Office o

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Foreword

The original *OPRR/ARENA IACUC Guidebook* was published in 1992 and has served as a useful resource to the animal research community. This revised edition, the ARENA/OLAW IACUC Guidebook, continues to support the fundamental principle on which the animal care and use program is based: self-regulation with oversight. It clearly demonstrates the increased role of the Institutional Animal Care and Use Committee (IACUC) in ensuring the ethical and sensitive care and use of animals in research, teaching and testing.

This *Guidebook* is the product of an ARENA-established editorial board of knowledgeable individuals who have IACUC experience and are familiar with the evolution of IACUC issues and relevant documents published during the past decade. Sections from the original document have been updated, and new sections added to incorporate state of the art knowledge regarding the functioning of IACUCs and institutional animal care and use programs. This *Guidebook* does not create new or different interpretations of the *PHS Policy on Humane Care and Use of Laboratory Animals*, legislation, or USDA animal

have been incorporated, and feedback from the field during the past ten years has resulted in emphasis on topics such as the role of the nonaffiliated member, the application of the three R's (reduction, refinement and replacement) of alternatives, and the development of humane endpoints.

It is with a great sense of gratitude and respect for my colleagues who served on the editorial board and to the 30 authors who generously shared their time and expertise that I submit this document to the Office of Laboratory Animal Welfare. I would especially like to express my appreciation to the Project Director, Carol Wigglesworth, and her colleagues in NIH's OLAW who gave untold hours of editing and guidance to make this project not only possible, but also enjoyable. ARENA also gratefully acknowledges the technical review for consistency with the provisions of the USDA animal welfare regulations provided by Dr. Ron DeHaven, Deputy Administrator, Animal Care, APHIS, and his headquarters staff. This has truly been a labor of love by many dedicated individuals in the animal research community and I feel honored to have been a part of this effort.

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Abbreviations and Acronyms

Abbreviations

G ide	ILAR *Guide for the Care and Use of Laboratory Animals*
PHS Polic	*PHS Policy on Humane Care and Use of Laboratory Animals*

Acronyms

A

AAALAC	Association for Assessment and Accreditation of Laboratory Animal Care International
AALAS	American Association for Laboratory Animal Science
AC	Animal Care, APHIS, USDA
ACLAM	American College of Laboratory Animal Medicine
AGRICOLA	National Agricultural Library's Agricultural OnLine Access (USDA)
APHIS	Animal and Plant Health Inspection Service (USDA)
ARENA	Applied Research Ethics National Association
ASLAP	American Society of Laboratory Animal Practitioners
AV	Attending Veterinarian
AVMA	American Veterinary Medical Association
AWA	Animal Welfare Act
AWIC	Animal Welfare Information Center
AWRs	Animal Welfare Regulations (USDA)

C

CAAT	Center for Alternatives to Animal Testing
CCAC	Canadian Council on Animal Care
CDC	Centers for Disease Control and Prevention
CEO	Chief Executive Officer
CFA	Complete Freund's Adjuvant
CFR	Code of Federal Regulations
CIRA	Center for Information on Research with Animals
CITES	Convention on International Trade in Endangered Species of Wild Fauna and Flora

D

DHHS	Department of Health and Human Services
DOI	Department of the Interior
DVM/VMD	Doctor of Veterinary Medicine or Veterinary Medical Doctor

E

EPA	Environmental Protection Agency
ESA	Endangered Species Act

F

FASEB	Federation of American Societies of Experimental Biology
FBR	Foundation for Biomedical Research
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency

A. The IACUC

A.1. Timeline, Background and History

Timeline

1950 Formal establishment of Animal Care Panel.

1963 First edition of the *Guide for the Care and Use of Laboratory Animals (Guide)* developed by the Animal Care Panel.

1965 Incorporation of the American Association for the Accreditation of Laboratory Animal Care (AAALAC).

1966 Congress passed the Laboratory Animal Welfare Act (PL 89-544) and the USDA was named the responsible agency.

1967 Animal Care Panel changed its name to the American Association for Laboratory Animal Science (AALAS).

1971 NIH Policy on Humane Care and Use of Laboratory Animals for PHS Supported Institutions.

1971 USDA promulgated standards known as Subpart F, Stolen Animals (AWA).

1973 First Public Health Service (PHS) Policy on Humane Care and Use of Laboratory Animals.

1974 Public Responsibility in Medicine and Research (PRIM&R) established.

1979 PHS Policy required each animal-using grantee institution to have a PHS Assurance and a committee to maintain oversight of its animal care program.

1979 USDA promulgated standards known as Subpart E, Identification of Animals (AWA).

1982 First PRIM&R Animal Care and Use meeting.

1985 U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research and Training promulgated.

1985 Health Research Extension Act (P.L.99-158) passed by Congress.

1985 Animal Welfar

reports on animal neglect, abuse and pet theft by animal dealers culmi nated in a 1966 major article and photographs in *Life* magazine. The article suggested a need for regulation and a system of enforcement, especially for dogs and cats used in research. Catalyzed in part by this article, the Laboratory Animal Welfare Act, the first version of what is now known as the Animal Welfare Act (AWA), was passed by Congress in 1966 (Public Law 89-544) establishing legal standards for laboratory animal care and use for the first time in this country. The United States Department of Agriculture (USDA) was named the responsible agency for implementing and enforcing this new law and it promptly began promulgating regula tions. Research laboratories and dealers were required to r

to inspect the institution's animal facilities at least once a year and report its findings and recommendations to responsible institutional officials. Records of activities and recommendations were required to be available for inspection by NIH representatives.

The first PHS policy regarding animal care and use replaced the NIH policy on July 1, 1973 and continued to accept AAALAC accreditation in lieu of an institutional committee. The January 1, 1979 revision of the PHS policy required each animal-using grantee institution to have "a committee to maintain oversight of its animal care program" and expanded the defini tion of animal to include all vertebrates. The revised policy also required an institution to submit an Assurance statement to the Office for Protection from Research Risks (OPRR), now the Office of Laboratory Animal Welfare (OLAW), that it is committed to follow the *Guide*, the Principles and the PHS policy requir

IACUC must evaluate and prepare reports on all of the institution's programs and facilities (including satellite facilities) for activities involving animals at least twice each year, and is required to review the care and use of animals in PHS-supported activities. The IACUC, through the Institutional Official (IO), is responsible for compliance with reporting requirements. Minority views filed by members of the IACUC must be included in reports filed under this *PHS Policy*. The *PHS Policy* also requires training or instruction for scientists, animal technicians and other personnel involved in animal care, treatment or use. This training or instruction must include information on the humane practice of animal care and use as well as training or instruction in research or testing methods that minimize the number of animals required to obtain valid results and minimize animal distress.

The Interagency Research Animal Committee, made up of representatives of federal agencies that use or require the use of experimental animals, promulgated the "U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research and Training" in 1985 (see Appendix F). These Principles were subsequently incorporated into the 1986 *PHS Policy*, and remain in effect today as a model for federal agencies that develop specific agency policies for the use of animals.

With the promulgation of the 1986 version of the *PHS Policy*, OPRR (now OLAW) embarked upon an extensive national education program. The program began with the co-sponsorship of one- to two-day workshops in conjunction with Assured institutions at different geographical locations. Many of the early workshops focused on basic provisions set forth in the 1986 *PHS Policy*, such as protocol review and semiannual program evaluations. That cosponsorship of approximately four to five workshops a year continues today, although the topics are now generally more specialized, covering areas such as performance standards, field studies, and laboratory animal management and technology. Since 1995 OLAW has expanded its educational role to include development of a Web-based tutorial, an extensive Web site with sample documents to assist institutions in their implementation of the *PHS Policy*, co-sponsorship of ARENA's IACUC 101 program, and this revised ARENA/OLAW Guidebook.

Special interest groups concerned about the acquisition and welfare of animals used in research continue to influence research animal care and use. These groups include local and national humane societies concerned about animal welfare and well-being, and antivivisectionist groups that are opposed to the use of animals in research. The activity of some animal

pr

A.2. Authority, Composition and Functions

Each institution that receives PHS support for activities involving vertebrate animals or is subject to the authority of the Animal Welfare Act (AWA) must operate an animal care and use pr

Alternate members may be appointed to the IACUC as long as they are appointed by the CEO or other official with authority to appoint members, and there is a specific one-to-one designation of IACUC members and alternates. An IACUC member and his/her alternate may not count toward a quorum at the same time or act in an official member capacity at the same time. Alternates should receive training similar or identical to the training provided to regular IACUC members.

Conflict of Interest

Both the AWRs and *PHS Policy* state that no IACUC member "may par ticipate in the IACUC review or approval of an activity in which that member has a conflicting interest, (e.g., is personally involved in the

to suspend an activity, the IACUC must review the matter at a convened meeting of a quorum of the IACUC and the suspension must be approved by a majority vote of the quorum present.

For reasons other than conflict of interest, abstentions from voting do not alter the quorum or change the number of votes required. For example: If an IACUC has 20 voting members, at least 11 members must be present at a convened meeting to constitute a quorum and appr

A.2. Table B. Federall Mandated Functions of the IACUC

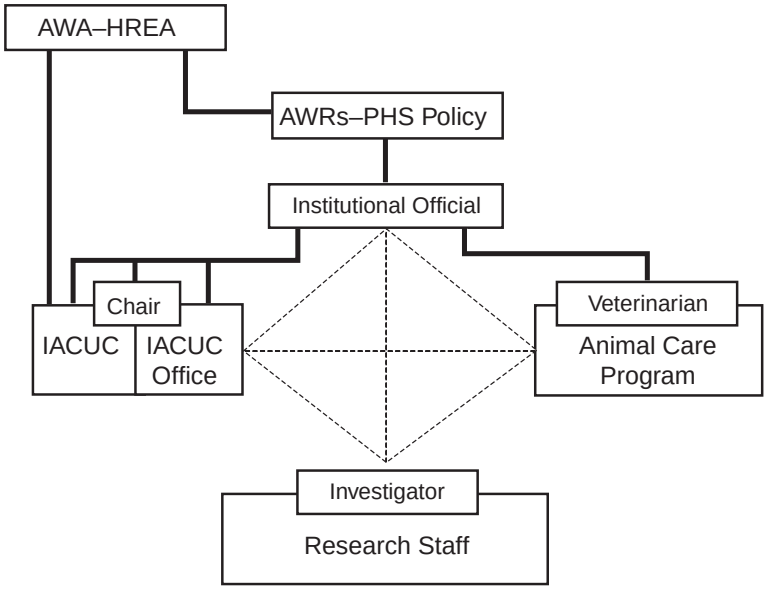
PHS PHS Policy. IV.B.1-8	USDA 9 CFR. 2.31 (c) (1) – (8) and 2.31(d) (5) (6) & (7)
1. Review, at least once every six months, the research facility's program for the humane care and use of animals, using the *Guide* as a basis for evaluation.	
2. Inspect, at least once every six months, all of the institution's animal facilities	

A.3. Operation and Administration

Institutional Responsibility for Animal Welfare

Assuring laboratory animal welfare necessitates a partnership among the Institutional Official (IO), the IACUC, the veterinarian and the investigators. Ultimately, accountability for assuring humane care and use of animals resides with the institution, but this may only be achieved when all of the players, i.e., the investigators and their research staff, the veterinary staff, animal caretakers and technicians, and the IACUC, contribute to a shared goal.

Each institution should provide a framework with appropriate resources for an animal care and use program that is managed in accordance with the *PHS Policy*, the *Guide*, and the Animal Welfare Regulations (AWRs). Organizations that function effectively have simple, clear and direct lines of responsibility and corresponding authority.



Components of an animal care and use program. Heavy lines represent the mandate from the Animal Welfare Act and Health Research Extension Act that the Secretaries of Agriculture and Health and Human Services develop guidelines for the use of animals in research and for IACUCs, and require established lines of authority from the IO to the IACUC, IACUC staff, and veterinarian. Dotted lines represent the need for cooperation and communication among components.

The *PHS Policy* and AWRs place a strong emphasis on senior management level responsibility and on use of the IACUC as an oversight committee to evaluate the program. The committee needs to work closely with the animal users, the animal care staff, and the responsible veterinarians to ensure a high quality animal care and use program. The IO must support the IACUC by providing appropriate resources.

Responsibilities of the Institutional Official

The IO must have the authority to allocate organizational resources needed to maintain a smoothly functioning animal care and use program based on the recommendations and advice received from:

- the IACUC,
- the veterinarian, and
- the IACUC professional and administrative staff.

The IO should also clearly define and assign responsibilities and reporting channels for other essential program elements such as:

- personnel training,-
- occupational health and safety, and-
- maintenance of facilities.

The IACUC, appointed by the organization's Chief Executive Officer (CEO), must report directly to the IO and be empowered to perform its duties without undue interference. OLAW's experience is that it is usually best for the veterinarian also to report directly to the IO in connection with his or her responsibility for implementing the animal care and use program. In order to provide the intended checks and balances in the system of self-regulation, it is advisable that the veterinarian not serve as Chair of the IACUC or as IO. While it is important that there be a collegial and effective working relationship between the IACUC and the veterinarian, it is impor tant to avoid the potential for real or perceived conflicts of interest.

Role and Responsibilities of the IACUC Staff

The nature of the institution and the volume of animal-based research determine the staffing requirements of an IACUC and the animal care program. Institutions with a high volume of proposals involving animals may require full time IACUC staff. A professional staff with expertise in animal welfare laws, regulations and policies is especially important to provide stability and continuity to animal care and use programs where IACUC chairs and members serve on a rotating basis.

The role of the IACUC staff is to provide administrative support to the IACUC and the IO. It is important however, that neither the IO nor the IACUC Chair over-invest authority or responsibility in the IACUC staff.

The IACUC staff often serve as the gatekeepers of information and com

Administrative duties include:

- preparation of minutes and other correspondence and reports, such as the PHS Assurance document, and annual PHS, USDA and AAALAC reports; and
- serving as an information resource for investigators and IACUC members regarding regulatory issues and the status of protocols.

Professional staff duties include:

- pr

reflected in the grant application, then the PHS funding component must be notified in the follow-up cer

In addition, while the approaches of funding and regulatory agencies are complementary, they also differ. The *PHS Policy* invests responsibility for animals in the entity that receives PHS funding, known in grant parlance as the "awardee" or "grantee" institution. Accordingly, if there is a concern about a PHS-funded animal activity PHS will likely "follow the money" to determine institutional accountability. Under the AWRs, responsibility generally resides with the institution that houses the animals and with the institution that owns the animals, which may not be the same institution.

PHS may award funds for an activity involving animals only to an entity that has an approved PHS Assurance. When more than one institution is in volved, one of the following four scenarios generally apply:

- An awardee institution and/or a subcontractor or collaborating insti tution can both have PHS Assurances. In this situation, two assured entities are responsible for determining which IACUC will review the research and under which institutional program the research will be covered. While PHS and USDA do not require dual review by both awardee and subcontractor IACUCs (i.e., only one of the assured IACUCs must review and approve the research), OLAW recommends the IACUC of the awardee institution have a mechanism for obtaining a copy of the performance site's IACUC approval. Many times however, both IACUCs will elect to review the research as evidence of shared responsibility and to ensure the research will be conducted in compliance with their own institutional policies and practices in addi tion to meeting the federal laws and regulations.
- If the awardee institution has a PHS Assurance, but the subcontractor or collaborating institution does not, the latter may be required to obtain one. The grant or contract may not be awarded until the Assurance is solicited by OLAW, submitted by the subcontractor, and approved by OLAW. The subcontractor must also submit the date of IACUC review.
- If the awardee institution has a PHS Assurance but the subcontractor or collaborating institution does not, the latter may be brought under the awardee institution's Assurance by an amendment to the Applica bility section of that Assurance. The IO signing the Assurance would then be responsible for the facilities and activities of the subcontrac tor, and the IACUC would be required to include relevant aspects of the subcontractor's facility and program in its semi-annual program review. The subcontractor, in turn, would be required to recognize the authority of the IO and the IACUC of the awardee institution. Most awardee institutions do not elect this option.

- Another possible collaboration, that may or may not involve subcontracting, occurs if an awardee institution does not have an animal program or facility and is therefore not assured, but the investigator will use the facilities of an assured institution. Under these circumstances OLAW requires an "Interinstitutional Agreement Assurance" whereby both IOs agree that the project will be conducted in accordance with the assured institution's Assurance and the investigator will abide by the determinations of the assured institution's IACUC. The effect of such an agreement is to extend the IACUC's oversight to include the particular project, and to meet the *PHS Policy* requirement that the grantee institution be assured.

References

Garnett, N.L., and W.R. DeHaven. Commentary: Protocol Review—Who's to Blame? *Lab Animal* 28(7), 1999.

NIH Guide for Grants and Contracts, Notice OD-01-017, February 12, 2001.

A.4. Training for Members

For the IACUC to discharge its responsibilities a program of education and training is essential. A well-defined and implemented program, while prima rily directed to the IACUC member, would also be of value to researchers, administrators and others with responsibilities associated with research involving animals.

It is the responsibility of the institution to provide suitable orientation, appropriate materials, adequate resources and training to enable IACUC members to carry out their duties consistent with the *Guide*, the *PHS Policy* and the Animal Welfare Regulations (AWRs). It is important to provide the tools necessary to assist members in understanding and evaluating issues that are brought before them. Appropriate training depends on the size, scope and needs of the research facility, but must incorporate the federal mandates of the IACUC.

