

CCAC guidelines on: animal use protocol review (1997)

The Canadian Council on Animal Care (CCAC) included Recommended Terms of Reference and Guidelines for Institutional Animal Care Committees in its [*Guide to the Care and Use of Experimental Animals, Vol. 1, 2nd Edn., 1993*](#). Subsequently, these Terms of Reference have been revised, and were published independently in February 1997, as a CCAC policy document [*Terms of Reference for Animal Care Committees*](#). The Terms of Reference address questions of membership, authority and responsibility for Animal Care Committees (ACCs), and outline the information to be included in the animal use protocol form submitted by investigators for ACC approval.

The following guidelines for protocol review are provided to assist ACC members and investigators in obtaining a complete and accurate description of the proposed animal use. As a definitive document, the approved protocol should support the premises upon which objective review of animal use in science is based:

- that the use of animals in research, teaching and testing is acceptable only if it promises to contribute to the understanding of environmental principles or issues; fundamental biological principles; or development of knowledge that can reasonably be expected to benefit humans, animals or the environment;
- that optimal standards for animal health and care result in enhanced credibility and reproducibility of experimental results;
- that acceptance of animal use in science critically depends on maintaining public confidence in the mechanisms and processes used to ensure necessary, humane and justified animal use; and
- that animals should be used only if the researcher's best efforts to find an alternative have failed. A continuing sharing of knowledge, review of the literature, and adherence to the Russell-Burch "Three R" tenet of "Replacement, Reduction and Refinement" are also requisites. Those using animals should employ the most humane methods on the smallest number of appropriate animals required to obtain valid information.

1. GENERAL PRINCIPLES

The following are general guiding principles for protocol review. Each ACC has an ethical, scientific, and social responsibility to apply protocol review and approval criteria in a fair, equitable and consistent manner. This requires the provision of complete and appropriate information by the investigator. Not all protocols, however, require the same level of review: the intensity of the review should vary directly with the level of invasiveness of the procedures ([*Categories of Invasiveness in Animal Experiments: CCAC, Guide to the Care and Use of Experimental Animals, Vol. 1, 2nd Edn., 1993*](#), pp. 201-202). Protocols involving physical and/or psychological distress (pain, fear) must be fully reviewed and require strong scientific justification that is clearly supported by current knowledge.

All aspects of the review process, including protocol approval status, amendments, clarifications, modifications, and renewals must be documented, regardless of the category of invasiveness.

A summary of the primary aims and proposed use of animals must be provided in a language understandable to a layperson. This should include a description of procedures

designed to assure that animal suffering will be prevented or at least minimized. The submission of sections of grant proposals containing excessive detail of procedures not related to the use of animals is inappropriate, but may be helpful if related to scientific merit or statistical analysis. The ACC members should request investigators to provide all descriptions with a minimum of technical jargon: the ACC is primarily interested in the responsible, humane use of animals.

Each protocol must be reviewed annually and must take into consideration changes in standards and guidelines, and developments in the replacement, reduction, and refinement of experimental animal use. Renewal applications should permit ACCs to review proposed modifications to the original protocol, if any, and the justification for the changes. Major modifications, including changes in animal species, category of invasiveness, the nature of the invasive procedure(s), or significant changes in the use of anesthetics/analgesics must be subjected to the same level of review and information requirements as a new application. All modifications must be approved and documented by the ACC before being initiated by the investigator. An ACC should not renew a protocol more than three times; after three renewals, a complete, new protocol should be submitted.

A faculty and/or staff member must accept responsibility for the project. In addition, a knowledgeable member of the research project must be available for contact at all times. Requirements for permits for wildlife studies, use of radioactive compounds, biohazards, and other special circumstances must be reported in the protocol. Generally, copies of permits/licences should be filed with the ACC before the project begins. When the acquisition of a Provincial Wildlife Permit is directly relevant to issues of animal use, a copy of the Permit should accompany the protocol.

