

Standards for the rearing environment of laboratory animals in the United States

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Abstract

The quality of the housing and care of research animals used in the United States is the result of a matrix of laws, regulations, policies and standards that has evolved and matured over the last 40 years. In addition to a variety of state laws, three national oversight agencies—two governmental and one private, non-profit organization—provide oversight of laboratory animal housing standards and research animal care. The similarities and differences in standards promulgated by the U.S. Department of Agriculture (USDA), the Office of Laboratory Animal Welfare (OLAW)/National Institutes of Health (NIH), and the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC International) will be described. For each oversight body, the species covered by the agency's standards, and those aspects of the standards that specifically apply to the animal's environment (cage size/animal density, light level, sound, temperature and humidity, air quality, food and water, bedding, enrichment) will be highlighted. Standards for related programmatic aspects, such as animal health status, sanitation, availability of emergency power and disaster planning, that can impact animal welfare are in force in the United States, and will be summarized. In addition, current efforts to refine the housing and husbandry of research animals will be discussed.

Keywords: laboratory animals, rearing environment, standards, United States

Introduction

The United States (U.S.) National Institutes of Health has produced a series of posters to be displayed across the intramural campus that address various topics related to laboratory animal care and use. One poster states that "Good animal care and good animal science go hand in hand." This message sets the stage for the discussion that the quality of the scientific data and quality of animal care are inexorably linked. This paper describes the variety of mechanisms of oversight in place in the U.S. to ensure good animal care, and thus sound animal science (Bayne & Harkness, 2006; Bayne & DeGreeve, 2004). In the U.S., oversight of animal care and use for research, testing and teaching is achieved by a system of Federal laws, regulations and policies; state laws and regulations; and a voluntary accreditation program.

State laws

State laws to protect animals have a long history: the first anti-cruelty law was passed in 1641 in the Massachusetts Bay Colony to prevent riding or driving farm animals beyond established limits (Office of Technology Assessment, 1986). Subsequently, all fifty states and the District of Columbia enacted anti-cruelty laws (Bayne, 1998). The overarching

goals of these laws are to protect animals from cruel treatment; to require that animals have access to suitable food and water, and that animals are provided shelter from extreme weather. State laws consist of a number of diverse approaches to providing protection to animals, however; for example, some states have additional provisions for animals used in research, while many states prohibit the sale of pound animals into the research stream. In general, criminal penalties are imposed for offenses.

Federal oversight

The principal Federal agencies providing oversight are the U.S. Department of Agriculture (USDA), the U.S. Food and Drug Administration (FDA), the U.S. Environmental Protection Agency (EPA), the U.S. Department of Defense (DoD), the Veterans Administration and the National Institutes of Health through its Office of Laboratory Animal Welfare (OLAW). Other guidance may be derived from scientific panels (e.g., convened by the National Academies) and endorsed by the government as required standards.

U.S. Government Principles

The activities of the Interagency Research Advisory Committee (IRAC) date back to 1983. The

IRAC's primary concerns are the "conservation, use, care and welfare of research animals" and its main responsibilities are "information exchange, program coordination, and contribution to policy development" (IRAC, 1985). In 1985, IRAC published the nine principles to be taken into consideration by Federal agencies that develop requirements for testing, research, or training procedures involving vertebrate animals. These principles are as follows:

I. The transportation, care, and use of animals should be in accordance with the Animal Welfare Act ... and other applicable Federal laws, guidelines, and policies.

II. Procedures involving animals should be designed and performed with due consideration of their relevance to human or animal health, the advancement of knowledge, or the good of society.

III. The animals selected for a procedure should be of an appropriate species and quality and the minimum number required to obtain valid results. Methods such as mathematical models, computer simulation, and in vitro biological systems should be considered.

IV. Proper use of animals, including the avoidance or minimization of discomfort, distress, and pain when consistent with sound scientific practices, is imperative. Unless the contrary is established, investigators should consider that procedures that cause pain or distress in human beings may cause pain or distress in other animals.

V. Procedures with animals that may cause more than momentary or slight pain or distress should be performed with appropriate sedation, analgesia, or anesthesia. Surgical or other painful procedures should not be performed on unanesthetized animals paralyzed by chemical agents.

VI. Animals that would otherwise suffer severe or chronic pain or distress that cannot be relieved should be painlessly killed at the end of the procedure or, if appropriate, during the procedure.