Local institutional policies and procedures need to be a part of the training and education program. Frequently

Program of Education and Training for New IACUC Members

Orientation Module

(Suggested time – approximately 2 hours)

Suggested Topics

Objectives

1. To introduce members to the role of the IACUC and its evolution-
2. To provide the basic information necessary for IACUC members to-discharge their responsibilities-
3. To provide a forum for response to, and discussion of, members'-concerns and questions-

Conducted by

The IACUC staff, the IACUC Chair or designee, veterinary staff, or consult--ants. Training can be provided by one or more of these individuals.-

Syllabus

1. The IACUC — its evolution and responsibilities-
   - 1.1. Genesis and chronology-
   - 1.2. U.S. Government Principles-
   - 1.3. Benefits and pitfalls of IACUCs-
   - 4.4. Criteria for membership-
   - 4.5. Authority of the IACUC-
   - 4.6. Unique role of the IACUC within the organization-
2. Operation and procedures-
   - 2.1 Proposal (protocol) submission-
   - 2.2 Proposal review-
     - 2.2.1 Process-
     - 2.2.2 IACUC review criteria-
     - 2.2.3 Review by quorum-
     - 2.2.4 Review by designated reviewers-
     - 2.2.5 Post-meeting process-
   - 2.3 Monitoring of approved protocols-
     - 2.3.1 Periodic review (continuing review)-

2.3.2 Protocol changes (amendments)

2.4 Records

2.5 Semiannual reviews

2.5.1 Animal care and use program

2.5.2 Institutional animal facilities

2.6. Handling animal welfare concerns

2.7. Roles, responsibilities, relationships

2.7.1. IACUC

2.7.2. IACUC Program office

2.7.3. Veterinarian

2.7.4. Animal Care Program (e.g., Department of Comparative Medicine or Laboratory Animal Resources)

2.7.5. Institutional Official (IO)

2.7.6. Office of Laboratory Animal Welfare (OLAW), NIH

2.7.7. Animal and Plant Health Inspection Service (APHIS), USDA

2.7.8. Project sponsor/grantor

2.7.9. Community

Suggested Resource Materials

- *Public Health Service Policy on Humane Care and Use of Laboratory Animals.* NIH. Reprinted 2000.
- Health Research Extension Act, P.L.99-158.
- Animal Welfare Act – P.L. 89-544 as amended by P.L. 94-279, P.L. 99-198, P.L. 91-579 and P.L. 101-624.
- Animal Welfare Regulations. 9 CFR.
- *Institutional Administrator's Guide for Animal Care and Use.*

Program of Education and Training for IACUC Members

Recommended Continuing Education Module

(Varying amounts of time – can be incorporated in each IACUC meeting and/or designated or *ad hoc* meetings)

Suggested Topics

Objectives

1. To increase members' knowledge, understanding and awareness
2. To keep members current on:
   - 2.1 Laws (federal, state, local)
   - 2.2 Regulations (proposed, promulgated/issued)
   - 2.3 Directives
   - 2.4 Guidelines
   - 2.5 Developments and trends
   - 2.6 Institutional policies
3. To address issues, concerns and questions raised by IACUC members, institutional staff, and the community.

Conducted by

The IACUC Staff, the Chair or designee, veterinary staff, or consultants.

Syllabus

Agenda based on:

1. Questions and concerns brought to the attention of the IACUC
1. Official directives
3. Publications
4. Notices of, and reports from, conferences, seminars, etc.
5. Animal facility staff and/or veterinarian's observations and recommendations
6. Facility inspections and program evaluations
7. Problem situations

Suggested Resources: See Appendix A.

A.5. Legal Concerns

The functions and activities of IACUCs are based on two federal laws: the Health Research Extension Act of 1985 (P.L.99-158) (HREA) and the 1985 amendments to the Animal Welfare Act (AWA), the Improved Stan dards for Laboratory Animals Act of 1985 (P.L. 99-198). In addition, other federal rules may pertain to IACUCs, such as the Occupational Safety and Health Administration (OSHA), Food and Drug Administration (FDA), and Good Laboratory Practice (GLP) regulations, and the Endangered Species Act (ESA). Committee members need to be aware of the legal obligations

to final Committee action, or agency funding. In the case of trade secrets or patent applications, such information is protected by law (7USC 2157, Section 27).

- IACUC members should understand that their signatures are legally binding on official IACUC reports such as the six-month program review and facilities inspection report.

Liability

Under *PHS Policy*, the primary responsibility for meeting applicable federal and state rules rests with the research facility or PHS awardee institution. The IO is the individual held responsible on behalf of the research facility for ensuring compliance. Failure to comply with *PHS Policy* could result in OLAW's withdrawal of approval of the institution's Animal Welfare Assurance, thereby making the institution ineligible to receive funds for activities involving animals.

Under applicable statutory provisions (7 U.S.C. Section 2149), the USDA has the authority to order a facility to cease and desist, and to impose a fine for noncompliance with the AWRs and AWA. The AWA provides for penalties of up to $2,500 per count and one year in prison, or both for violations of the AWRs.

Freedom of Information

The Freedom of Information Act (FOIA), 5.U.S.C.552, provides individ uals with a right to access to records in the possession of the federal government. The government may withhold information pursuant to the nine exemptions and three exclusions contained in the Act.

The Electronic FOIA Amendments of 1996 (Public Law 104-231) amended the law in a number of ways that primarily address information systems, use of telecommunications, and electronic reading rooms. Most federal agencies provide guidelines for submitting FOIA requests through their agency Web sites.

Information about federally conducted or supported research projects, PHS Assurance documents, USDA annual reports filed by research facilities, and inspection reports of USDA, Environmental Protection Agency (EPA) and FDA, are generally available to the public under FOIA.

Many states have public records laws and/or open meetings acts, known as “sunshine” laws, which may permit public access to information reviewed and generated by the IACUC, and public attendance at IACUC meetings. However, even in some “sunshine” law states, the IACUC, because it serves in an advisory capacity to the IO, may hold closed sessions. IACUC mem bers need to be aware of specific state laws regarding these issues and should always seek legal counsel if necessary to ensure compliance with applicable laws.

B. Oversight of the Animal Care and Use Program

B.1. Program and Facility Review

The *PHS Policy* and Animal Welfare Regulations (AWRs) stipulate that the IACUC must review the program for humane care and use of animals at least once every six months, using the *Guide* as the basis for evaluation for the PHS *Policy* and title 9, chapter I, subchapter A-Animal Welfare for the U.S. Department of Agriculture (USDA). Federal requirements also state that the IACUC must inspect all institutional animal facilities at least once every six months.

Benefits of the Reviews

- Reviews provide an ongoing mechanism for ensuring that the insti tution maintains compliance with applicable animal care and use policies, guidelines and laws.
- Reviews serve as an opportunity for constructive interaction and education for the animal care personnel, research staff and IACUC members.
- Reviews can help an institution prepare for subsequent visits by outside evaluators, such as USDA inspectors, Office of Laboratory Animal Welfare (OLAW) staff and Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC) site visitors.

A summary of recurring IACUC issues related to semiannual program review and facility inspection identified by AAALAC during site visits is provided in Appendix C.

Resources

OLAW has developed a sample format for the program review and facility inspection that may be modified to meet the institution's needs (see the OLAW Web site). The Table of Contents of the *Guide* or an institution's AAALAC Program Description can also serve as an outline for the semi-annual evaluation.

Conducting Program Evaluations

Key aspects of an animal care and use program that should be emphasized in the semiannual evaluation include:

- IACUC membership, functions and procedures, including protocol review (e.g., using page 10 of the *Guide* as a template, and *PHS Policy* IV.B. and C.);
- facility inspection process;
- provisions for reviewing and investigating concerns regarding animal care and use;
- recordkeeping practices;
- methods employed to meet reporting requirements;
- occupational health and safety program;
- veterinary medical care program; and
- personnel qualifications and training.

Specific procedures to accomplish program evaluation may include pre sentations by appropriate individuals (e.g., the veterinarian, an occupational health and safety representative, etc.) and review of written institutional policies such as standard operating procedures, guidelines on use of anes thetics and analgesics, and euthanasia procedures. Verifying conformance with the USDA Animal Care Policies (1999 *et seq*.) during the semiannual program review will help ensure that current practices are consistent with USDA regulatory interpretations.

Facility Review

All animal housing facilities must be inspected in the semiannual review, including:

- satellite facilities (containment areas outside the central/core animal facility where animals are housed for more than 24 hours *(PHS Policy)*,
- areas in which surgical manipulations are performed *(PHS Policy)*,
- animal study areas (locations where USDA-covered species are held for more than 12 hours) (AWRs), and
- holding facilities (AWRs).

Laboratories in which routine procedures, such as immunization, dosing, and weighing,

are conducted may be evaluated by other means such as random inspec tions. However, the institution, through its IACUC, is still responsible for all animal-related activities regardless of where animals are maintained or the duration of the housing. The IACUC must have reasonable access to these areas for the purpose of verifying that activities involving animals are being conducted in accordance with the proposal approved by the IACUC.

Staffing and Scheduling the Facility Inspections

The IACUC must conduct inspections of facilities at least once every six months. This may be accomplished by assigning specific facilities to sub-committees, which must consist of at least two IACUC members (AWRs). No IACUC member should be excluded should she or he wish to partici pate in an inspection. *Ad hoc* consultants may be used although the IACUC remains responsible for the evaluations and reports. The inspection team should have a working knowledge of the *Guide* and AWRs in order to fully evaluate the facilities that are being inspected. Section B.2. of this Guide-book also provides general guidance in this regard.

Categories to be Inspected

It is helpful for the inspection team to use a list of categories such as:

- sanitation,
- food and water provisions,
- animal identification,
- waste disposal,
- animal health records,
- controlled and/or expired drugs,
- environmental control,-
- occupational health and safety concerns,-
- staff training,
- knowledge of applicable rules and regulations, and
- security.

The IACUC may determine whether the supervisory personnel of various facilities should be notified of the date and time of an inspection. Advance notification allows individuals to be available to answer questions; an unexpected visit may show the facility during usual operations but also may result in a visit having to be rescheduled if key individuals are not available.

Performing Inspections

Adherence to the following recommendations will assist the IACUC in performing inspections:

- An updated list of all facilities to be inspected should be maintained by the IACUC.
- All proposals submitted to the IACUC should specify locations where animal procedures will be performed.
- It is helpful to maintain a list of all facilities including room number, function of the room, species, and deficiencies identified during the previous inspection.
- For satellite areas a contact person is useful.
- For facilities with multiple rooms a floor plan can assist the inspectors.
- If a subcommittee is performing the inspection, a blend of Committee members who last inspected the area with members who did not can bring both continuity and a fresh perspective to the inspection process.
- Notes should be taken throughout the visit to assist in preparation of the final report.
- Apparent deficiencies should be discussed with the person in charge of the facility to ensure that the team's perception of the situation is accurate. In some cases an apparent deviation will be due to the experiment in progress, e.g., withholding of food prior to surgery.
- Use of a checklist provides consistency and helps document that all categories were assessed.

While the inspection of each facility must occur semiannually, there is no regulatory requirement that all facilities at an institution must be inspected at the same time (e.g., during the same month). Therefore, IACUCs at large institutions can stagger these inspections throughout the year, as long as each animal area is inspected at least every six months.

Use of AAALAC Activities as Program Evaluation

Provisions permitting use of *ad hoc* consultants may be invoked by IACUCs to make use of either of the two AAALAC assessment programs (Program Status Evaluation or Accreditation), or pre-assessment preparation activities, to meet the requirements for an IACUC semiannual program evaluation and subsequent report. In order to utilize one of these AAALAC related activities as a semiannual evaluation, the IACUC must ensure that the report complies with IV.B.3. of the *PHS Policy*, and officially endorse the report and submit it to the IO. If an institution is covered by the AWRs, the report must comply with §2.31(c) of the AWRs, at least two IACUC members must participate, no member wishing to participate may be excluded, and the report must be signed by a majority of the IACUC mem bers and include any minority views.

Documentation

A written report of the semiannual program review and facility inspection must be prepared. The AWRs require the report to be signed by a majority of the IACUC. The report must describe the institution's adherence to the AWRs, the *PHS Policy*, and the *Guide*, and identify specifically any devia tions from these documents.

Any deficiencies identified in these reviews must be designated by the IACUC as minor or significant. A significant deficiency is defined as a situation that is or may be a threat to animal health or safety. The IACUC, through the IO, must promptly report to OLAW any serious or continuing noncompliance with the *PHS Policy* or any serious deviation from the provisions of the *Guide*. For both categories of deficiencies, a reasonable and specific plan and schedule with dates for correction must be included in the final report. All individuals to be involved in the corrections should be consulted to ensure that the plan is realistic. If the institution is unable to meet the plan, the IACUC, through the IO, must inform Animal and Plant Health Inspection Service (APHIS) officials within fifteen business days of the lapsed deadline (AWRs). If the activity is federally funded, the relevant funding agency also must be informed.

The report should indicate whether or not any minority views were filed, and minority views must be included in the final document. A copy of the report is sent to the IO and must be kept on file for a minimum of three years. It is often useful for the report to be delivered in person in order to emphasize the findings and plans for action. The institution must notify OLAW of the dates of the semiannual program evaluations and facility inspections in an annual report.

References

B.2. Animal Environment, Housing and Management

This section provides an overview of the IACUC's role regarding animal environment, housing and management. The *Guide* provides recom mendations that are written in general terms and require the application of sound pr

B.2.b. Animal Environment

Housing

The range of daily temperature fluctuations should be kept to a minimum (e.g., ± 2º F) to avoid large demands on the animals' metabolic and behav ioral processes. Relative humidity should also be controlled (e.g., 30% to 70%). In general, an air exchange rate of 10 to 15 changes per hour is considered an acceptable standard.

Light intensity, duration of exposure, wavelength of light, light history of the animal, pigmentation of the animal and other factors should be considered when establishing an illumination level in the animal room.

Because sound exposure can have variable effects on animals, noise gen erators (e.g., human activities, noisy animals, equipment) should be mini mized in animal areas. Environments should be designed to accommodate animals that make noise, rather than resorting to methods of reducing the noise made by animals.

A review of an animal care and use program should include consideration of environmental standards adopted for the facilities with adequate jus tification for deviations, which are reviewed and approved by the IACUC. While environmental control in outdoor facilities is much less stringent, acceptable ranges in temperature for several species are specified in the AWRs. Reliable methods for monitoring environmental control systems should be in place, including an after-hours monitoring and response program. Back-up heating, ventilation, air conditioning, and lighting sys tems are highly desirable.

B.2.c. Husbandry

Animal Identification

It is imperative that research animals be adequately and appropriately identified and that records pertaining to individuals or groups of animals be maintained. A wide range of acceptable identification methods can be employed, including:

- cage cards,
- subcutaneous transponders,
- ear notches and tags,
- collars,
- colored stains, and
- individual animal tattoos.

The use of toe-clipping to identify individual rodents is discouraged; when necessary, it should be rigorously justified for scientific necessity and done only on very young rodents.

Animal records may consist of a cage card or may involve detailed indi vidual animal information, depending principally on the species and research requirements. Cage cards should include:

- source of the animal,
- strain or stock,
- names and locations of responsible investigators,
- pertinent dates, and
- protocol number.

Feeding

All animals should receive food that is:

- palatable,
- free from contamination, and-
- of sufficient quantity and nutritive value to maintain their good health.-

Specific diets should be selected based on the needs of each species, with special consideration of the requirements for Vitamin C by guinea pigs and some species of nonhuman primates. Animals should be fed at least once a day except under conditions of hibernation, veterinary treatment, pre-procedural fasts, or other justified circumstances. In some species and in some circumstances, varying the diet by providing “treats” can improve animal health and well-being. However, caution should be exercised that animals do not forsake eating their nutritionally balanced diet for treats.

It is known that standard commercial dry bulk foods, when stored properly, retain their nutritional value for six months (generally three months for those containing Vitamin C, unless a stabilized form is used).

To help ensure that fresh, uncontaminated food is provided:

- bags should be stored off the floor,
- the milling date should be known (the date or a code is usually stamped on each bag), and
- the oldest stock should be used first.

Small quantities of food may be kept in animal rooms if stored in tightly covered, leak- and vermin-proof containers; these should not be moved from room to room.

Food should be provided in receptacles that are accessible to all animals in a cage or pen and placed so as to minimize contamination. More than one receptacle may be necessary for some socially housed animals. Food receptacles should be easily cleaned and sanitized, and those functions should be performed on a schedule that meets *Guide* and AWR require ments. With limited exceptions, (e.g., neonatal animals or animals with limited mobility) food should not be placed on the bottom of the cage. Although some species may prefer this presentation, it results in waste and contamination of the food.

Watering

Potable drinking water should be available continuously or provided as often as necessary for the health and well-being of the animal, considering the animal's species, age, condition, and any research requirements. Water may be provided in receptacles (e.g., bowls, bottles or via automatic water ing systems). Whatever method is used, care should be taken to ensure that water does not become contaminated and is actually available. Water may be treated or purified to eliminate contaminants; however, some water treatments may cause physiologic changes, alter microflora, or affect ex perimental results. Sipper tubes and automatic watering devices should be checked daily for patency and cleanliness. Animals occasionally need to be trained to use automatic watering devices. Water bottles generally should be replaced and sanitized rather than refilled.

Bedding

Bedding may be used in the housing of a variety of commonly used lab- oratory animals. Bedding material should be absorbent and free of any suh1hkanim he 6122840hin tigsome wat58er than on, a7oy for1.248laApgas

relatively odor free. Care should be taken to keep bedding from contacting water tubes as this may lead to leakage of water into the cage. The fre quency of bedding change depends on several factors, including the number of animals, species, type of caging, and type of bedding.

B.2.d. Facility Maintenance

Cleaning and Sanitation

Cleanliness and sanitation are essential to the operation of an animal facil ity. The *Guide* and AWRs set forth recommended frequencies and methods for cleaning and sanitation of facilities, equipment and accessories. In gen eral, the frequency and methods should ensure that animals are maintained in a clean, dry environment, free from exposure to harmful contamination and excessive animal odors. Cleaning agents that mask animal odors should not be used as a substitute for good sanitation practices. Cleaning equip ment such as mops and buckets should not be moved from room to room due to the potential for cross-contamination.