2. POTENTIAL BENEFIT OF THE RESEARCH

Clear statements on the purpose (specific scientific objectives) and potential value of the study (originality and importance of the new information) are required.

Information provided within the protocol review form should provide the ACC with a clear sense of the need for the experimental project, and of the relationship between the proposed experiment and the overall objective. ACCs must ensure that all approved proposals have been peer reviewed for scientific merit. Proposals associated with competitive funding applications to agencies with adequate peer review processes generally do not require review for scientific merit by the ACC. The requirement for scientific merit should normally be satisfied if the application is funded. Where ACC approval is required by the funding agency before it will review the application, ACC approval should be provisional, pending assurance from the funding agency that the application has high scientific merit.

Projects approved and funded by some agencies or organizations, or from internal funds may have been subjected to little or no peer review. Some funding agencies award "Program Grants" which, unlike their "Project Grants", may include animal use that is not subjected to a focused peer review for scientific merit. When evidence of good peer review is absent, the ACC should solicit two reviews of the objectives, hypotheses, methods and contributions of the project by knowledgeable scientists who do not collaborate with the investigator. As a minimum, one referee must be external to the Committee. The reviews must be documented and must contain sufficient information to support the reviewers' conclusion(s).

3. REPLACEMENT ALTERNATIVES TO ANIMAL USE

If the scientific objectives of the study can be achieved by using available non-animal models or animals of low sentience, the ACC must require consideration by the investigator of the alternative to live and/or more sentient animals and justification for its rejection. The absence of replacement alternatives should be supported by a brief description of the methods and sources used to determine that alternatives were not available, and/or an explanation of the aspects of the protocol that preclude using non-animal models or animals of lower sentience. A simple statement that there is no replacement alternative is insufficient.

4. ANIMAL MODEL SELECTION

The characteristics of the animal model that make the species/strain appropriate for the study should be described. This might include structural, behavioral, physiological, biochemical or other features or considerations (e.g., data from previous studies) which make the model compatible with the research objectives. Ordinarily, cost should not be a primary consideration.

5. REDUCTION OF ANIMAL USE/NUMBERS

The information provided must include a clear description of the experimental design along with the statistical rationale which supports the size of the control and test group(s). A pilot study may be recommended by the ACC, particularly when large numbers of animals are requested for a new study, to provide data for a more accurate assessment of the invasiveness of the procedure and number of animals required. Overall, the number of animals to be used must be optimized to the greatest extent possible consistent with sound scientific and statistical standards, i.e., not below or in excess of the number required to produce statistically valid experimental data.

6. REFINEMENT OF EXPERIMENTAL TECHNIQUE

Once it has been determined that the use of animals is necessary and there is appropriate justification for the number requested, the ACC and the investigator have a shared responsibility to ensure that the husbandry practices and experimental procedures employed minimize or eliminate physical and/or psychological distress within the limitations imposed by the objectives of the research.

All members of ACCs and all investigators have the responsibility to continuously refine procedures. Some examples of potential areas of refinement include: increased training and expertise of personnel; environmental enrichment for captive animals; well planned, pre-, intra-, and post-procedure care management; proper anesthesia/analgesia; selection of more humane endpoints; proper methods of euthanasia; less invasive surgery; less toxic adjuvants; and appropriate transportation/transfer methods.

7. SETTING ENDPOINTS

The lack of a well-defined, humane endpoint is often a key issue in protocol review. When morbidity is anticipated, its time course and severity, monitoring frequency, training and expertise of the monitors, care and treatment, and provision for unexpected complications are all important considerations for the ACC. If the expected frequency,

severity, and signs of morbidity are unknown, a pilot study under close veterinary observation should attempt to answer these questions. Death or moribundity as endpoints must be avoided. Animals must be euthanized at the earliest possible endpoint consistent with the scientific objective(s) of the proposal, and in accordance with acceptable criteria for determining the endpoint.

