

Recognition and Alleviation of Pain in Laboratory Animals

Minimizing and alleviating pain in laboratory animals without compromising the methodological integrity of a research project is important both ethically and legally. Fortunately, recent scientific progress has expanded the understanding of pain and increased the ability to prevent and alleviate it in laboratory animals. This report updates 1992 National Research Council guidelines for those involved in the care and use of animals in the research environment. It aims to increase awareness of the sources and recognition of pain in laboratory animals and to increase ethical sensitivity in those who use and care for them.

Many scientific advances in biomedical research would not be possible without the use of laboratory animals. Scientists rely on animals as one component of research to understand, treat, and cure diseases that plague both humans and the animals themselves. In most situations, laboratory animals need not experience pain. The alleviation and prevention of animal pain is both an ethical and moral imperative; minimizing animal pain is also scientifically and practically beneficial. For these and many other reasons, proper care and use of laboratory animals is a priority for the scientific community.

This report, written by a committee convened by the National Research Council at the request of the New Jersey Association for Biomedical Research, is an update of the 1992 National Research Council report *Recognition and Alleviation of Pain and Distress in Laboratory Animals*. Since that report was published, significant scientific progress has been made in the areas of animal welfare, stress, distress, and pain. Because the concepts of pain and distress are two distinct concepts from a scientific perspective, the update is being issued in two separate documents. The first, *Recognition and Alleviation of Distress in Laboratory Animals*, was published in March 2008.

This report's conclusions and recommendations are intended to help scientists, veterinarians, research administrators, institutional animal care



Image courtesy Maggie Bartlett, National Human Genome Research Institute.

and use committee (IACUC) members, and animal care staff to understand the basis of animal pain, recognize and evaluate its presence and severity, and appreciate the means by which pain can be minimized or abolished.

What is Pain?

According to the International Association for the Study of Pain, pain in humans is “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.” Assessing animal pain is complex and challenging to measure in an objective manner. Some behavioral signs, such as withdrawal reflexes in animals with central nervous system damage, do not necessar-

ily indicate pain. Determining whether such behavioral responses indicate pain, and, conversely, whether their cessation indicates the successful abolition of pain, is an ongoing challenge. Until better pain measurement tools are developed and validated, behavioral indices and careful extrapolation from the human experience are used to assess pain in research animals.

Based on an extensive review of the available scientific literature, the report concludes that all vertebrates should be considered capable of experiencing pain.

Pain in Animal Research

In most experimental and husbandry situations, laboratory animals need not experience pain. And if they do, its alleviation and prevention is both an ethical and moral imperative as well as scientifically and practically beneficial. For example, effective pain management can improve healing rates and avoid potentially confounding effects on such diverse biological functions as immunity and sleep.

There are some situations in which animal pain is unavoidable, such as when pain is a tool to motivate or shape behavior, or when pain is the focus of research. The ethical justification for such research should consider both the costs to the animal and the anticipated benefits of the research to humans and animals: the greater the cost to the research animals, the stronger the scientific and ethical justification of the research should be. These ethical expectations are embodied in the principles of the Three Rs: Replacement, Refinement, and Reduction (see box).

Replacement, Refinement, and Reduction

The “Three Rs” provide the underlying principle to the ethical care and use of laboratory animals:

- **Refinement** of experimental procedures to reduce or eliminate pain and distress. Where the use of animals is unavoidable, minimize pain, distress, lasting harm, or other threats to animal welfare. For example, researchers should ensure that accommodation meets animals’ needs; use pain treatment drugs; and specify humane endpoints—that is, when a study design should be changed or a study ended early due to concerns about animal pain, distress, or welfare.
- **Reduction** in the number of animals being used. Use methods that enable equivalent information to be obtained from fewer animals or more information from the same number of animals, such as through the use of advanced imaging techniques.
- **Replacement** of animals with other reliable models. For example, use alternative methodologies, such as computer modeling, or replace higher order animals with those of a lower order (such as using amphibians or invertebrates instead of mammals).

Anticipating and Recognizing Pain

Understanding the potential causes of pain in research animals is critical to anticipating and recognizing situations in which pain is likely. A general rule of thumb is summed up as “if it would hurt you, it probably hurts the animal.” However, there are well-documented variations in how different species respond to potentially painful events; therefore, pain in animals should be assessed on a case-by-case basis. One cannot assume that what causes pain in humans will do so in all other organisms, and conversely, that what does not cause humans pain is equally benign in all other organisms.

Circumstances Causing Pain

The report outlines five primary circumstances in which laboratory animals experience pain. These circumstances vary in their duration and intensity of pain, as well as in the nature and strength of their ethical justification.