The most efficient and effective method of cleaning and sanitizing cages and accessories (e.g., feeders, water bottles, sipper tubes) is the use of a mechanical washing machine that provides rinse water temperature of at least 82.2ºC (180ºF) for a time adequate to achieve sanitization. Alternatively, portable high pressure spray washing and disinfection may be used. Least efficient and effective is hand washing and disinfection of such equipment. In general, enclosures and accessories (e.g., cage tops) should be sanitized at least every two weeks. Solid bottom cages, water bottles and sipper tubes should usually be sanitized weekly. The supply lines of automatic watering systems should be flushed and disinfected on a regular basis.

Waste Disposal

A research animal facility generates a significant amount of waste that must be removed and disposed of on a regular, frequent basis. Waste containers should be readily accessible throughout the facility and should be leakproof and equipped with tight-fitting lids. Disposal methods, including incin eration and removal to land-fill, must conform to federal, state and local requirements. Some jurisdictions consider all soiled animal bedding from a research facility to be “medical waste,” with consequently more stringent disposal requirements.

If waste must be stored while awaiting disposal, the storage area should be outside the animal holding and clean equipment areas. Animal carcasses and tissues require a separate cold storage area and regularly scheduled removal. Hazardous waste, including carcasses of animals exposed to radioactive or biohazardous agents, must be adequately sterilized and/or contained prior to removal and disposal.

Pest Control

The research animal facility is an active place, with frequent movement of personnel, animals, equipment, containers, and food and bedding, creating ideal conditions for the introduction of pests, including arthropods, birds and wild rodents. Pest control programs are complicated by the potential for harm to animals and personnel, as well as interference with research data by many commonly used pesticides. A regularly scheduled, documented pest control and monitoring program should be implemented, which effectively combines elimination of all entry and harborage sites with good waste disposal and personnel training. If traps arfo Td(douobserv 0 Tdgenlifie(waste

- promoting the expression of species-typical activity in a cohesive behavioral management program for all vertebrate species.

The AWRs require that research facilities develop, document and follow a plan for environment enhancement adequate to promote the psychological well-being of nonhuman primates.

The plan must address:

- the social needs of nonhuman primates;
- environmental enrichment of the primary enclosure through provision of cage complexities, manipulanda, varied food items, foraging or task-oriented feeding methods, and safe personnel interaction; and
- special needs of certain classes of primates (e.g., young animals, animals in psychological distress, some individually housed primates, and some great apes).

Exemptions frogr1l <</MwTf-0.02t0 0 00 10 48 344.i5ge complexities/T1_0.:utex7 4

Oversight

The IACUC should provide oversight of the behavioral management program in a manner similar to its oversight of other husbandry components of the animal care and use program, and evaluate program outcomes during semiannual reviews.

To adequately discharge this responsibility, the IACUC should have access to training or other orientation materials that will assist the IACUC members in evaluating the adequacy of the program (Bayne 2000). Formal, written plans for nonhuman primate environmental enrichment and canine exercise, established to provide a framework to the behavioral management program, should be approved by the IACUC and reviewed periodically. The committee should idenimeGy wh it r

B.3. Role of the Veterinarian

Adequate veterinary medical care is an essential component of an animal care and use program and is required by the *PHS Policy* and Animal Welfare Regulations (AWRs). Institutions with smaller programs may opt for a part-time consulting veterinarian; the veterinarian's overall responsibilities remain the same in all cases.

It is the institution's responsibility to support ongoing improvements in the animal care and use program through the development and implementation of procedures and policies (e.g., IACUC guidelines) that enhance the health of the animals (ACLAM 1996). Clear provisions should be made to give the veterinarian appropriate authority to execute a program of adequate veterinary care, including access to all animals.

Qualifications

The veterinarian participating in a laboratory animal care and use program must have training or experience in laboratory animal science and medicine, or in care of the species of animals maintained by the institution. Veterinarians can demonstrate the breadth and relevance of their expertise by achieving certification as a Diplomate of the American College of Laboratory Animal Medicine (ACLAM) or through other work experience and career accomplishments. Specialty training programs are available at a number of government, academic and commercial institutions to prepare graduate veterinarians to pursue ACLAM certification. Alternatively, veterinarians may qualify for ACLAM certification by working in a laboratory animal resource program and meeting other specified criteria.

The veterinarian providing support to a laboratory animal care and use program must meet applicable state veterinary practice acts, inclusive of licensure requirements, particularly in the h1tresponsibep4g52omplumber of g3of

Responsibilities

The chief responsibility of the veterinarian is to provide for the health and welfare of animals. The Report of the American College of Laboratory Animal Medicine on Adequate Veterinary Care in Research, Testing and Teaching provides a detailed description of adequate veterinary care. The details of a veterinary care program will depend on the species of animals employed and the particulars of the laboratory animal use, but in all cases the program and care provided must comply with standard veterinary practice.

The introduction of new animals is an important aspect of the veterinary care program with such considerations as stabilization periods, isolation and quarantine. Animals should be obtained only from licensed dealers or other legitimate sources. One of the prime mechanisms for ensuring high quality laboratory animals is to purchase them from commercial vendors who produce specific pathogen-free stock and maintain rigor

These programs include:

- immunization against infectious pathogens;
- surveillance of colonies for specific infectious microbial agents;
- disease prophylaxis utilizing pharmaceutical agents;
- isolation and quarantine of incoming animals; and
- separate housing of animals according to species, source or different background microbial floras.

While preventive medicine programs are successful in reducing the incidence of disease, illness and injury may still occur in laboratory animal colonies. The veterinarian is responsible for monitoring animal health, providing adequate diagnostic support through clinical assessments, laboratory diagnosis and necropsy when required, and treating animals when illness or injury necessitates veterinary medical care. Using a documented process, the veterinarian may delegate responsibility for care to trained technical staff but must always be available to provide rapid diagnosis and treatment.

The AWRs stipulate that the veterinarian attend to not only the physical health of animals, but also the psychological well-being of nonhuman primates, and exercise for dogs. The plan for canine exercise must be approved by the Attending Veterinarian (AV) before it can be implemented. Additionally, animals that are exempted from either the canine exercise plan or the nonhuman primate psychological well-being enhancement plan for health, condition or behavioral reasons must be documented by the AV and, unless a permanent condition exists, reviewed by the AV every 30 days.

Specific areas requiring the veterinarian's attention and guidance are:

- the selection and utilization of suitable anesthetic and analgesic agents and methods of euthanasia;
- appropriate selection of species for research projects; and
- proper performance of surgical procedures and adequate pre-operative, surgical, and post-operative care.

The veterinarian should discuss with investigators the design and implementation of study proposals and may provide written guidelines dealing with these and other issues. Collegial exchanges between the investigator and the veterinarian before the submission of a proposal to the IACUC may address many of the Committee's concerns and expedite the review process.

many institutions. However, institutions should also be aware that the domination of IACUC activities by the veterinarian(s) may foster or be symptomatic of the disengagement of other members, thereby resulting in a less cohesive and effective IACUC.

The veterinarian should keep abreast of current literature on comparative medicine and laboratory animal science. The knowledge gained often leads to suggestions for alternative techniques, models or species that may enhance animal well-being, augment the study design and help ensure the completion of the proposed study.

Reference

American College of Laboratory Animal Medicine. 1996. Report of the American College of Laboratory Animal Medicine on Adequate Veterinary Care in Research, Testing and Teaching.

B.4. Occupational Health and Safety

The health and safety of individuals working in animal care and use programs is an area of institutional concern requiring commitment from the senior officials of the institution. The goal of the occupational health and safety program (OHSP) is to prevent occupational injury and illness by avoiding, controlling or eliminating hazards in the workplace. The emphasis of such a program is the prevention of illness and injury, but it also includes provisions for early diagnosis and treatment when necessary.

The IACUC also has a role in ensuring that personnel comply with health and safety requirements (e.g., ensuring personnel have received appropriate training, evaluating compliance with standard operating procedures or institutional policy during semiannual facility inspections, etc.).

Elements of an Occupational Health and Safety Program

An effective program design requires input from health and safety specialists and will include the following elements:

- administrative procedures,
- facility design and operation,
- risk assessment,
- exposure control,
- education and training,
- occupational health-care services,
- personal protective equipment,
- equipment performance,
- information management,
- emergency procedures, and
- program evaluation.

The details of each element will be dictated by the extent and nature of employees' exposure and the type of animal use program.

Personnel Participation in the Occupational Health and Safety Program

A wide range of personnel (e.g., animal care staff, investigators, technical staff, students, volunteers, engineers, housekeepers, security officers, and maintenance personnel who care for or use animals, their tissues or fluids, or who may be exposed to them as a consequence of their job) should be provided the opportunity to participate in the OHSP.

The extent and level of participation of personnel in the OHSP should be based on risk assessment, including:

- hazards posed by the animals and materials used;
- exposure intensity, duration, and frequency;

- susceptibility of personnel; and
- history of occupational illness and injury in the workplace.

Health and safety specialists should be involved in the assessment of risks associated with hazardous activities.

Education and Training

There are ethical and legal requirements to inform individuals of health risks that affect them and appropriate precautions. The objectives of an institution's OHSP can be achieved only if employees are appropriately trained to understand the hazards associated with their work area and job duties, and how those risks are mitigated through institutional policies, engineering controls, work practices, and personal protective equipment.

Training should include information about:

- zoonoses,
- chemical safety,
- microbiologic and physical hazards (e.g., allergens, radiation),
- hazards associated with experimental procedures,
- handling of waste materials, and
- personal hygiene.

Proficiency in work assignments through education and training will also contribute to a safer work environment. Training should be a continuous process, and records of OHSP training of personnel should be maintained.

Preventive Medicine and Provision of Medical Care

The principal means of preventing occupationally acquired illness or injury is by controlling or eliminating hazards. The efficacy of the prevention program will depend on the institution's resource allocation to hazard control and the cooperation or compliance of personnel who are potentially at risk. The quality of the preventive medicine program can also be increased if its development and implementation involves input from trained health professionals.

In addition to established mechanisms for reporting and treating accidents and injuries, the institution should have access to medical expertise in zoonotic diseases and other health risks associated with laboratory animal care. Good communication with medical staff will also facilitate better management of the health of animal care personnel and minimize repeat injuries and infections.

Specific Medical Concerns for Individuals Working in the Animal Research Environment

The complexity of the animal research environment creates numerous classes of hazards.

Physical hazards include:

- animal bites, scratches, and kicks;
- sharps;
- flammable materials;
- high pressure containers and equipment;
- low or single color lighting in animal rooms resulting in poor visibility;
- electric hazards, particularly in areas of water usage;
- ultraviolet and ionizing radiation;
- lasers used in surgical areas;
- inadequate housekeeping practices;
- ergonomic demands;
- machinery; and
- noise.

Chemical hazards result fr

reduce the potential development of laboratory animal allergy and possibly alter its severity.

Infectious diseases also pose a significant risk depending on the species and health status of animals involved and the level of exposure to them by animal care personnel.

Infectious diseases to which animal care personnel may be exposed include:

- viral infections, such as contagious ecthyma, the hepatitides, and *Cercopithecine herpes virus* 1 (Herpes B);
- rickettisal diseases, such as Q fever and cat scratch fever;
- bacterial diseases, such as tuberculosis, salmonellosis, and shigellosis;
- protozoal diseases, such as toxoplasmosis, giardiasis, and crypto-sporidiosis; and
- fungal diseases, such as dermatomycosis.

In addition to infections acquired from live animals, animal tissues and excrpr

B.5. Personnel Training and Education

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result in inadequate husbandry and poor peri-procedural care, which can undermine the physiological status of the animal thereby potentially impairing the integrity of research results.

Who Should Receive Training?

All staff should receive training if they interact directly with or work in the vicinity of animals. Training made available for each type of staff should be specific to the animal species involved and to the kind of procedures to be performed or animal-related interactions.

For training purposes, staff can be grouped as:

- researchers,
- animal care technicians, and
- other (e.g., maintenance or support staff).

In some institutions, staff may not be clearly divisible into these groups if job responsibilities are more diversified than this classification suggests. For example, facility staff such as animal health technicians may have job functions that include both animal care and research procedures.

Training should also be made available to temporary staff, such as students and visiting scientists. These groups may be difficult to intercept for training unless there is a way to identify them.

Development of a Training Program

A training program should meet the needs of each type of staff, as described above, who work with or around laboratory animals. There are many training resourcesd(esteam, madgicalehat inc be gr)usintere

All staff should have exposure through training to regulatory requirements for animal welfare and occupational health and safety considerations. Staff who work directly with animals should have training that supports the humane care and use of animals in the course of day-to-day procedures.

The AWRs, in Sec. 2.32 (c), require that training and instruction of personnel must include guidance in at least the following areas:

(1) Humane methods of animal maintenance and experimentation, including:

(i) The basic needs of each species of animal;

(ii) Proper handling and care for the various species of animals used

B.5. Table A. General Training Objectives

Topics	Animal Care Personnel	Research Personnel	Other Personnel
Animal welfare laws, regulations, policies, and guidelines	■	■	■
All animals are to be on a protocol	■	■	■
Cage card information	■	■	■
How to report perceived deficiencies in animal care and use	■	■	■
Recognizing pain and distress		■	
Alleviating pain and distress		■	
PI's responsibilities		■	
Protocol requirements	■	■	■
Role of the IACUC	■	■	■
Animal related hazards	■	■	■
Facility hazards	■	■	■
Occupational health and safety concerns	■	■	■
Behavior and appearance of healthy animals	■	■	■
Proper use of cage wash equipment	■		
Assure qualifications of research staff		■	
Humane techniques for animal procedures		■	

Personnel Training Records and Documentation

Although there is no specific requirement to document individual training activities, training records demonstrate that staff have met the training requirements related to their responsibilities in the research animal program, and regulatory or other oversight authorities often request to inspect personnel training records as evidence of an effective program.

Training records have value in tracking the range of topics offered, the frequency of training sessions, and the participation of institutional staff. Such records may include training received in informal settings, e.g., one-on-one instruction, common for teaching animal use methodologies.

Training records may be archived with the IACUC, a training coordinator, research departments or individual laboratories. Whatever the location, training records should be accessible to inspection by any oversight authority, including the IACUC. If training records of research staff are stored in laboratories, a good practice would be to include a brief review of training records among the objectives for the IACUC's semiannual inspection of facilities.

Training Personnel

Many institutions with a large research program have a training coordinator to oversee the training program for all personnel with animal care and use training needs. The training coordinator should be involved in IACUC meetings when institutional training issues are discussed.

Training coordinators should not be the only ones with training responsibilities. The facility staff, (e.g. veterinarians, veterinary technicians, facility managers and animal care technicians), also should be involved in training activities to the greatest extent possible. Their training activities, either with individuals or groups, should be acknowledged as a valuable contribution to the animal research program. In this way, individual expertise is fully utilized and every contact with facility staff offers a training opportunity.

In addition, other staff or outside consultants with specialized expertise can be incorporated into the training program. For example, occupational health professionals may be invited to take part in training on safety related issues. Training in specialized animal methodologies may be best performed by researchers who are accomplished in these techniques. Training program staff, if available, should participate in or oversee the training by outside experts to ensure that the training content is appropriate.

Institutional Support of Training

A high level of staff participation in a training program is essential for achieving the performance standard of staff qualifications necessary for quality research and expected by regulatory authorities. Institutions with mandatory training programs often have the most uniform results.

When training is not mandatory, there is much that an institution can do to encourage participation in the training program. When senior management and IACUC members take part in formal training programs, (e.g., on compliance issues), staff recognize an imperative to attend these sessions. The involvement of outside speakers with recognized expertise is often successful to draw larger groups to a training session. Letters urging staff participation in training programs are effective when sent by senior administrators and the IACUC to department chairpersons and principal investigators.

Methods that increase awareness and availability of information within the institution are valuable to support a training program. A combination of a training manual, newsletters, mailings, posted flyers, brochures and a Web site inform staff about the requirements for training, the institution's animal welfare standards, and the services available in the training program.

References

Russell, W. M. S. and R. L. Burch. 1959. *The Principles of Humane Experimental Techniques.* Methuen & Co., London. (Reprinted as a Special Edition in 1992 by the Universities Federation for Animal Welfare.)

NRC (National Research Council). 1991. *Education and Training in the Care and Use of Laboratory Animals: A Guide for Developing Institutional Programs.* A report of the Institute of Laboratory Animal Resources Committee on Educational Programs in Laboratory Animal Science. National Academy Press, Washington, DC.

B.6. Emergency Preparedness

B.6.a. Security and Crisis Management

Anti-animal research activities during the past several years against institutions using animals in research, testing and teaching programs have included demonstrations, break-ins, vandalism, life threats and harassment by mail or telephone, arson, and bomb threats. Since the IACUC has responsibility for the welfare of animals at its facility, it shares responsibility for the security of the animals and personnel who care for and use these animals with other units within the institution, such as the units responsible for security, public information, and governmental relations. Institutions receiving federal funds have an obligation to protect the federal investment in research by exercising due diligence in this area. The IACUC can serve a key r

is helpful for this team to meet periodically to keep abreast of current issues at the national and local level, and to be apprised of cur

d. Identify ongoing investigations by regulatory agencies.
e. Limit access of delivery persons within animal care facilities.
f. Keep duplicate physical layout plans available off site.
g. Share information with security personnel about activism at other research organizations.
h. Develop a document that will provide pertinent information to the police in the event of an incident such as type of incident, location, animals or property destroyed or stolen, people involved, time, method of entry, and need to check for hazardous materials.

5. Organize a communication plan in the event of an incident during the day, after hours, weekends and holidays.

Communications and Risk Reduction

Institutions using animals need to communicate effectively and on an ongoing basis with the internal and external community and the media. It is important to build these relationships over time and to keep individuals in all of these areas informed about the significance of the work in which animals are used, and the institution's commitment to scientific standards through quality animal care and use. Being proactive by conveying significant advances in research using animals ethically and humanely can reduce the potential for negative public reactions in a crisis situation.