VII. The living conditions of animals should be appropriate for their species and contribute to their health and comfort. Normally, the housing, feeding, and care of all animals used for biomedical purposes must be directed by a veterinarian or other scientist trained and experienced in the proper care, handling, and use of the species being maintained or studied. In any case, veterinary care shall be provided as indicated.

VIII. Investigators and other personnel shall be appropriately qualified and experienced for conducting procedures on living animals. Adequate arrangements shall be made for their in-service training, including the proper and humane care and use of laboratory animals.

IX. Where exceptions are required in relation to the provisions of these Principles, the decisions should not rest with the investigators directly concerned but

should be made, with due regard to Principle II, by an appropriate review group such as an institutional animal care and use committee. Such exceptions should not be made solely for the purposes of teaching or demonstration.

Because these Principles also appear in the Public Health Service (PHS) "Policy on Humane Care and Use of Animals" (OLAW, 2002) (PHS Policy, see below) and the Guide for the Care and Use of Laboratory Animals (Guide) (NRC, 1996), institutions required to conform with either or both of those documents must also adhere to these principles.

U.S. Department of Agriculture

The USDA has been vested by Congress with both promulgation and enforcement authority of the Animal Welfare Act (AWA) through the development of the Animal Welfare Regulations (AWRs, 9 CFR 1985). It is required that research facilities register with the USDA. Research facilities and Federal government agencies are required to purchase animals only from licensed sources. In addition, the USDA requires annual reporting from registered institutions. The USDA is required to conduct unannounced annual inspections of research facilities with follow-up inspections until any cited deficiencies have been corrected. Facilities that fail to comply with regulatory requirements can face fines, suspension of authority to operate, and even permanent revocation of the facility's license to operate. The AWRs provide minimum standards of care and treatment. They cover most warm-blooded animals, but exclude *Mus musculus* and *Rattus* sp. The AWRs require that the institution have an Institutional Animal Care and Use Committee (IACUC). The program must have available a knowledgeable Attending Veterinarian and have in place a "program of adequate veterinary care." The Regulations contain a section on personnel qualifications, to include specific topics to be addressed in a training program. The AWRs specify cage size requirements and other husbandry standards.

Highlights of the AWRs include the requirement that the investigator has considered alternatives to procedures that may cause more than momentary or slight pain or distress to the animal. There is a requirement that studies do not unnecessarily duplicate previous experiments. The Regulations stipulate that the animals' living conditions will be appropriate for their species and contribute to their health and comfort. The AWRs state that "training shall include the concept, availability, and use of research or testing methods that limit the use of animals or minimize animal distress." And, the Regulations have a requirement that the psychological well-being of nonhuman primates and exercise for dogs be addressed.

Public Health Service/Office of Laboratory Animal Welfare

The other Federal agency charged with oversight of research animal care and use is the PHS. Institutions conducting animal research using PHS funding (e.g., the National Institutes of Health), must comply with the PHS Policy (OLAW, 2002). The Policy requires submission by the funding recipient (referred to as an "awardee institution") of an Animal Welfare Assurance Statement, which must be approved by OLAW, which commits the institution to follow the U.S. Government Principles and the Guide. The PHS Policy covers all vertebrate animals used in research, testing or teaching. In addition to stating a commitment to animal welfare, the Animal Welfare Assurance Statement must designate clear lines of authority, inclusive of a designated "Institutional Official," who is ultimately responsible for the animal care and use program. The statement must also identify a qualified veterinarian involved in the program and must provide a description of the occupational health and safety program for relevant personnel in the program; a description of mandated training; and a description of the facility. Assurances are renegotiated with OLAW every 5 years. The awardee institution must also submit an annual report indicating any changes in the program or facilities, including changes in accreditation status.

Awardee institutions that do not comply with the standards of the Guide, the USDA's Animal Welfare Regulations, and other standards referenced in the PHS Policy may have their Assurance restricted, which in turn can limit access to PHS funds for research. Sustained non-compliance with the PHS Policy can result in withdrawing the approval of the Assurance and cessation of all PHS funding for animal-based activities.

OLAW conducts site visits of awardee institutions both "for cause" and "not for cause." In addition, an ongoing significant mission of OLAW is the educational outreach it performs in collaboration with awardee institutions. Jointly sponsored workshops focus on information of value to Institutional Officials and IACUC's to provide appropriate oversight of animal care and use. OLAW also provides guidance through articles in journals, commentary on other articles, NIH Guide Notices and a listserv.