Procedures that involve sustained and/or inescapable severe pain or deprivation in conscious animals, i.e., [Category E](#) experiments, are considered highly questionable or unacceptable, irrespective of the significance of anticipated results. The CCAC's [Ethics of Animal Investigation](#) document ([Appendix XV: CCAC, Guide to the Care and Use of Experimental Animals, Vol. 1, 2nd Edn., 1993](#)) states: "An animal observed to be experiencing severe, unrelievable pain or discomfort should immediately be humanely killed, using a method providing initial rapid unconsciousness" and "Studies such as toxicological and biological testing, cancer research and infectious disease investigation may, in the past, have required continuation until the death of the animal. However, in the face of distinct signs that such processes are causing irreversible pain or distress, alternative endpoints should be sought to satisfy both the requirements of the study and the needs of the animal".

8. PHYSICAL RESTRAINT

Physical restraint, e.g., short-term hand-held or mechanical (stocks or squeeze cages) restraint is often required for examination, collection of samples, and a variety of other clinical and experimental manipulations. Restraint induced stress can be minimized by conditioning of the animal, use of appropriate devices suitable in size and design, and proper operation by experienced personnel.

Physical restraint extending beyond a few minutes should only be used on conscious animals after alternative procedures have been considered and found to be inadequate. Steps must be taken to condition the animals to the restraining device to minimize stress and discomfort during the experimental procedures. If restraint is necessary, the device must provide the animal with the greatest opportunity to assume its normal postural adjustments, and the duration of restraint must be minimized. The prolonged chairing of non-human primates must be avoided.

The duration of restraint should take into consideration factors such as species, health and age of the animal, and level of restraint. A level of restraint which prevents movement of groups of muscles must be brief enough to avoid painful muscle cramping and requires constant supervision. Restraint which allows only restricted movement of muscle groups must also be brief enough to avoid painful physical discomfort or distress and requires constant supervision. Restraint which allows unrestricted movement of all muscle groups, but restricts locomotion and other activities requiring whole body movement should be interrupted regularly by periods of exercise. If not previously established, the acceptable duration and level of restraint should be established by a pilot study under veterinary supervision. Supervision of restrained animals must be done by qualified personnel.

9. INVASIVE/STRESSFUL PROCEDURES

A description of the preparative regimen should be provided which includes, as applicable, a description of the animal preparation and procedures, specification of any antibiotic or tranquilizers to be administered, ventilation procedures, instrumentation (i.v. lines, catheters, etc.). The dose (e.g., mg/kg) and route (e.g., i.m., i.v.) of any compound to be administered must be stated. When repetitive use of a particular

methodology is anticipated, the ACC should require the investigator to develop a detailed Standard Operating Procedure for submission to the ACC.

The type of monitoring and the criteria used to assess the level of anesthesia/analgesia, e.g., respiration/heart rate, EKG, toe pinch, corneal reflex, color of mucus membrane, muscular relaxation, should be provided, as well as a brief technical description of the procedure. Other information should include the source, method, volume and frequency of sampling when blood or tissue recovery is employed. There should be a clear relationship between each procedure and the objective(s) of the research.

Estimation in advance of any potential adverse effects on the animal will assist in developing plans to prevent, monitor and relieve as much suffering as possible during the post-procedure period. All animals must be monitored at appropriate intervals which are dictated by the nature of the procedure(s), the degree and duration of potential post-procedure physical and/or psychological distress, and possibility of complications. For example, monitoring may be required at more frequent intervals during the immediate post-surgical period (e.g., first 24 hours post-operatively) and during the latter stages of tumor induction or toxicology experiments that have associated morbidity and mortality.