The IACUC Chair and members can interact with institutional public information officers, researchers, veterinarians, technicians and the research administration to identify spokespersons to address animal research issues. These spokespersons should be provided adequate training. Fact sheets should be readily available about the institution's policies and commitment to humane and appropriate animal care and use, the quality of its animal care and use program (including accreditation), and brief summaries of the value and importance of any specific animal use under scrutiny. Written materials need to be written in language understandable to nonscientists. Institutions must be prepared to respond to allegations honestly (i.e., if real noncompliance with relevant policies or regulations is substantiated then the institution must take appropriate action and should be forthcoming about the situation).

In the event of a crisis the facility that is prepared can respond quickly through its spokespersons with accurate and factual information. It is also important for the institution to notify OLAW in such an event so they can confirm

the status of the institution's PHS Assurance and any PHS support, as well as AAALAC, which maintains a crisis communication plan to assist accredited institutions.

Maintaining a high quality animal care and use program, good relationships within the institution and the community, and an effective education program can help to prevent and alleviate many crisis situations and significantly reduce the need for long term damage control.

References

CBRA Crisis and Communications Manual, California Biomedical Research Association. April 2000.

Institutional Administrator's Manual for Laboratory Animal Care and Use. PHS. NIH Publication #88-2959.

B.6.b. Disaster Planning

As a fundamental component of the operational plans for most animal facilities, the Disaster Plan is a detailed, site-specific compilation of critical resources that are helpful in a variety of crisis events. The *Guide* recommends that all animal facilities have a Disaster Plan as part of their overall program and that the veterinarian or animal facility manager be part of the official institutional response team. While the *Guide* does not outline the elements of a Disaster Plan, it does suggest that facilities maintain sufficient emergency power necessary to maintain critical services (e.g., heating, ventilation and air conditioning (HVAC) system) and support functions (e.g., freezers, ventilated racks, isolators). Unique components of the facility may require special considerations. The proper institutional authority should approve the final plan so that appropriate resources can be committed during an emergency event. Typically, the IACUC does not have primary responsibility for emergency preparedness, but because emergency events could have significant impact on animals and the animal facility, the committee may choose to assess their site's preparedness during regular semiannual program reviews.

Emergency Management

In addition to the development of a Disaster Plan, an animal facility should consider approaching disaster preparedness from the more encompassing perspective of emergency management. One invaluable resource for emergency management information is the Federal Emergency Management

from the facility engineering/maintenance group, security, occupational health services, safety, public relations and risk management. Due to site-specific variables such as the type of facility, hazards, risks and available resources, teams will be as unique as the plan. One of the early actions of the team should be to define its mission, goals and methods of operation. The team will also need to enlist project support from senior management so that reson. mtjn /Att1on. m o-0t011d(ces, teams withe 9ifa(omimplor mae /Pagmetpson.

being made. If electrical power is lost, and the facility is relying on emergency back-up generators, there may be r

with the loss of a critical function or system. This approach is best when it includes evaluation of the reliability of the back-up systems affected during a complex emergency situation. Available resources should be clearly identified and information on how to access the resources included. Clear lines of authority and responsibility should be established and documented.

Training Staff and Testing Emergency Equipment

Personnel are usually familiar with “fire drills” through participation in regular emergency evacuation testing of buildings. Effective disaster planning borrows that concept and conducts the same types of rehearsals for other high-risk emergency situations. Exercising realistic scenarios not only provides practical training but also ‘”tests” the emergency plans for deficiencies or vulnerabilities. Similarly, emergency equipment should be tested and maintained in working order. Finally, the Disaster Plan should be made readily available to all staff members. Some facilities have the plan available on internal Web sites.

Conclusion

Animal facility management should recognize that emergencies and unexpected problems are inevitable. Adopting the mindset that emergencies are a fact of life and will occur is the first step towards their prevention. Preparedness is critical for emergency avoidance and can reduce, if not
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B.6. Table A. Examples of Categories of Emergencies

Natural Emergencies

Primary Emergency	*Secondary Effects*	*Risk of Occurrence*	*Impact*

B.6. Table A. Examples of Categories of Emergencies *(continued)*

Civil Emergencies

Primary Emergency	*Secondary Effects*	*Risk of Occurrence*	*Impact*
Terrorist threat/action			

Suggested Reading

Anderson, S. 1998. Hazard Analysis: Preparing for Natural Disasters, *Lab Animal* 27(1):24-29.

Federal Emergency Management Agency (FEMA) Web site: www.fema.gov.

“Animal in Disaster” a two module training program by FEMA.

Heath, S. E. 1999. *Animal Management in Disaster.* Mosby Year Book. St Louis, MO.

C. Review of Proposals

C.1. Fundamental Issues

The IACUC is responsible for overseeing and evaluating all aspects of animal care and use, and is charged with reviewing proposals* that involve animals to ensure that the criteria established in the *PHS Policy*

C.1. Table A. Regulator Criteria Applicable to Protocol Review as

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C.1. Table A. Regulator Criteria Applicable to Protocol Review as Defined in PHS Polic and USDA Regulations *(continued)*

U.S. Government Principles	PHS Polic on Humane Care and Use of Laborator Animals	USDA AWR 9 CFR Part 2, Subpart C
Principle 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		

C.1. Table A. Regulator Criteria Applicable to Protocol Review as Defined in PHS Polic and USDA Regulations *(continued)*

U.S. Government Principles	PHS Polic on Humane Care and Use of Laborator Animals	USDA AWR 9 CFR Part 2, Subpart C
		§2.31(d)(1) (ix): Activities that involve surgery include appropriate provision for pre-operative and post-operative care of the animals in accordance with established veterinary medical and nursing practices. All survival surgery will be performed using aseptic procedures, including surgical gloves, masks, sterile instruments, and aseptic techniques. Major operative procedures on non-rodents will be conducted only in facilities intended for that purpose which shall be operated and maintained under aseptic conditions. Non-major operative procedures and all surgery on rodents do not require a dedicated facility, but must be performed using aseptic procedures. Operative procedures conducted at field sites need not be performed in dedicated facilities, but must be performed using aseptic procedures; §2.31(d) (1) (x): No animal will be used in more than one major operative procedure from which it is allowed to recover, unless: (A) justified for scientific reasons by the principal investigator, in writing; (B) Required as routine veterinary procedure or to protect the health or well-being of the animal as determined by the attending veterinarian, or (C) In other special circumstances as determined by the Administrator on an individual basis.

Proposal Review Procedures

The procedural review requirements of the *PHS Policy* or the AWRs take precedence even though they may differ from some commonly used parliamentary procedures. Institutions may develop their own meeting procedures as long as the procedures do not contradict or are not inconsistent with the requirements of the *PHS Policy* or the AWRs.

If a proposal may cause more than momentary or slight pain or distress to animals, the AWRs specifically require investigators to consult with the AV or his or her designee during protocol development. Some committees find it helpful to assign a member a given proposal for in-depth review and liaison with the investigator prior to committee review. Still other committees assign this task to professional IACUC staff. The investigator may choose to consult with these individuals and request a preliminary review before formally submitting a proposal.

The *PHS Policy* and AWRs recognize two methods of review: full committee review and designated member review. The following pertains to review of initial protocols as well as to review of proposed significant changes in previously approved protocols.

Full committee review

Full committee review of proposals requires a convened meeting of a quorum of the IACUC members. The *PHS Policy* and AWRs are explicit that proposals reviewed by the full committee must receive the approval vote of a majority (>50%) of the quorum present in order receive approval (see A.2. Quorum requirements).

Some committees designate a specific member or members to serve as primary or primary and secondary reviewers. These individuals, usually chosen for their expertise or familiarity with a given topic, are responsible for an in-depth review of a proposal and sometimes take responsibility for describing the proposal to the full committee and answering questions about the proposal during review by the Committee. Primary and secondary reviewers can also take the initiative to contact the investigator prior to the meeting for clarifications, additional information, or in anticipation of questions the IACUC may raise. The use of primary

reviewers facilitates full committee review by distributing the workload among IACUC members so that each member has r

have the opportunity to request full committee review of any proposal. If no member requests full committee review, the Chair designates one or more qualified members to review the proposal (or proposed amendment). These designated members have authority to approve, require modifications in (to secure approval), or request full committee review.

IACUCs with a large volume of proposals to be reviewed find the designated member review option may allow for efficient management of the IACUC workload as well as timely turnaround of requests from investigators for protocol review. Some committees prefer to reserve the designated member review option for certain classes of protocols or amendments; conversely, some IACUCs have devised categories of research activities that must be reviewed by the full committee, e.g., nonhuman primate studies, survival surgeries, etc. If the designated member review method is to be used by PHS-supported institutions then the IACUC's specific procedures for using the method should be described in its PHS Assurance.

Categories of IACUC Actions

As a result of their review of a protocol, an IACUC may take one of several different actions depending upon the findings of the committee: approval, modifications required to secure approval, or withhold approval. An IACUC may also defer or table review if necessary.

The *PHS Policy* and AWRs require the IACUC to notify investigators and the institution in writing of its decision to approve or withhold approval, or of modifications required to secure approval. If approval is withheld the IACUC must provide the reasons for its decision and give the investigator an opportunity to respond.

Approval

When the IACUC has determined that all review criteria, based on the *PHS Policy* and AWRs, have been adequately addressed by the investigator, the IACUC may approve the proposal, thus providing the investigator permission to perform the experiments or procedures as described.

An IACUC-approved proposal may be subject to further appropriate review and approval by institutional officials due

Withhold approval

When the IACUC determines that a proposal has not adequately addressed all of the requirements of the *PHS Policy* and AWRs as applicable, the committee may withhold approval. A designated reviewer may not withhold approval; this action may only be taken if the review is conducted using the full committee method of review.

As indicated above, a higher institutional authority may not administratively overrule an IACUC decision to withhold approval of a proposal.

Defer or table review

If the proposal requires clarification in order for the IACUC to make a judgment, committee members with certain expertise are not present, the IACUC wishes to seek external consultation, or any of a number of other reasons prevent the IACUC from conducting its review, then the IACUC may wish to defer or table review. Good communication between the IACUC and the investigator can ensure that this action is needed infrequently. However, should it be necessary, the investigator should be informed so that he or she can respond or plan accordingly.

Review of Changes to Approved Protocols

Significant changes to an IACUC-approved protocol must be reviewed and approved by the IACUC before they occur (*PHS Policy* IV.C.1., and AWR §2.31[d][1]). It is prudent for an IACUC to develop a policy on the kinds of changes that are considered significant in order to avoid ambiguity. OLAW has identified the following kinds of significant changes that may serve as examples to guide the IACUC in its determinations:

- change in objectives of a study;
- proposals to switch from nonsurvival to survival surgery;
- change in degree of invasiveness of a procedure or discomfort to an animal;
- change in species or in the approximate number of animals used;
- change in personnel involved in animal procedures;
- change in anesthetic agent(s) or in the use or withholding of analgesics;

- change in methods of euthanasia; or
- change in duration, frequency or number of procedures performed on an animal.

Review of significant changes may be conducted using either the full committee review or the designated member review method described above.

Frequency of Review of Approved Protocols

The *PHS Policy* requires that a complete IACUC review of PHS supported protocols be conducted at least once every three years. This triennial review is interpreted by OLAW as a requirement for *de novo* review, meaning that the criteria and procedures for review specified in IV.C. of the *PHS Policy* must be applied not less than once every three years. The three-year period begins on the actual date of IACUC approval; IACUCs may not administratively extend approval beyond the three years. The triennial review may be conducted using either the full committee review or the designated member review method described above.

AWRs require an annual review, which may be a monitoring mechanism whereby the IACUC requires the investigator to annually report on the status of the protocol, verify that completed activities were conducted in accordance with the approved protocol, describe any proposed departures from the approved protocols, and solicit information about activities projected for the upcoming year. (Proposed significant changes would require IACUC review prior to initiation.) This kind of a monitoring system will satisfy the AWR requirement for annual review, but would not be sufficient for the complete IACUC review required on a triennial basis.

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C.2. Protocol Review Criteria

C.2.a. Alternatives – Replacement, Reduction and Refinement

There is significant interest in the application of alternatives to animals used in research, education and testing. The *PHS Policy* and the AWRs require research institutions to ensure that investigators have appropriately considered alternatives to procedures that can cause more than slight or momentary pain or distress in animals, consistent with sound research design. Through U.S. Government Principle III (Appendix F), the *PHS Policy* further requires that the minimum number of animals be used and that non-animal methods be considered.

The "3 Rs"

Alternatives are framed within the context of the "3 Rs" articulated originally by Russell and Burch in 1959; they include:

1. **Replacement**, or utilizing non-animal models;
2. **Reduction** of numbers of animals used; and

Nonliving systems include physical or mechanical systems and chemical techniques. Mechanical models may be used in the training of specific techniques (cardiopulmonary resuscitation, for example) and have replaced living animals in some cases. Chemical techniques are the most widely used nonliving systems and include such useful systems as the enzyme linked immunosorbent assay (ELISA). Techniques that identify the presence of chemical reactions and enzymes, or simply analyze chemical structure, can all be useful in the prediction of toxicity without the use of animals.

Computer simulations may replace some animal use and can be particularly useful when a question is well defined and there is existing data.

Although opportunities for replacement are numerous in product safety testing and education, they appear more limited in research. If it is demonstrated that there is no *in vitro* alternative to the use of animals, it is important for the IACUC members to focus on the other alternative approaches, reduction and refinement.

Reduction of numbers of animals may be accomplished by a variety of methods described in Table A:

C.2.a. Table A. Methods for Reduction of Numbers of Animals Used

Method	Examples
Rational selection of group size	• Pilot studies to estimate variability and evaluate procedures and effects • Power analysis
Careful experimental design	• Appropriate choice of control groups • Standardizing procedures to minimize variability
Maximizing use of animals	• Performing several terminal procedures per animal • Animals euthanized by one investigator used for tissue needed by another
Correct choice of model	• Use of healthy, genetically similar animals decreases variability
Minimizing loss of animals	• Good post-operative care • Avoid unintended breeding • Plan ahead so the appropriate number of animals needed for studies are ordered or bred
Statistical analysis	• Appropriate use of statistical software can generate maximum information from minimum number of animals

Refinement of technique to reduce or eliminate unnecessary pain and distress in study animals is the most commonly practiced of the 3 Rs, although it is not always recognized as one of the applications.

Investigators are required to consider alternatives to painful procedures, and to avoid or minimize discomfort, distress and pain, consistent with sound scientific practice and the goals of the research. This requires an understanding of the potential of pain or distress in the animals (see Section C.2.d.).

When there is no consensus among IACUC members as to whether a certain procedure actually causes pain or distress in the affected animals, U.S. Government Principle IV should be applied. This Principle states, “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.”

Pain-relieving drugs: While it is preferable to design a protocol that prevents pain and distress, when this is not possible the AWRs require that the AV (or designee) be consulted to develop an appropriate plan for the use of anesthetics, analgesics, or other measures, such as anti-inflammatory agents, antibiotics, or sedatives.

New diagnostic and therapeutic techniques: In addition to the use of pain relieving drugs, new diagnostic and therapeutic techniques may have the capability to dramatically reduce the invasiveness of data collection and thereby refine animal research. These include:

- use of sophisticated imaging equipment to replace invasive procedures, and
- blood and tissue sampling techniques that allow for easier collection and the processing of smaller sample sizes.

Environment: The IACUC should consider that environmental factors, such as noises, odors, infrequent or inexperienced handling, or boredom from lack of environmental stimulation can cause unnecessary distress, and that US Government Principle IV should be applied to this area as well. Aside from the AWR requirement to provide environment enhancement for non-human primates, many institutions have implemented environmental modifications for other species with a view to reducing unnecessary distress.

Humane endpoints: The establishment of the earliest possible humane endpoint consistent with the research design may provide an additional opportunity to significantly reduce pain and distress, thereby refining the experiment. For any study that defines death of the experimental animal as the endpoint, the IACUC should ask if there is an earlier point in the study when the necessary data have been collected and the animal could be euthanized without proceeding through more severe illness and death. Or, alternatively, if death is a necessary endpoint, the IACUC could ask for careful ongoing assessment of the animal, so that, when it is determined that death is inevitable, the animal can be euthanized. The Canadian Council on Animal Care Guidelines on Choosing an Appropriate Endpoint in Experiments Using Animals for Research, Teaching and Testing (1998) is an excellent resource for IACUCs. (See also chlUaP1316 Tw -2.2201 0 Td(efine2(escirTd(om)3

USDA Requirements for Consideration of Alternatives

USDA AWRs require that investigators consider alternatives to procedures that may cause more than momentary or slight pain or distress and provide a written narrative of the methods used and sources consulted to determine availability of alternatives. Animal Care Policy 12 provides guidance on the requirements for the written narrative, which should include adequate information for the IACUC to assess that a reasonable and good faith effort was made to determine the availability of alternatives or alternative methods. Resources in the area of alternatives include the USDA Animal Welfare Information Center (AWIC); ALTWEB, a Web site

- compatibility with requirement and purpose, including subsequent use of tissue;
- compatibility with species, age and health status; and
- drug availability and human abuse potential.

Recommended Methods

The 2000 Report of the AVMA Panel on Euthanasia categorizes methods as acceptable, conditionally acceptable, or unacceptable under specific circumstances.

Acceptable

a. Barbiturates (most species)
b. Carbon dioxide (CO_2)-bottled gas only (most species)
c. Inhalant anesthetics (most species)
d. Microwave irradiation (mice and rats)
e. Tricaine methane sulfate (TMS, MS222) (fish, amphibians)
f. Benzocaine hydrochloride (fish, amphibians)
g. Captive penetrating bolt (horse, ruminant, swine)
h. Ether and carbon monoxide are acceptable for many species, but relatively dangerous to personnel.

Conditionally Acceptable (Requires IACUC A 1 Tfw.(ous 9ci)016 oouET2.4JusET2cce anEMC / LI <

Various clinical signs are indicative of a moribund condition in laboratory animals. These typically include one or more of the following:

- impaired ambulation which prevents animals from reaching food or water,
- excessive weight loss and emaciation,
- lack of physical or mental alertness,
- difficult labored breathing, and
- inability to remain upright.