Other federal oversight agencies

Food and Drug Administration

The FDA promulgates "Good Laboratory Practice Regulations" (21 CFR 58) for the conduct of animal experiments relating to existing pharmaceutical medicinal substances, food additives, or other chemicals (1998). Companion regulations for conducting studies relating to health effects, environmental effects and chemical fate testing

are found in GLP regulations administered by the Environmental Protection Agency (EPA) (1997). Like the guidelines found within the AWRs and the *Guide*, both the FDA and EPA GLPs require that:

1. Personnel using animals be appropriately trained and qualified to conduct the work.
2. Animals be free of disease at the start of the study.
3. Sanitation of animal cages and equipment occur at suitable intervals and,
4. Food and water quality be free of contaminants at levels higher than those specified in the protocol.

Adherence to the regulations is achieved primarily through voluntary compliance. Compliance is assessed through an active program of periodic inspections carried out by trained field inspectors. Serious noncompliance is dealt with by procedures ranging from study rejection to laboratory disqualification (OLAW, 2006).

Department of Defense

The DoD developed a "Policy on Experimental Animals" in 1961 to ensure that all research at DoD facilities involving animals was conducted in accord with certain principles of animal care (Rozmiarek 2007). Later versions of this policy also included care in overseas sites. Subsequently, the DoD issued a 1995 Directive, "The Use of Laboratory Animals in DoD Programs," (DoD, 1995) that applies to the Office of the Secretary of Defense, the Military Departments, the Uniformed Services University of the Health Sciences and the Defense Agencies, which requires that all DoD facilities apply for accreditation by AAALAC International and establish local institutional animal care and use committees. The Directive also assigns to the DoD oversight responsibility for DoD sponsored, extramural animal-based research, testing, and training under DoD grants or contracts.

Veterans Administration

The Office of Research Oversight (ORO) serves as the primary component of the Veterans Health Administration (VA) to advise the Under Secretary for Health on all matters affecting the integrity of research by ensuring the welfare of research animals through promoting conformance with relevant regulations and policies. Through the VA Handbook 1200.7, the VA has adopted the standards of the PHS Policy for all animal research conducted under VA auspices, and further requires that VA medical centers conducting animal studies and accepting any PHS funds should have a PHS Animal Welfare Assurance (1200.7.7e).

Voluntary accreditation

The Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) International

is a non-profit organization incorporated in 1965. AAALAC's mission is to promote the humane treatment of animals in science through confidential, voluntary accreditation of animal care and use programs. The Association is comprised of a Board of Trustees of 69 scientific organizations, patient advocacy groups, animal welfare organizations, and research lobby groups; a Council on Accreditation made up of veterinarians, animal researchers, research administrators, and facility managers who are experts in the field of laboratory animal science and medicine; and an office staff. The Board of Trustees sets the vision and general direction of the Association, the Council on Accreditation is responsible for the conduct of site visits and for determining the accreditation status of institutions, and the office staff (U.S., Europe, and Pacific Rim regional offices) serves as a point of coordination of these activities and as an information resource to the laboratory animal using community.

AAALAC does not establish policies with which institutions must conform. Rather, AAALAC International relies principally on the *Guide*, as well as national laws, regulations and policies, and numerous scientifically-based standards, referred to as "reference resources" and which address specific subject areas (e.g., recombinant DNA, surgery, euthanasia), for evaluation of animal care and use programs around the world (Bayne & Martin, 1998; Bayne & Miller, 2000). The accreditation process includes an extensive internal review conducted by the institution which is summarized in an animal care and use Program Description. On-site visits are announced and are conducted every three years. There is also an annual report requirement. The standards and process for accreditation are described in the Association's Rules of Accreditation. Non-conformance with AAALAC International standards results in formal notification that Full Accreditation has not been granted and a provision of a timeline for correcting identified deficiencies. Revocation of accreditation can ultimately result from sustained non-conformance.

Conclusions

The system of setting and monitoring standards for the care and use of laboratory animals in the United States is a complex matrix of state, Federal and voluntary oversight. These systems interdigitate to provide extensive coverage for the welfare of research animals and rely heavily on the principles of the Three Rs. Through public input, the applicable regulations, policies and standards have evolved to keep pace with scientific progress and societal values.

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