Criteria should be established to assess the presence and severity of post-procedure distress, and to provide a basis for analgesic administration or other procedures to minimize or eliminate the distress. In evaluating distress in animals, species-specific behavioral changes, e.g., in vocalization, appearance/posture, locomotion, temperament and physiological signs, e.g., weight, heart rate, respiration, appearance of urine and feces, weakness/paralysis, must be looked for. It is important to note that many sources of distress may be unrelated to the procedures performed. These include: variable or inappropriate temperature, humidity, illumination or ventilation; inappropriate cage or enclosure space; inappropriate intensity or type of noise; unsatisfactory species-specific sanitation practices; and negative social conditions (e.g., overcrowding, isolation, incompatibility, maternal deprivation).

The administration of analgesics or use of other distress-reducing measures should be based on the premise that where physical and/or psychological distress is a concern, the animal should be given the benefit of the doubt. Conversely, the active withholding of these measures, where their use is indicated, must be based on scientific fact or experimental data, as documented by pertinent literature, or data from pilot studies.

Multiple surgical or other repetitive highly stressful procedures on a single animal are generally unacceptable and are not adequately justified by cost savings. These protocols must undergo stringent ethical and welfare review for justification.

10. EUTHANASIA

In addition to the selection of an appropriate method of euthanasia, the training and competence of the individual(s) performing euthanasia should be specific for the species and method used ([*Chapter XII-Euthanasia: CCAC, Guide to the Care and Use of Experimental Animals, Vol. 1, 2nd Edn., 1993*](#)). The criteria for euthanasia, in terms of species-specific behavioral changes and physiological signs, or in relation to the experimental design, must be clearly described.

If surviving animals are not to be euthanized during, or upon completion of the study, a description of their future disposition must be included.

11. HAZARDOUS MATERIALS

Appropriate approval for the use of hazardous agents (radioactive materials, recombinant DNA/RNA, human/plant/animal pathogens, acute toxins, chemical carcinogens, ethers) must be filed with the ACC before the project begins. Brief descriptions of the potential health risks to humans or animals, special animal care required, precautions for personnel, special containment requirements, specific storage, waste, and animal disposal requirements, and emergency procedures must be provided as part of the protocol form or in an appended copy of the approval application.

12. TEACHING PROTOCOLS

The use of animals for educational purposes is markedly different in its objectives than the use of animals in research or testing. Animals used for educational purposes are not being used to discover, prove or develop new ideas or techniques, but rather to demonstrate principles which are already well-known or to learn manual skills and techniques. The repetitive use of animals in this manner should be based on sound ethical justification and proven educational objectives.

There should be justification provided for the use of animals over the use of alternatives such as models, videos, computer simulations and emulations, etc. The level and type of training of the students (graduate/postgraduate, specialized/non-specialized) are important considerations in ascertaining the need to use animals.

Teaching protocols are subject to the relevant aforementioned review considerations, as well as to the factors of student inexperience and "group" projects. Thus, the description should include the number of students per animal, and the student/teacher ratio. The level of experience and competence of the instructors and/or teaching assistants must be adequate to assure successful preparations and procedures. The disposition of the animals at the end of the teaching session must be clearly described.

Painful experiments or multiple invasive procedures on an individual animal, conducted solely for the instruction of students in the classroom, or for the demonstration of established scientific knowledge, cannot be justified.

13. WILDLIFE FIELD STUDIES

Experimental procedures involving the capture, handling and release of wild animals are of special concern: lack of conditioning results in high degrees of stress in captured wild animals; therefore the necessity for capture, handling and/or administration of drugs or other compounds must be clearly established. Detailed descriptions of all pursuit, capture, handling and chemical restraint procedures, and explanations of their appropriateness, are essential. Criteria used to assess suitability for release must be clearly stated. Provision for recovery, treatment, or euthanasia of injured animals and disposal of carcasses must be specified.

If traps are to be used, the type of trap, its injury potential, and the monitoring frequency of the traps are important considerations. The collection of samples and affixing of devices to the animal subject(s) must be described (weight, method of attachment, duration) and be clearly related to the objective(s) of the study. Protocols for field studies involving population sampling by killing of animals, using methods such as

shooting, must include justification for the method used. The use of such methods must be by individuals with sufficient experience and expertise to ensure that animals are humanely killed.