Animals should be observed frequently enough to detect signs of impending death so they can be euthanized in a timely manner. When increased morbidity or mortality is expected, a minimum of twice daily observation is recommended. Animals not likely to survive until the next scheduled observation should normally be euthanized. In situations where animals are often found dead, closer and more frequent observation for moribund animals should be considered to reduce spontaneous deaths. Euthanasia of animals that are moribund or experiencing severe pain and distress should always be done in a manner that produces the least possible amount of additional pain and distress.

Other Humane Endpoints in Research

Animals used to study tumor biology, to develop new cancer therapies, and to evaluate the carcinogenic potential of substances may experience pain and distress. Frequent and appropriate monitoring of animals during tumor development is necessary to allow for appropriate intervention before significant deterioration or death. Effective monitoring systems and endpoints should include limits on tumor size and severity of tumor-associated disease. Altered physiologic, biochemical, and other biomarkers may be potentially more objective and reproducible endpoints than clinical signs for such studies.

Genetically engineered animal models are sometimes accompanied by unintended and unpredicted alterations that adversely affect animal well-being. Investigators need to establish a plan for addressing unanticipated adverse outcomes for genetically altered animals. There should be a plan for systematic characterization of phenotypes to facilitate assessment of their possible utility and timely decisions on disposition or retention. IACUCs should provide oversight of such studies to ensure that animal welfare problems are handled in an effective and prompt manner.

Animals with induced infections may experience significant pain and/or distress during progression of the disease. Early physiologic and biochemical changes during infection have been found to be useful humane endpoints rather than death or moribund condition. Specific decreases in body temperature have been found to be effective early predictors of eventual death for some infections in rodents. Vaccine potency testing typically involves challenging immunized animals with infectious agents. While such testing has commonly used lethality as the endpoint indicative of insufficient protection, some regulatory authorities now allow euthanasia of moribund animals.

Toxicity Testing

Animals used in toxicity testing can experience pain and distress when toxic effects are produced. Toxicity testing regulations allow treatment of pain and distress in test animals only if there is no interference with the study. As a result, animals are rarely treated in toxicology studies because of the potential confounding effects of analgesics. Consequently, management of pain and distress in toxicity studies is accomplished largely by euthanizing animals that are experiencing significant pain and distress.

Current regulatory guidelines state that animals in toxicology studies obviously in pain or showing signs of severe and enduring distress should be euthanized, rather than allowing them to survive to the end of the scheduled study. Humane endpoints should be established and used for toxicology studies in or. Humane bunq(o2r 0 Td(. Humane endpocTd-t, e0l(ox)Tj0 n, T

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C.2.d. Minimization of Pain and Distress

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It is the responsibility of the IACUC to critically evaluate all research protocols for the potential to cause pain or distress and assess the steps that are to be taken to enhance animal well-being.

As required by the *PHS Policy* and the AWRs, and reiterated in the *Guide*, the IACUC is mandated to review protocols to ensure that pain and distress are minimized in laboratory animals. The AWRs stipulate that the IACUC determine that the principal investigator has considered alternatives to procedures that may cause more than momentary or slight pain or distress to the animal and has provided a written narrative description of the methods and sources used to determine that alternatives were not available. Additional guidance from the USDA on this subject is provided in their policies. The *Guide* states that the IACUC should ensur

Examples of procedures which the *Guide* suggests may have the potential to cause pain or distress, include:

- physical restraint,
- survival surgeries,
- food or water restriction,
- death as an endpoint,
- noxious stimuli,
- skin or corneal irritancy testing,
- tumor burdens,
- intracardiac or orbital sinus blood sampling, and
- abnormal environmental conditions.

Assessing Pain and Distress

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observations with the aid of descriptors. It is often useful to start with a general set of observations for assessing pain and distress such as change in body weight, physical appearance/posture or changes in unprovoked and provoked behavior. The assessment system should then be modified on a case-by-case basis using specific changes that may be anticipated in a particular study.

Alleviation of Pain and Distress

Accepted best practices for dealing with the possibility of unrelieved pain and distress should be considered and incorporated into protocols unless there is a sound scientific rationale for deviation from those practices. The investigator must also provide an assurance that unrelieved pain will continue for only the minimum period of time necessary to attain the study objectives.

Protocol methodology should be considered which decreases the potential for pain or distress. In addition to thorough searches of the literature, this can be done through the careful use of pilot studies to determine earlier endpoints or less invasive alternatives.

Pharmacologic treatment of pain or distress should be given as consistent with the type of pain/distress and the needs of the research question. The veterinarian must be consulted for all such protocols and should provide guidance to investigators and the IACUC. The responses of different species to different anesthetics, analgesics or tranquilizers vary and are not fully defined. Often the effects of a given drug have only been examined in a single species and definitive information, for example, on cardiovascular and respiratory function or on the ability to relieve the perception of noxious stimuli, is missing. As a result, dosages have been developed on the basis of the amount required to produce cessation of movement when the animal is confronted by what is assumed to be a painful manipulation, in conjunction with an adequate recovery. Because of the imprecise nature of the studies, dosage ranges are often quite wide, requiring a very conservative approach to their use. The use of drug mixtures further complicates the choice of an adequate dose. Numerous reference texts exist and IACUCs may request that the veterinarian prepare current charts of recommended doses as an institutional resource for investigators.

Non-pharmacologic treatments should also be employed. This may include special housing considerations, dietary and other environmental enrichments, adjustments and careful supportive care.

Summary

It is the responsibility of the investigator to show she or he has considered all the options for minimizing pain and distress that do not compromise the scientific validity of the experiment. The committee's deliberations regarding the management of potential pain and distress in a protocol should be documented. Personnel should be trained in pain and distress management. The IACUC should ensure that there is a mechanism in place for prompt reporting of sick animals to the veterinary staff.

C.2.d. Table A. Definitions of Terminolog Related to Pain and Distress

Analgesia	A complete loss of sensitivity to pain.
Anesthesia	A total loss of sensation in a part of or in the entire body.
Distress	An aversive state in which an animal is unable to adapt completely to stressors and the resulting stress and shows maladaptive behavior.
Pain	An unpleasant sensory or emotional experience associated with actual or potential tissue damage.
Sedation	A state characterized by decreased awareness of surroundings,

C.2.d. Table C. Signs, Degree and Length of Surgicall Produced Pain*

Surgical Site	Signs of Pain	Degree of Pain	Length of Pain
Head, eye, ear, mouth	Attempts to rub or scratch, self-mutilation, shaking, reluctance to eat, drink, or swallow, reluctance to move	Moderate to high	Intermittent to continual
Rectal area	Rubbing, licking, biting, abnormal bowel movement or excretory behavior	Moderate to high	Intermittent to continual
Bones	Reluctance to move, lameness, abnormal posture, guarding, licking, self-mutilation	Moderate to high: upper part of axial skeleton (humerus, femur) especially painful	Intermittent
Abdomen	Abnormal posture (hunched), anorexia, guarding	Not obvious to moderate	Short
Thorax	Reluctance to move, respiratory changes (rapid, shallow), depression	Sternal approach, high; lateral approach, slight to moderate	Continual
Spine, cervical	Abnormal posture of head and neck, reluctance to move, abnormal gait—"walking on eggs"	Moderate to severe	Continual
Spine, thoracic or lumbar	Few signs, often moving immediately	Slight	Short

**Based on observations of dogs.*

Reprinted with permission from Recognition and Alleviation of Pain and Distress in Laboratory Animals. Committee on Pain and Distress in Laboratory Animals, Institute of Laboratory Animal Resources, Commission on Life Sciences, National Research Council. National Academy Press, Washington, DC. 1992.

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C.2.e. Personnel Qualifican /As

In evaluaacng proposs[/Tr esearch projects, the *PHS Policy* and the A WRs require the IACUC to assess whether personnel conducacng procedures are appr oprianely qualifi[/Tand train[/Tin thos[pr ocedur es (IV .C.1.fTand 2.31(d)(1)(viii)). A similar requirement can be found /Atpage 10 of the *Guide* an/Tin U.S. Government Principle VIII (see Appendix F).

Developcng Guidelin[s

To t <ilitane evaluaac/Atof personnel qualifican /As and traincng durcng tor col review, eed IACUC should develop a listtof items to be assess[/Tas well as a listtof classifican /As of personnel required to pafaccipane in sud traincng. This could be a listtof qualifican /As and traincng items specific to protocols accordcng to procedures and /r manipulan /As pr opos[/T/r the listtcould be broad enough to cover all aspects of the institun /A's traincng requirements (see Secac/AtA.4).

A procedure specific checklisttmight include:

- proficiency in handlcng specific specie(s),
- proficiency in pain-relieving methods,
- proficiency in surgical manipulan /As,
- proficiency in aseptic techniques,
- proficiency in pain management,
- proficiency in euthanasia,
- proficiency in pre- and post-operan ve cae,
- Drug Enforcement Admincstraac/At(DEA) license, and
- approval by safety office.

A checklist of institutional requirements that need to be satisfied as a component of protocol review might include the following in addition to those above:

- completion of occupational health and safety risk assessment,
- demonstrated knowledge of relevant rules and regulations,
- enrollment in occupational health and safety program,
- attendance at compliance training session, and
- viewing of safety training video.

Classifications of employees whose qualifications and training may require assessment include:

- investigators,
- research technicians,
- animal husbandry personnel, and
- veterinarian and veterinary technicians.

An important decision to be made by the IACUC is the level of training required of an investigator not actually involved in the day-to-day manipulation and care of the animals. If the investigator is responsible for the research activity and the animals involved, should she or he demonstrate proficiency in the areas indicated above? Is the investigator responsible for training personnel in the lab? If yes, should she or he demonstrate proficiency in those areas? An IACUC policy on this issue will prevent conflict later.

Evaluating Qualifications and Training

To prevent problems related to assessment of qualifications and training during protocol review, it is helpful if the IACUC determines any training needs during the protocol development and veterinary consultation. Discussion of new techniques, procedures, or manipulations at this time can provide the impetus for a training opportunity for both the veterinary staff and the research staff with demonstrated proficiency completed prior to protocol review. This training experience should be so noted in the protocol or otherwise documented.

expertise can be an administrative task performed by the IACUC or staff assigned to assist with managing the animal care program. If a deficiency is noted, a follow-up memo can be sent to the investigator stating that protocol review is pending until training requirements have been completed.

IACUCs should note that high morbidity or mortality rates or requests for more animals than originally planned may indicate a training opportunity and should be followed up in the context of the relevant protocol, either immediately or during the semiannual review.

Evaluating the qualifications and training of new personnel or those proposing to use new techniques, procedures, or manipulations will necessitate another approach by the IACUC.

New Personnel

One way to manage the training of new personnel is to initiate an IACUC policy that no protocol will be reviewed until training requirements have been satisfied. Such training would need to incorporate all institutional requirements as well as those specific to the work expectations of the individual, and might include those listed above.

New Techniques, Procedures or Manipulations

When an investigator proposes new techniques, procedures, or manipulations, the IACUC must assure itself that the personnel are qualified to perform the work. If no training module on a particular technique, procedure, or manipulation exists, it is possible that the most closely aligned existing module can be used. If the personnel have not demonstrated proficiency through one of the training modules (see Section A.4), the IACUC can consider the following options:

- The IACUC may mandate that the individual(s) complete pertinent training before the protocol can be reviewed. This assumes the IACUC has a policy that stipulates adequate qualifications and training as a condition of protocol review.
- If no rther IACUC or Tows3-1218 Tew technique43pr

and training. This should not be viewed as a confrontational event, but rather one with educational value for both the veterinarian and the research staff. Documentation of this training experience should be made in the IACUC files or database.

In summary, evaluation of personnel qualifications and training is an essential component of the review of animal use protocols to ensure the humane care and use of laborator

The veterinarian plays a key role in IACUC protocol review, as described below.

Reviewing Animal Use Protocols

The veterinarian can integrate his or her experience and training with that of the investigator and advise the investigator on selection of species, their sex, age and/or size. The veterinarian can assess the ability of the animal facility and its staff to support the proposed species and associated procedures.

When the selection criteria have been established, the veterinarian can assist the IACUC in reviewing the proposed procedures and techniques appropriate to the goals of the study.

Reviewing Protocols for Potential Pain and Distress

The AWRs require that investigators proposing procedures that may cause more than momentary or slight pain or distress to the animals will consult with the AV or his or her designee. Similarly, the veterinarian has implicit responsibilities outlined in the AWRs to assess the potential for pain and distress that might be associated with the proposed animal activities, and to recommend the use of pain alleviating drugs, whenever possible, to counteract those conditions.

Reviewing Protocols Involving Surgery

The veterinarian can ensure that appropriate provision is made for pre-operative and post-operative care of the animals in accordance with established veterinary medical and nursing practices. As noted in the AWRs and the *Guide*, all survival surgery should be performed using aseptic procedures, including the use of surgical gloves, masks, sterile instruments, and aseptic techniques.

The veterinarian may provide the IACUC with assessment of the following:

- preparation of the animal for the surgical intervention, to include the use of pre-anesthetic drugs where indicated, and appropriate anesthetic agents;
- that the individual(s) performing the surgery has adequate experience or training for the specific procedures outlined in the study;

- that aseptic techniques are appropriate for the procedure; and
- that adequate post-operative care, to include post-operative analgesics where indicated, is provided.

Reviewing Protocols To Ensure Humane Euthanasia of Animals

The American Veterinary Medical Association (AVMA) provides guidance on the most humane methods to be used for euthanasia of animals, to include those used in research, testing and training. Their most recent recommendations are contained in the "2000 Report of the AVMA Panel on Euthanasia" (*JAVMA* Vol. 218, No. 5, pages 669-696). The veterinarian on the IACUC, using that publication or subsequent editions as the principal reference, can assess the investigator's proposed method of euthanasia.

After Protocol Review and Approval

Following IACUC approval of protocols, the veterinarian is in a position, through periodic visits to the animal facility and animal activity areas, to observe and evaluate animal well-being and decide whether the animal activities are being conducted in accordance with the conditions described or referenced in the protocol. The veterinarian, by virtue of training and experience, is able to serve in advocacy, oversight, and intervention roles that are distinct and unique among the IACUC members and research staff.

Checklist

*Some Examples of the Veterinarian's Responsibilities During Protocol Development and Review**

- Choice and use of appropriate analgesics/anesthetics
- Verification of appropriate drug dosages, route of administration and choice of agent
- Assistance in selection of appropriate animal model
- Identification of refinement initiatives to ensure that manipulations have a minimal impact on animal welfare
- Oversight of aseptic surgery and peri-operative care
- Oversight of animal health and husbandry pertinent to the protocol and the entire colony

- Identification of possible iatrogenic complications of model and procedures selected
-

C.3. Other Protocol Review Considerations

C.3.a. Agricultural Research

Farm animals are used in a variety of research contexts, including:

- vaccine trials,
- studies of basic biological processes,
- studies of pharmacokinetics and organ transplantation, and

Standards for Evaluation of Agricultural Animal Research and Teaching

In 1988, a consortium of organizations and agencies developed guidelines for the care and use of farm animals, the *Guide for the Care and Use of Agricultural Animals in Agricultural Research and Teaching* (known as the *Ag Guide*). The *Ag Guide*, revised in 1999, was written to aid IACUCs in the evaluation of projects involving farm animal research or teaching "for which the scientific objectives are to improve understanding of the animal's use in production agriculture and that may require a simulated or actual production setting." The *Ag Guide* is comprised of overview chapters covering institutional policies, veterinary care, husbandry, and physical plant, as well as specific species chapters for horses, cattle, poultry, and sheep and goats. Adoption of the *Ag Guide* by an institution is voluntary, although the USDA endorses it as a basis for animal care review of USDA competitive grant submissions and projects receiving experiment station funding.

This dual system of oversight for research and agricultural animals can pose challenges for IACUCs. In order to be relevant to commercial production, agricultural research must often be conducted under conditions similar to those found on commercial farms. However, there are practices that are common in commercial agriculture that would not ordinarily be permitted under the regulations governing research; for example, castrating young animals without anesthesia or closely confining animals in cages or stalls throughout the production cycle. But determining whether a particular protocol is agricultural or biomedical research, and which standards should be applied, is not always straightforward. For example, studies of basic biological processes in farm animals may benefit food and fiber production, but may also have human health implications. USDA Policy 26 provides some clarification, stating that farm animals used to manufacture and test biologicals for nonagricultural or nonproduction animals, or for humans, are considered research animals and thus are regulated under the AWA. But gray areas remain, and IACUCs need to consider animal welfare, protocol requirements, and research or teaching goals when setting standards.

Recently, there has been recognition that some melding of these different guidelines and standards may be necessary and appropriate. For example, the *Guide*, while intended to apply only to farm animals used for research purposes, recognizes that such animals may sometimes be housed in farm settings, and recommends the *Ag Guide* as a useful resource in such situations. And although USDA-APHIS decided to regulate farm animals used in research in 1991, they did not develop specific standards; instead, they adopted the *Ag Guide* and the *Guide* as guidance documents (Policy 29).

AAALAC also uses both the *Guide* and *Ag Guide* as reference documents for the accreditation of farm animal facilities and programs. Thus, the use of a performance-based approach is desirable.

Review of Protocols and Facilities

Institutions employ a number of different approaches to reviewing activities involving animals used for agricultural research and teaching. Some have a single committee that reviews all protocols, while others have a subcommittee or even a separate committee that reviews agricultural animal research protocols. (As applicable, committees must comply with the membership and review procedures required by the *PHS Policy* and the AWRs.) There are benefits and limitations associated with each of these approaches. However, what is most important is that the institution ensures uniform and high-quality oversight of all research, teaching, and testing activities involving animals, regardless of the species or the type of research being conducted.

