

## ANIMAL RESEARCH

# Harmonization of Animal Care and Use Guidance

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Societal expectations for improvements in the health of humans and animals require scientific studies involving the use of animals. At the same time, the public is concerned about the welfare of animals used in science.

Animal welfare is also of importance because of the link between healthy, well-cared-for animals and sound science.

Most national oversight mechanisms emphasize basic principles of humane science, in particular the “three R’s” tenet of replacement, reduction, and refinement of animal use (1). However, the oversight of animal care and use occurs through a wide variety of local, national, and international mechanisms, some based on legislation [the European Union (EU); (2)], others on peer review or other forms of nonlegislated oversight (Canada) and yet others on a combination of legislated and nonlegislated oversight (United States). This patchwork of mechanisms can cause problems, given the global nature of science.

Different standards for animal care and use can complicate the comparison of results from animal-based studies and the reproducibility of such results and can also slow international scientific collaboration. For example, CO<sub>2</sub> euthanasia is more commonly used for rodents in

the United States than in the EU, and T-61 (a combination of three drugs—a local anesthetic, a general anesthetic, and a curariform drug) is available to animal users in Europe but not the United States. There are also international trade implications: multinational companies face the challenge of having to work with research and testing sites operating within very different regulatory structures. Specific standards of animal care and use required by scientific journals can also present a barrier to publication. The patchwork of mechanisms can be especially daunting for developing countries, in elaborating their own mechanisms and in international collaboration. Finally, there is concern that differences in animal care and use requirements may lead to the transfer of animal-based studies to countries with weaker requirements. As far back as 1985, the Committee of International Organizations of Medical Science (CIOMS),

International guidance for animal care and use is important to facilitate conduct of appropriate animal-based science on a global level and to protect the welfare of animals used in science.

which works closely with the World Health Organization, said “The varying approaches in different countries to the use of animals for biomedical purposes, and the lack of relevant legislation or of formal self regulatory mechanisms in

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some, point to the need for international guiding principles elaborated as a result of international and interdisciplinary consultations” (3).

There are international efforts to use guidance that is based on performance standards [i.e., standards that define an outcome and provide criteria for assessing that outcome, but do not limit the methods by which that outcome may be achieved (4)], and to work on filling gaps in the science needed for sound animal welfare guidance. Examples of international collaboration include the CIOMS Principles, the Mutual Acceptance of Data Program of the Organisation for Economic Cooperation and Development (OECD), and the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). These instances of collaboration have reduced unnecessary duplication of studies involving animals by developing internationally accepted common methods for chemical testing and drug development.

Guidance on the recognition of clinical signs as humane end points is now being implemented by member nations of the OECD, in conjunction with the OECD test guidelines for safety evaluation, which means that regulatory agencies in these countries should no longer require death in extremis as an end point for safety tests (5). In countries that are not OECD members, death may still be commonly accepted as an end point.

The International Council for Laboratory Animal Science [ICLAS (6)] has brought members of the

## Principles for Establishment of Humane End Points

1. There is strong evidence that animals experience pain and distress in situations comparable to those that cause pain and distress for humans.
2. Death or severe pain and distress should be avoided as end points.
3. The earliest possible end point should be used that is consistent with the scientific objectives.
4. Studies should be designed to minimize any pain or distress likely to be experienced by the animals, while meeting the scientific objectives.
5. The duration of studies involving pain and distress should be kept to a minimum.
6. Pilot studies should be encouraged as a means of determining morbidity, time course of effects, and frequency of observations required to set an earlier end point.
7. Before commencing the experiment, agreement should be reached on (i) appropriate end points for the study and (ii) the person or persons to be responsible for making the judgment that the end point has been reached.
8. A team approach should be used, employing the professional judgment of the scientist, veterinarian, animal care staff, and ethics committee to agree on the appropriate end point for the study.
9. Research and animal care staff must be adequately trained and competent in recognition of species-specific behavior and, in particular, species-specific signs of pain, distress, and moribundity.
10. Animals should be monitored by means of behavioral, physiological, and/or clinical signs at an appropriate frequency to permit timely termination of the experiment once the end point has been reached.

All of the authors are members of the Working Group on Harmonization of Guidelines for ICLAS. G. Demers is the President of ICLAS, and G. De Vroey and J. R. Haywood are members of the ICLAS Governing Board; J. R. Haywood represents the International Union of Basic and Clinical Pharmacology. In addition, G. De Vroey was the chair of the subcommittee (of the ICLAS Working Group on Harmonization) on euthanasia and J. R. Haywood the chair of the subcommittee on endpoints. <sup>1</sup>ICLAS, St-Hilaire, Quebec, QC, Canada J3H 4W1. <sup>2</sup>Canadian Council on Animal Care, Ottawa, ON, Canada K1P 5G4. <sup>3</sup>Johnson & Johnson, B-2340 Beerse, Belgium. <sup>4</sup>Department of Pharmacology and Toxicology, Michigan State University, East Lansing, MI 48824, USA. <sup>5</sup>Institute for Laboratory Animal Research, National Academy of Science, Washington, DC 20001, USA.