Wildlife research may involve the use of specialized holding areas and transportation of animals. The potential for injury to personnel and the animal subjects during these procedures should be minimized. The holding of wild animals in highly confined enclosures for extended periods should be avoided.

Ecological disruption may result from the performance of some types of field studies. The type and degree of disruption expected (or its potential) must be indicated, e.g., the adverse consequences to survival and reproduction experienced by the herd, colony, or individual animal subject due to the study procedures.

14. CONCLUSION

The ACC attempts to reconcile public demands for medical, scientific and economic progress with demands for reduction in animal use, pain, and suffering. The cost, in terms of animal welfare and integrity must be measured against the expectation of a proportional contribution to the understanding of fundamental biological principles, or to improvement of human or animal health and welfare. Protocol review by the institutional ACC provides a mechanism for achieving this "cost/benefit assessment" which involves consideration of relevant ethical, scientific, and social issues.

Approval of a protocol does not guarantee that a benefit will be realized, but does mean that there will be a cost imposed on the animals. The ACC must be convinced therefore of the need for animal use, and that the expected benefit will outweigh the cost.

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READING LIST

ANIMAL WELFARE INFORMATION CENTER (1996). *Newsletter* **7**:1-2, 14-15.

ASSOCIATION FOR THE STUDY OF ANIMAL BEHAVIOUR (1994). Guidelines for the treatment of animals in behavioral research and teaching. *Animal Behaviour* **47**:245-250.

BAKER, R.M., BURRELL, J.H. and ROSE, M.A., eds. (1992). Effective Animal Experimentation Ethics Committees. Proceedings of the ANZCCART (Australian and New Zealand Council for the Care of Animals in Research and Teaching) Conference, 136 pp. Adelaide: Australia.

BALLS, M. (1994). Replacement of animal procedures: alternatives in research, education and testing. *Laboratory Animals* **28**:193-211.

BALLS, M. *et al.* (1995). The Three Rs: the way forward. *ATLA* **23**:838-866.

BAYNE, K.A.L. and KREGER, M.D., eds. (1994). Wildlife Mammals as Research Models: In the Laboratory and Field, 66 pp. Greenbelt MD: Scientists Center for Animal Welfare.

BEKOFF, M. (1995). Marking, trapping, and manipulating animals: Some methodological and ethical considerations. In: *Wildlife Mammals as Research Models: in the Laboratory and in the Field* (eds. K.A.L. Bayne and M.D. Kreger), pp. 31-47, Greenbelt MD: Scientists Center for Animal Welfare.

BENN, D.M. (1995). Innovations in research animal care. *Journal of the American Veterinary Medical Association* **206**:465-468.

CANADIAN COUNCIL ON ANIMAL CARE (1984). [Guide to the Care and Use of Experimental Animals. Vol. 2](#), 208 pp. Ottawa ON: CCAC.

CANADIAN COUNCIL ON ANIMAL CARE (1992). Proceedings of the CCAC Workshop - Animal Care Committees: Role and Responsibilities, 122 pp. February 10-11. Ottawa ON: CCAC.

CANADIAN COUNCIL ON ANIMAL CARE (1993). [Guide to the Care and Use of Experimental Animals. Vol. 1, 2nd Edn.](#), 212 pp. Ottawa ON: CCAC.

CANADIAN COUNCIL ON ANIMAL CARE (1993). Atelier de travail - Comité de protection des animaux: Rôle et responsabilités, 54 pp. 5 octobre, Région du Québec. St-Hyacinthe QC.

CANADIAN COUNCIL ON ANIMAL CARE (1994). Preparing for a CCAC Assessment Visit. *RESOURCE* Supplement, Fall.