For thorough oversight of agricultural animal care and use, it is particularly important that there be agricultural expertise on the IACUC. The *Ag Guide* suggests that the IACUC include, among other members:

- a scientist from the institution with experience in agricultural research or teaching involving agricultural animals;
- an animal, dairy or poultry scientist who has training and experience in the management of agricultural animals; and
- a veterinarian who has training and experience in agricultural animal medicine and who is licensed or eligible to be licensed to practice veterinary medicine.

There are unusual aspects of agricultural research that deserve careful consideration by IACUCs. As mentioned previously, there are certain husbandry practices common on commercial farms that have the potential to cause pain or distress that would not ordinarily be permitted under the regulations governing research. The *Ag Guide* recommends that IACUCs review these procedures, as well as husbandry conditions that do not meet the standards outlined in the *Ag Guide*, even if they are considered normal practice. Another unusual aspect of agricultural research is that the animals may be killed and marketed for human food at the end of studies, which means that there are special considerations with respect to avoiding residues from therapeutics and other drugs.

Stricklin, W.R. and J.A. Mench. 1994. Oversight of the use of agricultural animals in university teaching and research. *ILAR News* 36:9-14.

Swanson, J.C. 1998. Oversight of farm animals in research. *Lab Animal* 27, 28-31.

Tillman, P. 1994. Integrating agricultural and biomedical research policies: conflicts and opportunities. *ILAR News* 36:29-35.

AAALAC International Position Statement on “Farm Animals”.

C.3.b. Antibody Production

Antibodies are important tools for research. Depending on research needs antibodies may be produced by polyclonal or monoclonal technique. Each technique requires that specific issues be addressed in animal protocols. IACUCs should ensure adequate training of personnel in the use of proper technique when any method of immunization is proposed. The advantages of a centralized service utilizing skilled technicians to meet multiple research groups’ needs for polyclonal and monoclonal antibodies is another refinement which may enhance animal welfare in larger research pr

Because of the severity of the secondary immune response to mycobacterium in CFA, IFA must be used with booster antigen administrations in cases where CFA has been used in the initial injection.

For many years CFA was the only ef

Sometimes direct inoculation into lymph nodes, such as the popliteal lymph node, is used. With practice these nodes often can be palpated and the injection performed percutaneously.

Intramuscular injections, usually made in the biceps femoris or quadriceps muscle mass, generally are lower volumes of 0.25 ml to 0.20 –0.40 ml. Care must be exercised to avoid adjacent nerves and blood vessels as well as fascial planes when injecting into a muscle bundle. Disagreement exists as to the appropriateness of intramuscular injection of CFA. The intramuscular route of injection is recommended in some institutional guidelines and specifically discouraged in other guidelines. Intramuscular injection is generally not recommended in rodents because of limited muscle mass.

For TiterMax®, intradermal, subcutaneous, and intramuscular routes are recommended with volumes per injection site ranging from 0.01 to 0.25 ml in small and large animals. For Ribi®, intradermal, subcutaneous and intramuscular routes are recommended with volumes per injection site ranging from 0.05 to 0.50 in small and large animals.

Monoclonal Antibody Production

Monoclonal antibodies (mAbs) are homogeneous because they are produced by hybrid cells derived from a single antigen-stimulated B cell. The production of mAbs involves two phases. In the first phase an animal (usually a mouse) is immunized with the antigen of interest. Immunization of the antigen is often performed with an adjuvant, as discussed above. Splenocytes are harvested from the responding animal, and are fused with a myeloma cell line for *in vitro* propagation.

Before the immunization protocol begins, the methodology for detecting the specific antibody of interest in the mouse sera and tissue culture supernatants is developed. Otherwise, significant time and animal resources may be wasted later in the mAb-developing phase. Test bleeds should be performed in order to determine if the mice are responding to the immunizations. Most immunologically based assays for determining if the desired antibodies are being produced require less than 10 microliters of mouse serum. Once an appropriate response has been confirmed the mice should be boosted again and typically after three days from the boost the mice should be euthanized and spleens harvested.

The second phase is production of adequate quantities of mAb for a project or analysis. There are two major methods: *in vitro* and the ascites method.

The ascites method has been one of the most popular means for producing large quantities of highly concentrated monoclonal antibodies since its inception in 1972. However, improved techniques and culture media have demonstrated that mAbs can be produced by *in vitro* techniques at a quality and concentration that are similar to that of ascites. The National Research Council's report on Monoclonal Antibody Production specifically states "*in vitro* methods for the production of monoclonal antibodies should be adopted as a routine method unless there is a clear reason why they cannot be used…". In accordance with the *PHS Policy* and the *Guide*, alternatives to the use of animals (*in vitro* techniques) for the production of mAbs must be considered in place of the ascites method. (See the Office of Extramural Research Guidance concerning the Production of Monoclonal Antibodies in Animals, *NIH Guide for Grants and Contracts*, Notice OD-00-019, 2/3/2000, and the 11/17/97 OPRR Dear Colleague letter on Production of mABs Using Mouse Ascites Method).

The ascites method should only be used after *in vitro* failure of each cell line has been demonstrated, or other adequate justification is provided. Analysis of individual cell lines is necessary because the production performance

Monoclonal Antibody References

Kohler G., and C. Milstein.1975. Continuous culture of fused cells secreting antibody of predefined specificity. *Nature* 256:495-497.

Heidel J. 1997. Monoclonal Antibody Production in Gas-permeable Tissue Culture Bags Using Serum free Media. *Center for Alternative to Animal Testing: Alternatives in Monoclonal Antibody Production*, 8:18-20.

Jackson L.R., L. J. Trudel, J.G. Fox, and N.S. Lipman. 1996. Evaluation of hollow fiber bioreactors as an alternative to murine ascites production for small scale monoclonal antibody production. *J Immunol Methods* 189: 217-231.

OPRR Reports, 11/17/97, Number 98-01 Animal Welfare, Production of Monoclonal Antibodies Using Mouse Ascites Method.

Peterson N., and J. Peavey. 1998. Practical applications of *in vitro* monoclonal antibody production. C*ontemporary Topics Lab Animal Science* 37:61-66.

Monoclonal Antibody Production. 1999. National Academy Press, Washington, DC.

Jackson L., L. Trudel, J. Fox, and N. Lipman. 1999. Monoclonal antibody production in murine ascites. I. Clinical and pathologic features. *Lab Animal Science* 49:70-80.

NIH Guide for Grants and Contracts. Notice OD-00-019, 2/3/00.

Polyclonal Antibody References

NIH's ARAC Guidelines: Recommendations for Consideration in the Research Use of Inflammatory Agents. Adopted by full Committee of the NIHARC on 8/13/86. Reapproved - 5/8/96.

Halliday, L.C. et al. 2000. Physiologic and Behavioral Assessment of Rabbits Immunized with Freund's Complete Adjuvant. *Contemporary Topics* 39(5):8-13.

Jackson, J.R. and J.G. Fox. 1995. Institutional Policies and Guidelines on Adjuvants and Antibody Production. *ILAR Journal* 37(3):141-152.

Sigel, M.B., Y.N. Sinha and W.P. VanderLaan. 1983. Production of antibodies by inoculation into lymph nodes. *Methods Enzymol* 93:3-12.

C.3.c. Breeding Colonies

Investigators maintain breeding colonies for a variety of reasons. A breeding colony may be required for an established animal model because:

- the animal model is not commercially available,
- young animals have very specific age or weight requirements that cannot be fulfilled by a commercial breeding colony, or
- physiological status of the mutant animal is too severely affected for it to survive shipment.

or fine mapping to determine chromosomal location of a mutant gene. It is possible for the investigator to estimate the number of animals required, but difficult for the IACUC to evaluate this estimate in the absence of experience.

be included in the number of animals used. If suckling animals will be euthanized at or prior to weaning because they are the wrong genotype or sex for the experiment, then they may be included as animals held or euthanized but not subject to experimental manipulations.

One option is for the IACUC to request estimated animal numbers as follows:

Estimated number of weaned and adult animals to be subject to experimental manipulations _____*

Estimated number of suckling animals to be subject to experimental manipulations _____*

TOTAL _____

*Estimated numbers should be further subdivided based on invasiveness of procedures using institutional criteria:

Estimated number of breeders held but not subject to experimental manipulations _____

Estimated number of suckling animals to be euthanized at or prior to weaning, and not subject to experimental manipulation _____

In summary, the IACUC's role for oversight regarding breeding colonies includes ensuring that the need for a breeding colony has been established based on scientific or animal welfare concerns, that the procedures used in the breeding colony are evaluated and approved by the IACUC on a regular basis (e.g., as part of the semiannual program review), that there is a mechanism for tracking animals, and that the standards of care and animal well-being for the animals in the breeding colony are consistent with the *Guide*.

References

Beamer, W.G., Senior Staff Scientist, The Jackson Laboratory. Bar Harbor, ME. Personal communication.

Festing, M.F.W. 1987. Animal production and breeding methods. In: *The UFAW Handbook on the Care and Management of Laboratory Animals*. 6th ed., pp. 18-34. T B Poole (ed). Churchill Livingstone Inc., New York.

Fox, R.R. and B.A. Witham (eds). 1997. *Handbook on Genetically Standardized JX mice*. 5th edition, pp. 43-44, 120-125. The Jackson Laboratory. Bar Harbor, ME.

C.3.d. Field Studies

Federal requirements and the *Guide* focus primarily on the care and use of laboratory animals in research facilities. The same guiding principles, however, apply to the use of vertebrate species in field studies.

Application of the requirements and guidelines often pose unique challenges to the investigator and the IACUC because of the nature of field research. For example, field sites are often at a distance and may be remote, making it impractical for IACUC inspections. One solution is to require the investigator to provide photos, videotapes or other information that can help the committee evaluate the use of animals. For some 1.248 ation t.0367lOne solution is t

Species Selection

The investigator should provide information on the population to be studied and a rationale for choosing that particular population. The U.S. Fish and Wildlife Service (USFWS) issues many of the necessary permits. In issuing

marked. If the animals are to be artificially marked, there must be a description of methods to be used and potential trauma (e.g., paint markings may increase visibility to predators). Capture and marking methods are often a matter of practicality and usually have been developed and evaluated over a period of time. There is a substantial body of literature regarding the effect of mark-and-recapture studies and other study techniques on wild animals. The IACUC or investigator may rely on consultation with experts in the relevant discipline for this information. In issuing permits the USFWS also assesses capture and marking activities, and the IACUC may rely on that assessment in considering the appropriateness of a particular technique.

Field experimental procedures are commonly used to test hypotheses. In all instances, any potential pain or distress to an individual animal must be assessed and the investigator's justification evaluated in the context of the potential value of the data to be obtained.

Techniques for remotely recording behavioral or phyos ar

Euthanasia of wildlife in the field can raise unique and challenging issues. The Report of the AVMA Panel on Euthanasia includes considerations and techniques for euthanasia of wildlife and should be used by the IACUC as a resource.

Conclusion

Many of these issues are difficult to address definitively, but their consideration will help the IACUC judge the potential impact and value of the study proposed, and can be expected to assist the investigator in obtaining maximum information from the study with minimum negative impact on the animals studied or their environment. The IACUC should ensure that the investigator complies with applicable regulations and policies and obtains any required permits; the IACUC may wish to obtain copies. Many of the issues arising from proposals to conduct field research on vertebrate animals will require the judgment of experienced professionals in the field and the IACUC should feel free to seek advice or consultation if necessary.

References

Acceptable field methods in mammalogy: Preliminary guidelines approved by the American Society of Mammalogists. 1987. *J Mammalogy 68(4, Suppl.): 1-18.*

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Burghardt, Z.M. and H.A. Herzog, Jr. 1980. Beyond conspecifics: Is Brer Rabbit our brother? *Bioscience 30: 763-768.*

Guidelines for the Capture, Handling, and Care of Mammals. Undated. American Society of Mammologists. (http:www.mammalsociety.org/committees/commanimalcareuse/98acucguidelines.PDF)

Guidelines for the treatment of animals in behavioural research and teaching. 2000. *Animal Behavior 59:253-257.*

Guidelines for the use of fishes in biological research. Undated. American Society of Ichthyologists and Herpetologists. (http://www.asih.org/policy.htm)

Radioactive Materials

Hazardous Chemicals

In addition to animal care concerns, activities involving hazardous chemicals require procedures for:

- chemical storage and disbursement,
- dosage preparation and challenge procedures, and
- waste management and disposal practices.

It is also necessary to determine whether the chemicals will be present in feed, feces or urine. A rigorous review to ensure appropriate safety practices, containment equipment and facility safeguards is essential for animal experiments involving chemical inhalation.

Proposals submitted to the IACUC must include sufficient documentation to assess the adequacy of precautions to control exposure of personnel to the hazardous agents involved in animal experiments. The identification by the IACUC of protocols involving hazardous chemicals (e.g., the use of known carcinogens to induce tumors in animal models, determinations of carcinogenicity, mutagenicity, or teratogenicity, or acute toxicity studies) is essential for institutional compliance with health and safety standards. The Occupational Safety and Health Administration (OSHA) laboratory standard "Occupational Exposure to Hazardous Chemicals in the Laboratory" is of particular importance. The IACUC should be familiar with the requirement in this standard for a chemical hygiene plan for controlling exposures to hazardous chemicals. Written standard operating procedures may be required describing appropriate safety precautions and specific "designated areas" where hazardous chemicals will be used or stored.

One health and safety issue common to most IACUCs concerns the use of the inhalation agent ether for anesthesia and euthanasia. Ether forms explosive peroxide when stored in metal containers and must be used with special precautions because of its volatility and flammability. Ether must be used with special ventilation and kept away from flames or electrical ignition sources. Carcasses of animals euthanized with ether should be stored in explosion proof well-ventilated areas and not incinerated until the ether is volatilized. Other inhalation anesthetics, such as halothane, methoxyflurane and nitrous oxide, although not without some degree of toxicity in an occupational setting, are less hazardous when used with proper precautions and a waste gas scavenging system. Methoxyflurane is the most toxic of these inhalation agents to humans, and safe practices should be closely scrutinized by the IACUC.

C.3.f. Instructional Use of Animals

Any instructional use of live, vertebrate animals that is supported by the PHS is governed by the *PHS Policy*. The applicability of the AWRs depends upon the species used. Most institutions have chosen to require that all instructional use of animals, regardless of funding source or species, be reviewed by the IACUC.

It may be appropriate for students, at both undergraduate and graduate levels, to participate in the conduct of experiments involving laboratory animals for the purpose of education. All instructional proposals should clearly identify the learning objectives and justify the particular value of animal use as part of the course, whether it is demonstration of a known phenomenon, acquisition of practical skills, or exposure to research. In all cases, consideration must be given to alternative approaches to attaining the desired educational objectives, in accordance with the U.S. Government Principles.

Adequate supervision and training are especially important as the techniques learned by students may be carried into subsequent research careers. It is recommended that students receive instruction in the ethics of animal research and applicable rules and regulations prior to undertaking any experimentation. When students work in an investigator's laboratory, the IACUC must ensure that the students receive appropriate supervision and training in animal care and use. The *PHS Policy* and AWRs have specific training requirements that apply to all animal users, including students. Student projects involving protocols different from those approved for the instructor's laboratory must be reviewed and approved on their own merits by the IACUC.

Experiments sometimes entail behavioral observation with no intervention, or minor painless interventions, such as choices of food or living accommodations. Such projects teach the rigors of conducting a research project and the variability inherent to biological or biobehavioral systems. These exercises generally involve little or no distress to the animals, but still require IACUC approval.

Some procedures present additional concerns. Selected examples are listed below:

- Behavioral studies that involve conditioning procedures in which animals are trained to perform tasks using mildly aversive stimuli, such as the noise of a buzzer, may be potentially stressful to the animals.

For other behavioral studies using non-aversive stimuli, such as running mazes, it may be necessary to maintain animals at a reduced body weight to enable food treats to be used as an effective reward. Experiments involving food and water r

available for surgical neutering. Plastic models and other model systems are increasingly being used to teach manual skills.

Animals that develop unique and/or terminal conditions may be donated to a veterinary school for research and/or teaching purposes. The use of these animals needs full IACUC review.

Animal Use in Agricultural Instruction

Flocks and herds of agricultural animals are often maintained by agricultural schools to teach husbandry, production, and showmanship. Animals used for these practices are not covered by the *PHS Policy* (unless supported by PHS) or the AWRs. However, research procedures (e.g., *in vitro* fertilization), should have committee review. IACUCs charged with reviewing the use of animals in activities with agricultural applications will find *A Guide for the Care and Use of Agricultural Animals in Agriculture Research and Teaching* useful in conducting their evaluation.

References

Boschert, K. Oct. 1993. *An overview of animal use alternatives in veterinary education. Lab Animal* 22 (10) p. 36-42. Nature Publishing Company. New York, N.Y.

Kahler, Susan C. March 15, 2000. Laboratories terminated, but lessons learned. *JAVMA* 216, No. 6,

Smith, A., R. Fosse, D. Dewhurst, and K. Smith. 1997. Educational simulation models in the biomedical sciences. *ILAR Journal* 38 (2) p. 82-88. Institute of Laboratory Animal Resources, National Research Council. Washington, DC.

Ungar, K. and D.C. Anderson. Summer 1994. An inventory of databases and other sources of information on alternatives to the use of animals in science education. Johns Hopkins Cent. Altern. Animal Test. *The Center* 11 (3) p. 12-18. Baltimore, MD.

Use of animals in medical education. Aug. 14, 1991. *JAMA* 266 (6):836-837. The Association. Chicago, Ill.

White, K.K., L.G. Wheaton, and S.A. Greene. Winter 1992. Curriculum change related to live animal use: A four-year surgical curriculum. *J Vet Med Educ* Vol. 19 (1):6-10. The Association of American Veterinary Medical Colleges. Blacksburg, Va.

C.3.g. Surgery

Surgical procedures are a common component of animal research activities, and IACUCs are often called upon to assess the details of these procedures. Further, the IACUC is responsible for determining that personnel are qualified and trained in the procedures to be performed.