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international community together to identify and to recommend acceptance of guidance documents. ICLAS believes in the harmonization of animal care and use guidance as a reflection of the globalization of research. However, harmonization must be distinguished from standardization (one worldwide set of regulations); ICLAS believes that each country should be able to maintain an oversight mechanism for animals used in science that reflects its cultures, traditions, religions, laws, and regulations.

ICLAS first worked with the Canadian Council on Animal Care (CCAC) on best practices to minimize pain and distress for animals used in regulatory testing; these were agreed upon and published (7). Two guidance documents on humane end points were recognized as effective refinement tools (5, 8).

In November 2003, the Institute for Laboratory Animal Research (ILAR) organized an international workshop (9) to discuss harmonization. During this workshop, many experts from around the world independently reported about a desire for and worldwide pressures to have international benchmarks for animal welfare. However, many participants pointed out that there are strong attachments to existing national guidance and gaps in the science needed as a basis for some of the regulations, standards, and guidelines.

ICLAS held its First International Meeting for the Harmonization of Guidelines on the Use of Animals in Science in Nantes, France, on 13 and 14 June 2004 (10). An ICLAS Working Group on Harmonization of Guidelines, composed of representatives from major organizations producing and/or using guidelines for the use of animals in science, was created at the meeting (11). The working group agreed on general principles for the establishment of humane end points that are based on the earlier documents from the OECD and CCAC (5, 8, 12). The working group encourages consultation of the extensive literature available on end points and recognizes the need for research to support performance-based standards. The current general principles for humane end points defined by the working group are described in the table above.

The working group also agreed on general principles for euthanasia and recommended two documents (13, 14) as international references

### Principles for Animal Euthanasia

1. Whenever an animal's life is to be taken, it should be treated with the highest respect.
2. Euthanasia should place emphasis on making the animal's death painless and distress-free. The method likely to cause the least pain and distress to the animals should be used whenever possible.
3. Euthanasia techniques should result in rapid loss of consciousness, followed by cardiac or respiratory arrest and ultimate loss of brain function.
4. Techniques should require minimum restraint of the animal and should minimize distress and anxiety experienced by the animal, before loss of consciousness.
5. Techniques used should be appropriate for the species, age, and health of the animal.
6. Death must be verified following euthanasia and before disposal of the animal.
7. Personnel responsible for carrying out the euthanasia techniques should be trained: (i) to carry out euthanasia in the most effective and humane manner; (ii) to recognize signs of pain, fear, and distress in relevant species; and (iii) to recognize and confirm death in relevant species.
8. Human psychological responses to euthanasia should be taken into account when selecting the method of euthanasia, but should not take precedence over animal welfare considerations.
9. Ethics committees should be responsible for approval of the method of euthanasia (in line with any relevant legislation). This should include euthanasia as part of the experimental protocol, as well as euthanasia for animals experiencing unanticipated pain and distress.
10. A veterinarian experienced with the species in question should be consulted when selecting the method of euthanasia, particularly when little species-specific euthanasia research has been done.

(15). Both documents provide general principles and guidance on ways to ensure that euthanasia methods meet the goal of assuring the humane death of animals. There are some areas of inconsistency between the two references. This is partly because the American Veterinary Medical Association document is designed for a more general audience (i.e., not only for animal use in science) and because of differing practices and traditions in the United States and Europe, but mostly it is due to insufficient knowledge about the best methods of euthanasia for various species at different life stages. The areas in which further research will be needed were identified as mass animal euthanasia, euthanasia of fetuses and neonates, euthanasia of cold-blooded animals, proper use of CO<sub>2</sub> for various species, decapitation with or without prior anesthesia, cervical dislocation, and the use of N<sub>2</sub> and/or argon gas. With more research in these areas, the working group felt that the discrepancies between the documents could be addressed and better guidance incorporated into future versions of the guidelines. The general principles for euthanasia defined by the working group are shown in the table above.

ICLAS will continue to work with its many partners around the world to identify solid, practical guidance that can easily be used by the international community to promote good animal welfare while conducting sound animal-based science.

### References and Notes

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15. ICLAS, "International harmonization of guidelines on euthanasia" (ICLAS, Nantes, France, 2004), approved in Buenos Aires, Argentina, November 2004, available on *Science Online*.
16. ICLAS thanks all those who have volunteered their time and expertise for its work, in particular those working on international harmonization.

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### Supporting Online Material

[www.sciencemag.org/cgi/content/full/312/5774/700/DC1](http://www.sciencemag.org/cgi/content/full/312/5774/700/DC1)