- Pain as a result of non-research related disease or injury (such as from aging-related diseases).
- Pain as a result of animal care or veterinary treatment (such as castration, microchip implantation, or injections).
- Pain as a by-product of research, in which pain is a consequence of research but is not an element of the research or the study focus (examples include animals involved in research on disease, toxins, tissue damage, drug dependence, or surgery).
- Pain as a tool to motivate or “shape” behavior.
- Pain as the focus of research.

Assessing Pain

Recent scientific research has considerably advanced our understanding of animal pain; however, there are still few scientifically validated pain assessment techniques. Therefore, in most circumstances, pain is assessed based on the appearance of an animal and its overall behavior. Current best practice is to combine a structured clinical examination with a good knowledge of the normal appearance and behavior of the animals involved.

All vertebrates should be considered capable of experiencing the aversive state of pain.

This report provides a pain assessment checklist for laboratory technicians and animal caretakers, along with a detailed list of behavioral signs of persistent pain (such as guarding, abnormal appearance and behavior, vocalization, and refusal to eat or drink). The report also describes species-specific manifestations of pain in nonhuman primates, dogs, cats, laboratory rodents, rabbits, farm animals, birds, reptiles, fish, and amphibians.

Alleviating and Treating Pain

Laws and regulations require that investigators adequately control pain in research animals, unless the outcomes of an experiment would be negatively impacted. Alleviating pain in research animals typically refers to reducing its duration and/or intensity, as those two characteristics affect aversiveness. Although regulations suggest that only non-brief pain requires treatment, animals subjected to multiple episodes of momentary pain also may benefit from pain alleviation.

Pain alleviation strategies may include preventative measures, therapeutic measures, or a combination of the two. Preventative measures include appropriate animal handling and restraint, minimization of tissue trauma during surgery, the use of minimally invasive surgery techniques (such as fiberoptic technologies), and other non-pharmacological methods.

Therapeutic measures include the use of general and local anesthetics, analgesics, and sedatives or drugs that relieve anxiety. Pain management goals range from total elimination of pain as, for example, during general anesthesia for a surgical procedure, to pain that is tolerated without compromising the animal's well-being. The report provides reference tables to inform which approaches laboratory personnel should consider in circumstances of low, medium, and high levels of pain, as well as tables outlining the properties of various classes of drugs and when to use them.

- **General anesthesia:** Animals are anesthetized (completely numbed) in order to undertake procedures that would otherwise cause pain.

- **Sedation/anxiety relief:** These drugs are often used in combination or with general anesthetics to modulate, block, or relieve pain.
- **Analgesia:** These reduce pain locally or temporarily. Although analgesia is defined as “lack of pain,” complete elimination of pain in awake animals is commonly neither achievable nor desirable (the ability to feel some pain prevents an animal from further damaging an injured area, for example).

Humane Endpoints

Humane endpoints define when a study should end or the study design be changed due to animal pain, distress, and welfare considerations. Adopting humane endpoints is necessary for the sake of ani-



Those who care for and use laboratory animals are responsible for minimizing animal pain whenever possible. The report describes ways to recognize pain in nonhuman primates, dogs, cats, laboratory rodents, rabbits, farm animals, birds, reptiles, fish, and amphibians.

mals, but it is not necessarily an easy process. It is important to ensure the endpoints are validated and based on sound science rather than subjective judgment.

More effort should be taken to identify appropriate humane endpoints. In particular, pilot studies, in which a proposed study is first conducted on a small number of animals to verify the anticipated results, can be a powerful tool to determine appropriate endpoints. This approach helps researchers refine their study design to avoid causing unnecessary pain when using larger numbers of animals. Good communication between researchers, veterinary staff, animal care staff, and the IACUC can help facilitate the determination of humane endpoints.

Education

Investigators, veterinarians and animal care staff must be aware of the basic principles, causes, and signs of pain, and should be knowledgeable about pain treatment options and their potential deleterious effects. As the field of pain medicine benefits from new insights and methods for preventing and treating pain in humans, so should laboratory animals benefit from the research for which they are a currently indispensable underpinning.

By urging laboratory animal veterinarians to understand current pain management, and by suitably updating regulatory policy, the ability to minimize pain in laboratory animals can proceed in tandem with advancing scientific progress.

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The National Academies appointed the above committee of experts to address the specific task requested by the U.S. Department of Agriculture. The members volunteered their time for this activity; their report is peer-reviewed and the final product signed off by both the committee members and the National Academies. This report brief was prepared by the National Research Council based on the committee's report.



For more information, contact visit the Institute for Laboratory Animal Research at <http://nationalacademies.org/ilar>. Copies of *Recognition and Alleviation of Pain in Laboratory Animals* are available from the National Academies Press, 500 Fifth Street, NW, Washington, D.C. 20001; (800) 624-6242; www.nap.edu.

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