Definitions

Major surgery: Penetrates and exposes a body cavity or produces substantial impairment of physical or physiologic functions.

Minor surgery: Does not expose a body cavity and causes little or no physical impairment.

Survival surgery: The animal awakes from surgical anesthesia.

Non-survival surgery: The animal is euthanized before recovery from anesthesia.

Reviewing Protocols for Surgical Procedures

Some of the aspects of a surgical procedure that the IACUC reviews are:

- details of the procedure (e.g., the actual procedure itself, pre- and post-operative care, aseptic technique, sequence of multiple procedures);
- appropriateness of the species for the procedure proposed;
- qualifications of the personnel performing the surgical procedures;
- species-specific and procedure-specific facility requirements;
- patient monitoring practices in the surgical and post-surgical periods; and
- personnel occupational health and safety issues.

The veterinarian should always be one of the IACUC's primary sources of information on surgery and post-operative issues. Other sources include the AWRs (9 CFR 2.31(d)(1) (ix) and (x)), the *PHS Policy,* the *Guide*, and other publications referenced at the end of this section. While the numerous references available provide background and a basis for reviewing surgical protocols, the IACUC relies on professional judgment to review the unique situations surrounding surgery in an experimental setting. Surgical procedures performed in a research setting have review requirements that may be different from those in a routine veterinary clinical setting.

If a procedure may cause more than momentary or slight pain or distress, the AWRs prohibit the use of paralytics without concurrent anesthesia.

Some procedures may require specialized facilities to ensure their success. For example, major survival surgery in non-rodents requires dedicated surgical facilities. Details of such physical requirements can be found in the *Guide*. The IACUC should assess the availability of necessary facilities

Occupational Health and Safety

Surgical situations can present certain occupational health and safety risks related to:

- use of inhalation anesthetics,
- use of certain species or a species under certain circumstances (e.g., pregnant sheep), or
- use of certain devices (e.g., lasers).

If the circumstances warrant it, the IACUC should consult with the applicable biosafety personnel.

References

Brown, M.J., P.T. Pearson, and F.N. Tomson. 1993. Guidelines for animal surgery in research and teaching. *AJVR* (54), 9:1544-1559.

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Many blastocysts have to be injected to obtain a few new ‘knock-out’ mice, and only a few of the new ‘knock-out’ mice will incorporate the ‘knocked-out’ gene in their germ cells and become ‘founders’.

If a project uses a spontaneous or induced mutant model and the mutant animal can be purchased from a resource or commercial colony, review of this project is similar to review of any other project. If a project uses an induced mutant model and only breeders are available from the source, review of this project is similar to review of any other breeding colony**.** In either case, the IACUC should determine if the mutant gene will result in a severely debilitating phenotype, if anything can or will be done to ameliorate such phenotype, and what endpoints will be used to determine when a mutant animal will be euthanized. Simple husbandry measures can modify the severity of some mutant phenotypes. For example, ground feed or moist feed can extend life and improve growth of mutants with missing or malformed teeth. Food and water on the bottom of the cage may be easier for mutant rodents with neuromuscular abnormalities to access than food in a traditional feeder built into a cage lid. Extra bedding helps dwarf mice reach food and water. Extra bedding helps absorb urine produced by diabetic mice or other mice that excrete large quantities of urine. A normal cage mate, a solid bottom cage with extra bedding, or a slight increase in room temperature can benefit mutant rodents that have problems maintaining body temperature (Beamer, 1986).

When an investigator prepares a proposal that includes development of a new mutant model, information about clinical abnormalities associated with the phenotype, special husbandry requirements, etc. will not be available. However, the investigator should include general criteria for euthanasia if a severe debilitating phenotype develops, and provide the IACUC with this information when the new mutant has been developed or at the next annual review.

The standard of ‘normal’ for a mutant animal may or may not be the same as for a non-mutant animal. If the mutant phenotype does not impact clinical well-being of the animal, the same standard of ‘normal’ can be used for mutant and non-mutant animal. In the mouse, brown (gene symbol Tyr<b>) and short ear (Bmp5<se>) are examples of spontaneous mutations

that produce no observable, clinical impact on the well-being of the mouse. If the mutant phenotype has minimal impact on the well-being of the animal, the standard of ‘normal’ can be similar for mutant and non-mutant animal. Hypogondal (Gnhr<hpg>) and ‘little’ (Ghrhr<lit>) are examples of spontaneous mutations with minimal impact on well being of the mouse. Homozygous hypogondal mice are normal in all ways except for small, non-functional gonads. Homozygous ‘little’ mice are smaller than non-mutant littermates. Growth hormone transgenic mice tend to have larger body size than normal, but are otherwise clinically normal with the exception of reduced fertility.

In the case of mutants where phenotype involves clinical abnormalities, the standard for ’normal’ may have to be modified to encompass the expected phenotype. For example, 4 to 5 week old homozygous dystrophic mice (Lama<dy-2J>) have difficulty abducting hindlegs and have an abnormal gait. As these mice age, muscular weakness progresses in hindlegs and eventually extends to involve all skeletal muscles. The standard for ‘normal’ for homozygous dystrophic mice must include difficulty abducting hindlegs and an abnormal gait. Adenopolyposis coli ‘knock-out’ mutant mice (Apc<Min>) are clinically normal until the intestinal polyps develop, after which time the mice become anemic and lose weight. Experimental endpoints for these latter and similar mutant models should focus on (1) ability of the mutant to access feed and water, (2) response of the mutant to stimuli, and (3) general condition of the mutant (i.e., is the mutant excessively thin, showing progressive weight loss or hunched posture?).

Many institutions have a centralized induced mutant facility that receives the genetic material from investigators and performs the manipulations to develop ‘founder’ transgenic or ‘knock-out’ mice. The ‘founder’ mice are returned to the investigator who undertakes breeding to expand the line. Review of the centralized induced mutant facility should focus on personnel qualifications, animal related practices such as aseptic surgery, and average number of mice required to produce ‘founders’ for a single DNA construct, recognizing, however, that the number of mice required is a very rough estimate because of differences in responses of different strains or stocks that tha-1.25(n frs to)

In many non-mutant model experiments, an investigator can accurately estimate the exact number of animals required to test a hypothesis. However, when creating an induced mutant, there are major variables that make it difficult to accurately estimate the number of required animals, including:

- differences in percent successful microinjections of pronuclei or successful incorporations of altered gene into ES cells,
- differences in percent successful surgical transfers of fertilized eggs or blastocysts, and
- differences in percent successful incorporation of exogenous DNA or altered gene into germ cells of induced mutant mice.

Different strains of mice vary in their responses to each of these manipulations. Different genes ('constructs') vary in the ease with which they insert as a transgene or are 'knocked-out'. These variables remain even when the same skilled people perform each manipulation.

References

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C.4. Monitoring of Approved Protocols

After the IACUC has approved a protocol, it has a responsibility to ensure that procedures are carried out in the laboratory or classr

laboratories to ensure that actual procedures used are consistent with protocols. The survey may include meeting with investigators and staff to review concerns, answer questions, and identify procedur

Review of Publications

In academic institutions and many companies, much research is eventually published. Some IACUCs choose to review some published descriptions of animal use to verify that work was done according to the approved protocol.

Conclusion

Although no IACUC has the staff or time to observe all animal use in an institution, the IACUC can help establish a climate of compliance. To ensure that animal use conforms to local policy and federal regulations, it is prudent for the IACUC to confirm that animals are used according to protocol.

D. Evaluation of Animal Care and Use Concerns

Evaluation of Animal Care and Use Concerns

To help ensure that laboratory animals receive humane care and use or tr

in these procedures ar

Suggessted IACUC Procedures for the Investigation of Animal Care and Use Concerns*

Initial Evaluation and Actions

Upon receipt of a concern the IACUC Chair should convene a meeting of the IACUC. After initial review of the complaint the IACUC should determine whether it requires further investigation and immediate action, further investigation but no immediate action, or no action. Once this decision has been made, the IACUC should determine which individuals or other institu tional or noninstitutional offices may require notification at this time.

If immediate action appears warranted because animal or human welfare may be compromised, the IACUC should notify the IO and proceed accord ingly. Veterinary medical intervention, suspension of a research activity, and/ or notification of appropriate safety, occupational health, or other officials, are examples of actions that may be taken immediately to protect animal or human welfare. In accordance with the AWRs (9 CFR Part 2, Subpart C, Section 2.31[d][7]), if an activity is suspended, the IO shall report that action to APHIS and any federal agency funding that activity. If the activity is supported in any way by the PHS, the IACUC, through the IO, must promptly notify OLAW (PHS Policy, IV.F.3.) (OPRR Reports 94-02, 1/12/94).

Investigation

Should the IACUC determine that further investigation is required, the Chair, or another individual or subcommittee appointed by the Chair, should conduct the investigation and report back to the IACUC. It is important to avoid actual or perceived conflicts of interest in this process.

The IACUC should charge the designated person or group with its require ments for information gathering and impose a completion date. The assigned completion date will depend on the IACUC's determination of whether immediate remedial action may be required.

***DISCLAIMER**

Neither the AWRs nor the PHS Policy provide specific guidance regarding the consideration of concerns or the institutional conduct of investigations. Owing to the considerable diversity of concerns that may arise and the contexts in which they may be voiced, no one set of procedures will be suitable for investigating all potential situations that involve violations of or deviations from animal care and use practices required by the PHS Policy, AWRs, the Guide and other federal statutes and regulations regarding animals. Consequently, the following suggestions are broad, intended for general use, and not intended for application in all situations.

Concerns Unrelated to Animal Care and Use

The IACUC may determine, either in its initial evaluation of a concern or as a result of investigation, that violations of non-animal-r

E. Recordkeeping and Communications

E.1. Recordkeeping and Reporting

Introduction

The *PHS Policy* and AWRs include recordkeeping and reporting requirements. The responsibility for these functions should be clearly delegated. Usually the IACUC office is assigned this task. The individuals responsible should understand federal animal use requirements and the institution's program, and should also be aware of the Freedom of Information Act (FOIA) and any state open records laws. Many of the reports written may be accessible under such laws, and care should be taken to use language that is clear and precise to ensure accurate interpretation.

Recordkeeping

Minutes

The *PHS Policy* and the AWRs require that the institution maintain "minutes of IACUC meetings, including records of attendance, activities of the Committee, and Committee deliberations" (PHS Policy IV. E; 9 CFR Part 2 Subpart C 2.35 (a)(1)). The IACUC has some latitude in the degree of detail in these minutes.

Records of attendance: Although members may arrive late or leave during a meeting, generally a member is marked as either present or absent. An exception would be when the IACUC member leaves the meeting room during discussion of a protocol on which that member is a participant. If the temporary absence of a member drops the number of members present below the quorum, this should be noted in the minutes. Certain official IACUC actions require a quorum (see Section A.2. Quorum Requirements).

Activities of the Committee include corrections or approval of previous minutes; presentation of program, policy, facility and compliance reports; and decisions on policies, protocols, and amendments.

Deliberations refers to the discussion and reasons leading to particular IACUC decisions. Although some IACUCs maintain a verbatim record (e.g., audio or videotapes), minutes should include as a minimum a summary of the key points discussed prior to a committee decision.

Protocols

The *PHS Policy* and the AWRs require that animal applications and proposed significant changes be retained for the duration of the animal activity and for an additional three years after the end of the activity. Proposals submitted to the IACUC must be kept for three years even if approval was not granted or animals were not used. The records must show whether or not IACUC approval was given.

Other records

Both the *PHS Policy* and the AWRs require that semiannual IACUC reports and recommendations be retained by the institution. PHS also requires that the OLAW Assurance and reports of accrediting agencies (e.g., AAALAC) be kept on file. USDA requires additional records on dogs and cats acquired, transported, sold, or euthanized by the research facility. Animal health records are not usually maintained by the IACUC but are kept in the animal facility. All these records must be kept for at least three years; and must be accessible to PHS, APHIS, and funding agencies for inspection or copying (see Table A).

Reporting Requirements

PHS Assurance

In order to qualify for support from the PHS for activities involving animals, institutions must provide an Assurance of Compliance with the *PHS Policy*. The Assurance is a written agreement that fully describes the institution's program and commits the organization to comply with the PHS Policy, and in which the institution outlines in detail its policies and procedures. A sample Assurance is available at the OLAW Web site. Institutions that are not accredited by AAALAC must submit, with their Assurance, the most recent IACUC semiannual program evaluation. The completed Assurance, signed by the IO with appropriate authority, is submitted to and evaluated by OLAW. Upon final approval by OLAW an Assurance number (in the format A####-01 where # is a digit) is assigned to the institution. Assurances are approved for a period of up to five years, after which time the institution must submit a new Assurance. A list of institutions with approved Assurances is available on the OLAW Web site.

It is important that the approved Assurance document is distributed appropriately within the institution and that members of the IACUC are familiar with this document, as compliance with the Assurance is required to be eligible for PHS funding.

USDA Registration

Institutions that use species of animals covered by the AWRs for research, testing, experiments, or teaching on its premises as specified in the AWA are required to be registered with the Animal Care division of the Animal and Plant Health Inspection Service (APHIS), using APHIS form 7011. The form is submitted to APHIS via the Regional Director of Animal Care (AC) for the state in which the facility has its principal place of business. At academic institutions, the submission is usually made by the institution, not the individual departments or schools, and signed by the IO. An approved USDA registration is given a number in the format ##-X-####, where X is a letter (R for research institution) and # is usually a digit. The registration may be renewed every three years. The institution is required to notify the AC Regional Director within ten (10) days of any change in the name, address, ownership or operations affecting its status as a research facility. The Regional Director may place a facility that has not housed animals for two years in inactive status. The registration can be cancelled by written request if a facility no longer uses, or intends to use, animals (see Table B).

Semiannual Facility Inspections and Program Evaluations

The *PHS Policy* and the AWRs require that the IACUC evaluate the institution's animal program at least once every six months, including an inspection of facilities, and submit a report to the IO. The *PHS Policy* allows the IACUC discretion in how it evaluates its facilities and program. The report format is not mandated, but OLAW offers models for both facility inspections and program reviews on its Web site.

The report must contain a description of the nature and extent of the institution's compliance with the *PHS Policy* and *Guide*; any departures must a7.4935 0

Minor and significant deficiencies must be distinguished. A significant deficiency is defined as one that "is or may be a threat to the health or safety of animals." Program or facility deficiencies, including accidents or natural disasters, which cause injury, death, or severe distress in animals, are, by definition, 'significant.' Examples of minor deficiencies include chipped paint and burnt-out light bulbs. The report must also identify any facilities that are AAALAC accredited.

The IACUC may utilize AAALAC program status evaluations, accreditation, or pre-assessment preparation activities as a semiannual evaluation. To be used as the semiannual report, the report must include all the information required in Section IV.B.3 of the *PHS Policy* (see Table C), and be approved by vote of the IACUC.

Semiannual reports are only submitted to OLAW under two circumstances:

1) If an institution is not accredited by AAALAC, a copy of the most recent semiannual report must be submitted to OLAW with a new or renewal Assurance.
2) Upon request by OLAW or other PHS representatives.

USDA requirements are essentially the same as those for PHS with three exceptions:

1) The AWRs include additional reporting requirements if the schedule and plan for correcting a deficiency is not followed. Failure to correct a significant deficiency in accordance with the specified schedule and plan must be reported in writing within fifteen business days by the IACUC, through the IO, to APHIS and any federal agency funding the activity.
2) USDA requires that reports be reviewed and signed by a majority of IACUC members.
3) USDA does not require the identification of facilities accredited by A

If the IACUC suspends any activities involving USDA-covered animals, the IO files a report with the AC Regional Director, in consultation with the IACUC. After reviewing the reasons for the suspension and taking appropriate corrective actions, the IO is responsible for submitting a full explanation to APHIS and any federal 7UC. After r

E.1. Table C. Federal Requirements: Report of Semiannual Evaluations

	PHS Semiannual Report	USDA Semiannual Report
Timetable	• Every six months; an AAALAC report may	• Every six months; an AAALAC report may

E.1. Table E. Federal Requirements: Suspensions and Noncompliance

	PHS Suspension/ Noncompliance Report	USDA Suspension Report
Submitted by	• IACUC through IO	• IO with IACUC consultation
Submit to	• OLAW	• APHIS and federal agency funding the activity
When required	• Suspension of an activity by the IACUC • Serious deviation from the *Guide* (unless previously approved by the IACUC) • Serious or continuing noncompliance with the *PHS Policy*	• Suspension of an activity by the IACUC
Contents	• Full explanation of circumstances • Description of corrective action taken • Minority views filed by IACUC	• Full explanation of circumstances • Description of corrective action taken
Reference	PHS Policy IV.C.6. & 7. and IV.F.3. & 4	9 CFR Part 2, Subpart C 2.31(d)(7)

References

AAALAC International. *Connection Newsletter* Summer 2000, pages 1-4.

Potkay, S., et al. Frequently Asked Questions about the Public Health Service Policy on Humane Care and Use of Laboratory Animals. *Contemporary Topics* 36(2)47-50, March, 1997.

NIH Guide to Grants and Contracts. Notice OD-00-007, 12/21/99.

E.2. Communications

It has never been easier to communicate with others, and at the beginning of the 21st century the use of nontraditional means of communication such as electronic mail (email), Web sites, and Internet chat rooms provide new opportunities for rapid communication.

Electronic communication offers advantages and disadvantages. Modes of communication available to the IACUC vary in speed and ease of use, clarity, and security. Some permit easy communication with an entire committee or an entire institution; and some include a permanent record that can be retained for later reference.

Regulations and Policies

Most of the regulations governing the IACUC were written before the Internet became pervasive, but OLAW has presented some guidelines for the IACUC regarding the use of email and similar modes of communication (Garnett and Potkay, *ILAR Journal* 37:190-192, 1995).

