been considered, the researcher must provide a rationale on the appropriateness of the numbers to be used. Lastly, refinement efforts are captured in the detailed description of the procedures designed

to assure that discomfort and pain to animals will be limited to that which is unavoidable for the conduct of scientifically valuable research.

It is expected the Institutional Animal Care and Use Committee (IACUC), in their oversight capacity, will discuss these efforts with the principal investigator during their review of the protocol. These discussions become part of the meeting minutes and are available for USDA inspector review. If the IACUC determines that the written narrative provided by the researcher provides adequate assurance that alternatives were considered, the meeting minutes need only reflect this determination. However, research facilities will be held responsible if it is subsequently determined that an alternative procedure was available to accomplish the objectives of the proposed experiment (USDA, 1989).

Discussion: Promoting consideration, acceptance and use of alternatives

As outlined above, there is a regulatory requirement to consider alternatives to any procedure that may cause pain or distress to an animal. In finalizing the amendments to the Animal Welfare Act, it is clear Congress intended for researchers to be provided ready access to methods of research and testing involving fewer or no animals, or reduced pain or distress through the National Agriculture Library in cooperation with the National Library of Medicine (US Congress, 1985). The Animal Welfare Information Center at the National Agricultural Library provides information on improved animal care, holds workshops on meeting the information requirements of the Animal Welfare Act, and conducts extensive literature searches on a cost-recovery basis.

Additional regulatory guidance is found in the U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research and Training, as followed by U.S. Government agencies. Principle III refers to the concept of reduction and replacement; Principle IV to refinement (the avoidance or minimization of discomfort, distress, and pain). Accredited research institutions will find these concepts embodied in the "Guide for the Care and Use of Laboratory Animals" (ILAR, 1996).

Acceptance of an alternative method relies much on the ability of that method to "prove its worth". The research community embraces alternatives when they have been shown to be based on sound science, reliable, and an improvement over the use of the animal. Some examples include the Ames test (using bacteria to screen for carcinogenicity), the use of a virus titer for potency testing for serial release of modified live veterinary vaccines (as opposed to an animal challenge test), and the use of simulator models for teaching students.

U.S. Government regulatory agencies rely

on the validation of alternative test methods to provide sufficient evidence of their usefulness. The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) was authorized by Congress in 2000 "to establish, wherever feasible, guidelines, recommendations, and regulations that promote the regulatory acceptance of new or revised scientifically valid toxicological tests that protect human and animal health and the environment while reducing, refining, or replacing animal tests and ensuring human safety and product effectiveness" (U.S. Public Law, 2000). ICCVAM is composed of representatives from fifteen (15) Federal regulatory and research agencies that use, generate or disseminate toxicological information. Over 150 test methods have been, or are in the process of being evaluated by ICCVAM for regulatory purposes.

However, it must be noted there are provisions in the Animal Welfare Act that specifically prohibit the federal government from writing any regulations with regard to the design of actual research or experimentation, as determined by the research facility. Therefore, certain State authorities have taken it upon themselves to introduce legislation for their local jurisdiction. For example, New Jersey is considering a law that would prohibit product testing with traditional animal methods if a federally-recommended alternative test method exists (New Jersey, 2007). New York is considering a law that would require teachers to notify students of their right to an alternative to the dissection of animals (New York, 2007).

Conclusion

There is much interest in the United States in assuring pain or distress experienced by animals used in research is minimized or eliminated. Investigators are required to consider alternatives (replacement, reduction, refinement procedures) and it is expected these will undergo due discussion and deliberation by the research institution, and used when appropriate. An increased awareness of the availability of an alternative--whether it be an accepted regulatory test or a refinement included in the "materials and methods" section of a published paper--will certainly help in this effort.

References

- Institute of Laboratory Animal Resources, Committee on Pain and Distress in Laboratory Animals (1992) *Recognition and Alleviation of Pain and Distress in Laboratory Animals*, National Academy Press, Washington D.C.
- Institute of Laboratory Animal Resources, Committee to Revise the Guide for the Care and Use of Laboratory Animals (1996) *Guide for the Care and Use of Laboratory Animals*, National Academy Press, Washington D.C.
- Johns Hopkins University, Center for Alternatives to Animal Testing, Altweb, (2007), *Search for Alternatives* webpage, <http://altweb.jhsph.edu/searchalt.htm>

- Kulpa-Eddy, J.A. (2005) Overview of the Regulatory Requirements for the Consideration of Alternatives, *ALTEX* (22, Special Issue 2), 167-169.
- New Jersey proposed bills: Assembly #909 and Senate #1956 (2007), *An Act concerning the use of animals in product testing*.
- New York proposed bills: Assembly #A00585 and Senate #5408 (2007), *An Act to amend the education law, in relation to the humane treatment of animals*.
- U.S. Congress (1985) House Conference Report 99-447, Joint Explanatory Statement of the Committee of Conference. Government Printing Office, Washington, p. 596.
- U.S. Department of Agriculture, Agricultural Research Service, National Agricultural Library, Animal Welfare Information Center (2007) *Literature Searching and Databases* webpage, http://awic.nal.usda.gov/nal_display/index.php?info_center=3&tax_level=1&tax_subject=184 and <http://www.nal.usda.gov/awic/alternatives/searches/altwksht.pdf>
- U.S. Department of Agriculture, Agricultural Research Service, National Agricultural Library, Animal Welfare Information Center (2007) *Pain and Distress* webpage, http://awic.nal.usda.gov/nal_display/index.php?info_center=3&tax_level=1&tax_subject=310
- U.S. Department of Agriculture, Animal and Plant Health Inspection Service (1989) 9 CFR Parts 1, 2 and 3: Animal Welfare; Final Rules. *Federal Register* 54(168): 36129-36130.
- U.S. Department of Agriculture, Animal and Plant Health Inspection Service, Animal Care (1997), Policy #11 Painful Procedures, *Animal Care Policy Manual*, April 14, 1997.
- U.S. Department of Agriculture, Animal and Plant Health Inspection Service, Animal Care (2000), Policy #12 Consideration of Alternatives to Painful/Distressful Procedures, *Animal Care Policy Manual*, August 26, 2002.
- U.S. House of Representatives, Hearings before the Subcommittee on Department Operations, Research, and Foreign Agriculture of the Committee on Agriculture. Improved Standards for Laboratory Animals Act; And Enforcement of the Animal Welfare Act By the Animal and Plant Health Inspection Service (1984). U.S. Government Printing Office, Washington: 1985, p. 22.
- U.S. House of Representatives, Hearings before the Subcommittee on Science, Research, and Technology of the Committee on Science and Technology. The Use of Animals in Medical Research and Testing. (1981). U.S. Government Printing Office, Washington: 1982, pp.1-3, 7.
- U.S. Public Law 99-198 (1985), The Improved Standards for Laboratory Animals Act, *Food Security Act of 1985, Subtitle F – Animal Welfare*, Findings (Section 1751).
- U.S. Public Law 106-545 (2000), The ICCVAM Authorization Act of 2000, (42 U.S. Code, Sections 2851-2853).