CANADIAN COUNCIL ON ANIMAL CARE (1994). Proceedings of the CCAC National Workshop - Animal Care Committees: Role and Responsibilities, 146 pp. February 6-8. Ottawa ON: CCAC.

CANADIAN COUNCIL ON ANIMAL CARE (1994). Proceedings of the CCAC Western Regional Workshop - Animal Care Committees: Role and Responsibilities, 38 pp. April 28. Vancouver BC.

CANADIAN COUNCIL ON ANIMAL CARE (1994). Proceedings of the CCAC 1994 Ontario Regional Workshop - Animal Care Committees: Role and Responsibilities, 50 pp. November 24. North York ON.

CANADIAN COUNCIL ON ANIMAL CARE (1995). Community Representation: The Public Conscience. *RESOURCE* Supplement, Fall.

CANADIAN FEDERATION OF HUMANE SOCIETIES (1990). Guidelines for Lay Members of Animal Care Committees, 50 pp. Nepean ON: CFHS.

DE COCK BUNING, T. and THEUNE, E. (1994). A comparison of three models for ethical evaluation of proposed animal experiments. *Animal Welfare* **3**:107-128.

DONNELLY, H. (1995). Quality in laboratory animals. In: *Laboratory Animals - An Introduction for Experimenters* (ed. A.A. Tuffery), pp. 181-203. Chichester UK: John Wiley & Sons.

FESTING, M.F.W. (1992). The scope for improving the design of laboratory animal experiments. *Laboratory Animals* **26**:256-267.

FESTING, M.F.W. (1994). Reduction of animal use: experimental design and quality of experiments. *Laboratory Animals* **28**:212-221.

FLECKNELL, P.A. (1994). Refinement of animal use - assessment and alleviation of pain and distress. *Laboratory Animals* **28**:222-231.

FRASER, D. (1995). Science, values and animal welfare: exploring the "Inextricable Connection". *Animal Welfare* **4**:103-117.

GAMBLE, M.R. (1995). Design of experiments. In: *Laboratory Animals - An Introduction for Experimenters* (ed. A.A. Tuffery), pp. 205-213. Chichester UK: John Wiley & Sons.

HAMM, T.E. (1995). Proposed institutional animal care and use committee guidelines for death as an endpoint in rodent studies. *Contemporary Topics in Laboratory Animal Science* **34**:69-71.

JAMES, M.L., MININNI, L.A. and ANDERSON, L.C. (1995). Establishment of an animal alternatives committee. *Contemporary Topics in Laboratory Animal Science* **34**:61-64.

JENNINGS, M. (1994). Ethics committees for laboratory animals: a basis for their composition and function, 12 pp. Horsham UK: RSPCA (Royal Society for the Prevention of Cruelty to Animals).

JOHNSTON, N.E., ed. (1995). Proceedings of Animals in Science Conference: Perspectives on Their Use, Care and Welfare. Clayton Australia: Monash University.

LANG, C.M. (1995). A necessity for biomedical research. *Scandinavian Journal of Laboratory Animal Science* Suppl. **22**:37-45.

MATFIELD, M. (1995). The public debate about animal experimentation. *ATLA* **23**:312-316.

MCGARRY, M.P., JIVIDEN, J.L. and PICCIONE, D.J. (1995). Implementation of the protocol: a process. *Contemporary Topics in Laboratory Animal Science* **34**:75-77.

MOORE, C.J. and MEPHAM, T.B. (1995). Transgenesis and animal welfare. *ATLA* **23**:380-397.

MORTON, D.B. and TOWNSEND, P. (1995). Dealing with adverse effects and suffering during animal research. In: *Laboratory Animals - An Introduction for Experimenters* (ed. A.A. Tuffery), pp. 215-231. Chichester UK: John Wiley & Sons.

NATIONAL INSTITUTES OF HEALTH (1992). Institutional Animal Care and Use Committee Guidebook (Publication no. 92-3415). Washington DC: NIH.