The guidelines state that email is an appropriate medium for transmitting animal protocols, IACUC meeting agenda and minutes, institutional policies, and other matters related to the animal care and use program. However, OLAW states that the conduct of IACUC meetings should allow greater opportunity for members to interact than that permitted by email. Sequential, one-on-one communication (polling) by email, telephone, or fax should not take the place of a convened IACUC meeting or voting, although it is an appropriate mechanism for providing all IACUC members with the opportunity to call for full committee review of a protocol prior to initiating the designated reviewer method of protocol review. OLAW recommends that traditional meetings, in which a quorum of IACUC members is in the same room, should be the standard method for conducting IACUC business such as protocol review, review of annual and semiannual reports, and suspensions.

Under “exceptional circumstances” an IACUC may be permitted to conduct a meeting using electronic conferencing such as telephone or audio-visual conferences. To be considered a valid convened meeting,

Appendices

American Society of Laboratory Animal Practitioners (ASLAP)

11300 Rockville Pike
Suite 1211
Rockville, MD 20852
Tel: 301-231-6349
Fax: 301-231-6071
Email: aslap@aaalac.org
Web: *http://www.aslap.org/*

The ASLAP is an organization of veterinarians and veterinary students that promotes the acquisition and dissemination of education and training in the practice of laboratory animal medicine.

American Veterinary Medical Association (AVMA)

1931 North Meacham Road
Suite 100
Schaumburg, IL 60173
Tel: 847-925-8070
Fax: 847-925-1329
Email: avmainfo@avma.org
Web: *http://www.avma.org*

The AVMA, a not-for-profit national association of veterinarians, was established in 1863 and has a current membership representing approximately 85% of the veterinary medical profession. The Association aims to advance the science and art of veterinary medicine, including its relationship to public health, biological science, and agriculture. It provides a forum for the discussion of issues of importance to the veterinary profession, and for the development of official positions. The Association is the authorized voice for the profession in presenting its views to government, academia, pet owners, the media, and other concerned publics.

Animal Welfare Information Center (AWIC)

National Agricultural Library, USDA
10301 Baltimore Avenue, 5th Floor
Beltsville, MD 20705-2351
Tel: 301-504-6212
Fax: 301-504-7125
Email: awic@nal.usda.gov
Web: *http://www.nal.usda.gov/awic/*

AWIC, a component of the USDA National Agricultural Library, is dedicated to providing information for improved animal care and use in research, teaching, and testing. AWIC also offers educational activities that are geared towards meeting the information requirements of the Animal Welfare Act, and publishes bibliographies, information resource guides, and other publications.

Applied Research Ethics National Association (ARENA)

132 Boylston Street
Fourth Floor
Boston, MA 02116
Tel: 617-423-4112
Fax: 617-423-1185
Email: PRMR@aol.com
Web: *http://www.arena.org/*

ARENA is a membership organization for those involved in the day-to-day application of ethical principles, governmental regulations, and other policies regarding research and clinical practice. ARENA services include sponsorship of national and regional meetings, the dissemination of current information on research ethics, and the provision of opportunities for networking among members through a quarterly newsletter.

Center for Alternatives to Animal Testing

Johns Hopkins University School of Hygiene and Public Health
111 Market Place, Suite 840
Baltimore, MD 21202-6709
Tel: 410-223-1612
Fax: 410-223-1603
Email: caat@jhsph.edu

Institute for Laboratory Animal Resources (ILAR)

2101 Constitution Avenue, NW
Washington, DC 20418
Tel: 202-334-2590
Fax: 202-334-1687
Email: ILAR@nas.edu
Web: *http://www4.nas.edu/cls/ilarhome.nsf*

A component of the National Academy of Sciences, ILAR is responsible for authoritative reports on subjects of importance to the animal care and use community, and for serving as a clearinghouse for information about animal resources. Its mission is to develop and make available scientific and technical information on laboratory animals and other biological research resources to the scientific community, the federal government, and the public.

NETVET Veterinary Resources

Web: *http://netvet.wustl.edu/vet.htm*

NETVET is a comprehensive website that categorizes and organizes veterinary medical and animal-related information on the Internet in a relevant, user friendly format. Much of the information is of interest to IACUCs.

Office of Laboratory Animal Welfare (OLAW)

National Institutes of Health
RKL1, MSC 7982
6705 Rockledge Drive
Bethesda, MD 20892-7982
Tel: 301-496-7163
Fax: 301-402-2803
Email: olaw@od.nih.gov
Web: *http://grants.nih.gov/grants/olaw/olaw.htm*

OLAW is responsible for the administration and implementation of the Public Health Service (PHS) Policy on Humane Care and Use of Laboratory Animals. Located at the National Institutes of Health, OLAW administers an educational program for PHS-supported institutions and investigators, negotiates Animal Welfare Assurances, and evaluates compliance with the *PHS Policy*.

Public Responsibility in Medicine and Research (PRIM&R)

132 Boylston Street
Fourth Floor
Boston, MA 02116
Tel: 617-423-4112
Fax: 617-423-1185
Email: PRMR@aol.com
Web: *http://www.primr.org/*

PRIM&R is a national nonprofit organization dedicated to educating the medical and legal professions, industry and the public about the ethical, legal, and policy dimensions of appropriate and ethical research. Through PRIM&R conferences a broad range of issues regarding research, clinical practice, ethics, and the law are addressed, including the operation of Institutional Animal Care and Use Committees.

Scientists Center for Animal Welfare (SCAW)

7833 Walker Drive, Suite 410
Greenbelt, MD 20770
Tel: 301-345-3500
Fax: 301-345-3503
Email: info@scaw.com
Web: *http://www.scaw.com/*

The SCAW is a non-profit educational association of individuals and institutions whose mission is to promote humane care, use, and management of animals involved in research, testing or education in laboratory, agricultural, wildlife or other settings. It offers an ongoing forum for the exchange and evaluation of scientific information about the care, treatment, well-being and ethical use of animals.

United States Department of Agriculture (USDA), Animal Care (AC)

4700 River Road, Unit 84
Riverdale, MD 20737-1234
Tel: 301-734-7833
Fax: 301-734-4978
Email: ace@aphis.usda.gov
Web: *http://www.aphis.usda.gov/ac/*

The Animal Care (AC) component of the USDA's Animal and Plant Health Inspection Service (APHIS) is responsible for the enforcement of the Animal Welfare Act (AWA). The AWA sets minimum standards of care and treatment for most warm-blooded animals used in research. Three regional offices employ field veterinary medical officers (VMOs) who regularly conduct unannounced inspections of research facilities for compliance with the USDA animal welfare regulations.

University of California Center for Animal Alternatives (UCCAA)

One Shields Avenue
Davis, CA 95616-8684
Tel: 530-752-1800
Fax: 530-754-8606
Email: animalalternatives@ucdavis.edu
Web: *http://www.vetmed.ucdavis.edu/Animal_Alternatives/main.htm*

The UCCAA collects, disseminates, and facilitates access to information concerning animal alternatives, serving primarily the scientists and staff on the nine University of California campuses. The purpose is to improve the well-being and quality of life of research animals, but also to optimize their contribution to education and research.

ResearchTraining.org

Web: *http://www.researchtraining.org*

ResearchTraining.org is a Website developed by the Medical Research Service in the VA Office of Research and Development. Its purpose is to help VA and non-VA institutions meet research training mandates. The site includes free web-based courses and exams for research staff and IACUC members, and an IACUC Administrator's site where administrators can review the records of staff members who pass exams.

Appendix B: Office of Laboratory Animal Welfare

Appendix C: Mandatory IACUC Issues Identified During AAALAC International Site Visits

(See Section B.1. Program and Facility Review)

- Inadequate review and follow-up of the animal care and use program
- Need for more rigorous protocol review
- Inadequate records of IACUC activities
- Assurance of participation in and adequacy of training programs
- Inadequately addressing issues pertaining to pain and distress
- Need for IACUC to review and approve deviations from the *Guide*
- IACUC assurance of adequate veterinary care
- Inadequate IACUC oversight of animals in satellite/contract facilities
- Committee composition and participation
- Changes in protocol without IACUC review and approval
- No three year complete review of protocols/annual review of PHS-funded research
- Allowing ordering of animals without assignment to an animal use protocol
- Not all animals covered by a protocol (e.g., breeding animals)
- Absence of exercise and psychological well-being plans for dogs and nonhuman primates
- Committee not appointed by the CEO
- Inadequate facility inspections (e.g., laboratories)
- Inadequate training of IACUC
- Inadequate intensity of oversight of program

Presented in order of most common citation to least frequent citation.

Carbon Dioxide (CO_2): Carbon dioxide is an effective and widely used agent to euthanize rodents. This method causes hypoxia attributable to depression of vital centers. Use of carbon dioxide generated by other methods (e.g., dry ice, fire extinguishers) is not acceptable. Compressed CO_2 gas in cylinders is the only recommended source of carbon dioxide, since the inflow to the euthanasia chamber can be regulated. An optimal flow rate will displace at least 20% of the chamber volume per minute. In some species (e.g., rats) prefilling the chamber to 70% or more will produce rapid unconsciousness with minimal distress. Young animals, and some burrowing and diving animals, are relatively resistant to the hypoxemic effect of CO_2. Since the effects of carbon dioxide are reversible, it is important to ensure that the animals are dead.

Other agents: Nitrogen and argon are listed as conditionally acceptable methods for death by hypoxemia, and are relatively safe. Although effective, they may cause distress and other methods are preferred. Carbon monoxide induces unconsciousness without significant discomfort, and is considered acceptable for euthanasia for dogs, cats, and other small mammals. However, it is dangerous to use, and the Panel recommends it only if proper precautions are observed.

Non-inhalant Agents

Barbiturates: InjectiT1_0 1c7larbd(, it is dam(2)Dathoisted as conditio0j3.2161 0uCO)T

Potassium Chloride (KCl): KCl induces immediate cardiac arrest without any significant depression of the central nervous system. Hence, it must only be used after the animal is deeply anesthetized.

Neuromuscular Blocking Agents (Succinycholine, Curare, etc.): These drugs induce muscular paralysis and death by suffocation. They are not acceptable for euthanasia.

Physical Methods

Physical methods are sometimes necessary to obtain scientifically valid data and, while aesthetically displeasing to some individuals, are humane when properly performed by skilled and experienced personnel with appropriate, well-maintained equipment. The Panel considers most physical methods to be conditionally acceptable.

Cervical Dislocation: This is frequently used for mice, poultry and other small birds, immature rats weighing less than 200 grams and rabbits weighing less than one kilogram. Cervical dislocation is described in the 2000 AVMA Report as a humane technique for euthanasia of rodents and small rabbits in research, which induces rapid loss of consciousness without chemically contaminating tissue. Its use must be scientifically justified and approved by the IACUC on a case-by-case basis. As part of the approval process the IACUC must be assured that the personnel are appropriately qualified in the use of this method for the specific species involved. It is critical that personnel performing these procedures are thoroughly trained, usually by practicing the procedure on anesthetized animals.

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Decapitation: Decapitation may be used to euthanize rodents and small

Penetrating Captive Bolt: This method is conditionally acceptable for ruminants, horses, and swine when chemical agents are scientifically contraindicated. Use of a non-penetrating captive bolt only stuns and should not be attempted as the sole means of euthanasia.

Euthanasia of Poikilothermic (Cold-blooded) Animals

The 2000 Report of the AVMA Panel on Euthanasia addressed the euthanasia of poikilothermic animals and in doing so pointed out that the available objective information on these species in the literature limits the guidelines that can be developed. The Panel also pointed out the differences in the metabolism, respiration and tolerance to cerebral hypoxia between these species and homeothermic animals must be considered when selecting a method of euthanasia.

Chemical Agents: Intraperitoneal administration of pentobarbital is an effective method of euthanasia in amphibians, turtles and snakes. Tricaine methane sulfonate (MS222) or benzocaine hydrochloride may be placed in the water of amphibians and fish to produce anesthesia and prolonged contact will produce death. Inhalant anesthetics may be used for amphibians and reptiles. Due to the low oxygen requirements for reptiles, the onset of unconsciousness and death will be significantly lengthened.

Physical Methods: Poikilotherms may be euthanized by stunning followed by decapitation, pithing, or some other method to ensure death. In frogs and toads, pithing the brain and spinal cord (double pithing) is an effective and acceptable method.

Additional and Adjunctive Methods

The 2000 Report of the AVMA Panel on Euthanasia included additional methods that, under appropriate circumstances, would produce a humane death. For specifics, consult the Panel report published in *JAVMA* Vol. 218, No. 5, March 1, 2001.

Appendix E: Federal and State Permits Required for Field Studies

(See Section C.3.d. Field Studies)

One research protocol may be subject to multiple laws and therefore multiple permits might be required. It is most commonly the case that both state and federal permits are needed in addition to site-specific permits for research conducted on federal- or state-owned property.

U.S. Fish and Wildlife Service

The permits administered by the U.S. Fish and Wildlife Service (USFWS) are found in 50 CFR, Sections 1 - 100. The general permit conditions found in 50 CFR 13 state that any person accepting and holding a permit acknowledges the necessity for close regulation and monitoring of the permitted activity by the Government. By accepting such permit, the permittee consents to and must allow entry by agents or employees of the USFWS upon premises where the permitted activity is conducted at any reasonable hour. Service agents or employees may enter such premises to inspect the location; any books, records, or permits required to be kept by this subchapter; and any wildlife or plants kept under authority of the permit. The regulations also provide for permit suspension and revocation if permit terms and conditions are violated.

USFWS has developed a system to assess the impact of permitted activities on populations. Known as the Service-wide Permits Issuance and Tracking system, this tool allows permit biologists to determine the cumulative impact of permitted activities on wildlife populations with a high degree of precision.

To take, possess, or transport any bald eagle (*Haliaeetus leucocephalus*) or any golden eagle (*Aquila chrysaetos)*, or the parts, nests, or eggs of such birds, a Bald and Golden Eagle Protection Act permit is required, although banding and marking may be authorized under a Migratory Bird Treaty Act permit. The USFWS will accept a single application for both permits provided that it includes all of the information required for an application under each applicable part.

An issued permit may contain conditions that the permitting authority chooses to impose, including requirements for humane conditions (50 CFR 13.41). For instance, the permit may limit the time a researcher may spend in a colony of seabirds, limit capture methods, or otherwise dictate limits on research methodology. Applications for endangered species permits are published in the Federal Register and afford the public an opportunity to comment or object.

Lacey Act

The original Lacey Act dates back to 1900; what is currently referred to as the Lacey Act is actually the Lacey Act Amendments of 1981. It is not spe• cific to research, but pertains to r

moratorium on the taking and importation of marine mammals as well as products taken from them, and establishes procedur

The title “Migratory Bird Treaty Act” (MBTA) is a misnomer because the Act does not apply only to birds that migrate long distances or across international borders, but to nearly 830 species of birds. Permits for the taking of birds protected by the MBTA are found at 50 CFR 21.

Banding and marking activities require a permit under 50 CFR 21.22. These permits are issued by the U.S. Geological Survey–Biological Resources Division’s Bird Banding Laboratory. A banding permit authorizes the placement of USFWS-issued bands on birds. Additional authorization is required for the use of auxiliary markers (such as colored leg bands, paint marks, wing tagging, radio transmitters), mist nets, cannon or rocket nets, or chemical means of capturing birds. Permits are specific to taxa or even species. Special authorization is required for endangered species, eagles, waterfowl, and hummingbirds. The Bird Banding Laboratory may also authorize the taking of blood and feather samples. Requests to band in more than one state must be justified.

Other MBTA permits are obtained from the USFWS. These include permits

system. Researchers are required to submit research proposals, which are reviewed by the NPS for scientific validity and actual or potential impact to park resources, among other things. The NPS may impose any conditions it deems appropriate. In reviewing applications, the NPS considers, among other things, whether the proposed research contributes information useful to an increased understanding of park resources or addr

management plan required under the National Forest Management Act and 36 CFR part 219, and that the proposed activity does not materially impact

Professional Societies

Animal Behavior Society

Website: *http://www.animalbehavior.org/*

Contact: Animal Behavior Society
Indiana University
2611 East 10th Street, #170
Bloomington, IN 47408-2603
(812) 856-5541

American Fisheries Society

Website: *http://www.fisheries.org*

Contact: American Fisheries Society
5410 Grosvenor Lane, Suite 110
Bethesda, MD 20814-2199
(301) 897-8616

American Society of Ichthyologists and Herpetologists

Website: *http://199.245.200.110/*

Contact: ASIH has no staffed office. Leadership and committee members, including the Animal Care and Use Committee, are listed on the ASIH website, which also includes an on-line directory of members' e-mail addresses.

American Society of Mammalogists

Website: *http://www.mammalsociety.org/*

Contact: ASM has no staffed office. Leadership and committee members are listed on the ASM website.

The Ornithological Council

Website: *http://www.nmnh.si.edu/BIRDNET*

Contact: The Ornithological Council
3713 Chevy Chase Lake Drive, Apt 3
Chevy Chase, MD 20815
(301) 986-8568

The Wildlife Society

Website: *www.wildlife.org*

Contact: The Wildlife Society
5410 Grosvenor Lane
Bethesda, MD 20814
(301) 897-9770
(301) 530-2471 Fax

Appendix F: U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research and Training

The development of knowledge necessary for the improvement of the health and well-being of humans as well as other animals requires *in vivo* experimentation with a wide variety of animal species. Whenever U.S. Gov• ernment agencies develop requirements for testing, research, or training procedures involving the use of vertebrate animals, the following principles shall be considered; and whenever these agencies actually perform or spon• sor such procedures, the responsible Institutional Official shall ensure that these principles are adhered to:

I.- The transportation, care, and use of animals should be in accor• dance with the Animal Welfare Act (7 U.S.C. 2131 et. seq.) 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 simu• lation, 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, investi• gators 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 seda• tion, 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 dis• tress 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.

* *For guidance throughout these Principles, the reader is referred to the* Guide for the Care and Use of Laboratory Animals *prepared by the Institute of Laboratory Animal Resources, National Academy of Sciences.*

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