NATIONAL RESEARCH COUNCIL (1996). Guide for the Care and Use of Laboratory Animals (Institute for Laboratory Animal Resources), 125 pp. Washington DC: National Academy Press.

NIEMI, S.M. and WILLSON, J.E. (1993). Refinement and reduction in animal testing. In: *Scientists Center for Animal Welfare, Proceedings of September 1992 Conference, Philadelphia*, 138 pp. Bethesda MD: SCAW.

OLFERT, E.D. (1995). Defining an acceptable endpoint in invasive experiments. *Animal Welfare Information Center Newsletter* **6**:3-7.

OLFERT, E.D. (1996). Considerations for defining an acceptable endpoint in toxicological experiments. *Lab Animal* **25**:38-43.

ORLANS, F.B. (1987). Research protocol review for animal welfare. *Investigative Radiology* **22**:253-258.

ORLANS, F.B., SIMMONDS, R.C. and DODDS, W.J., eds. (1987). *Effective animal care and use committees*, 178 pp. (Scientists Center for Animal Welfare) Workshops in Laboratory Animal Science. Bethesda MD: SCAW.

ORLANS, F.B. (1993). *In the Name of Science: Issues in Responsible Animal Experimentation*, 297 pp. New York NY: Oxford University Press.

POOLE, T.B. (1995). Welfare consideration with regard to transgenic animals. *Animal Welfare* **4**:81-85.

PRENTICE, E.D., CROUSE, D.A. and RINGS, R.W. (1990). Approaches to increasing the ethical consistency of prior review of animal research. *Investigative Radiology* **25**:271-274.

PRENTICE, E., CROUSE, D. and MANN, M. (1992). Scientific merit review: the role of the IACUC. *ILAR (Institute for Laboratory Animal Resources) Newsletter*. Winter/Spring **34**:15-19.

QUIMBY, F.W. (1995). The role of attending veterinarians in laboratory animal welfare. *Journal of the American Veterinary Medical Association* **206**:461-465.

ROWAN, A.N. (1995). The third R: Refinement. *ATLA* **23**:332-346.

ROWAN, A.N. and LOEW, F.M. (1995). *The animal research controversy: Protest, process & public policy: an analysis of strategic issues*, 210 pp. North Grafton MA: Center for Animals & Public Policy, Tufts University School of Veterinary Medicine.

SMITH, C.P. (1994). AWIC tips for searching for alternatives to animal research and testing, 6 pp. Beltsville MD: Animal Welfare Information Center.

SMITH, J.A. and BOYD, K.M., eds. (1991). *Lives in the Balance: The Ethics of Using Animals in Biomedical Research*, 352 pp. New York NY: Oxford University Press.

STOKES, W.S. and JENSEN, D.J.B. (1995). Guidelines for institutional animal care and use committees: consideration of alternatives. *Contemporary Topics in Laboratory Animal Science* **34**:51-60.

VAN ZUTPHEN, L.F.M., BAUMANS, V. and BEYNEN, A.C., eds. (1993). *Principles of Laboratory Animal Science: A contribution to the humane use and care of animals and to the quality of experimental results*, 389 pp. Amsterdam: Elsevier.

VAN ZUTPHEN, L.F.M. (1995). A contribution to animal welfare and quality of experiments. *Scandinavian Journal of Laboratory Animal Science Suppl.* **22**:51-56.

VAN ZUTPHEN, L.F.M. and VAN DER VALK, J.B.F. (1995). Education and training: a basis for the introduction of the three Rs alternatives into animal research. *ATLA* **23**:123-127.

WEIGLER, B.J. (1995). Justifying the number of animals in IACUC proposals. *Contemporary Topics in Laboratory Animal Science* **34**:47-50.

WIEPKEMA, P.R. and KOOLHAAS, J.M. (1993). Stress and animal welfare. *Animal Welfare* **2**:195-218.