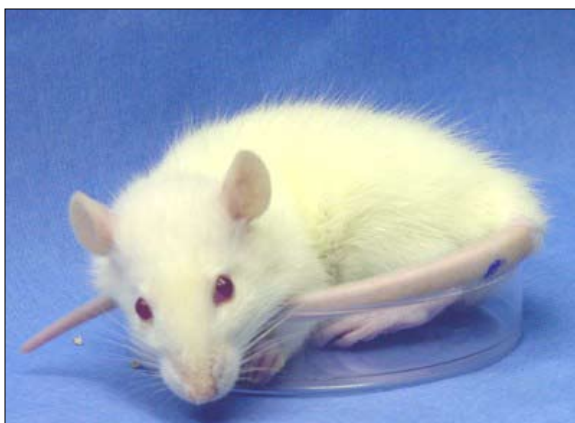


Recognition and Alleviation of Distress in Laboratory Animals

Recent scientific progress in the fields of stress and distress and greater sensitivity by scientific investigators and the public have warranted the development of an updated set of guidelines for the recognition and alleviation of distress in laboratory animals. This report updates 1992 National Research Council guidelines for investigators, laboratory animal veterinarians, animal care staff, and institutional animal care and use committee (IACUC) members who make decisions regarding the care and use of animals in the research environment. The report concludes that more research in the area of distress is necessary in order for scientists to make objective, informed decisions concerning the improvement of laboratory animal welfare.

Many scientific advancements 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 the many diseases that plague humans as well as the animals themselves. Although a majority of the public supports the use of animals in biomedical research, that support diminishes if the animals are subjected to painful procedures and/or experience distress. Proper care of animals used in research has been an ongoing priority for the scientific community, and there are many laws and regulations that govern the use of animals in research.

It has become widely recognized that animals may experience distress in a laboratory setting, and that this distress may interfere with the animal's overall welfare, disrupt scientific experiments, and result in unforeseen behavioral and physical changes. U.S. regulations based on the Animal Welfare Act and the Public



Health Service Policy reflect these views by mandating that pain and distress in laboratory animals be minimized or eliminated, except where scientifically justified. Furthermore, the U.S. Government Principles also state that "... unless the contrary is established, investigators should consider that procedures that cause pain or distress in humans may cause pain or distress in other animals..."

Even though the minimization or elimination of distress experienced by laboratory animals is not only a regulatory requirement but also a moral obligation, the subject has not been adequately researched.

Moreover, a universally accepted scientific definition of distress has yet to be established. The absence of reliable guidance in recognizing, assessing, or alleviating distress has made it difficult to implement and adhere to mandates. Animal users and care providers are often forced to rely on best practices and personal experience.

This report is an update of the 1992 National Research Council report *Recognition and Alleviation of Pain and Distress in Laboratory Animals*. It provides guidance to investigators, researchers, laboratory animal veterinarians, animal care staff, and IACUC members in recognizing and assessing whether a proposed protocol would cause distress or whether an animal is experiencing unexpected distress, and how to best respond to such situations. It also identifies research needed to further advance the field.

Defining Stress vs. Distress

A variety of views, definitions, and language have been used in the discussion of stress and distress. According to the report, stress is considered “a real or perceived perturbation to an organism’s physiological homeostasis or psychological well-being.” While the set of biological responses that represent stress are fairly well understood and agreed upon, the scientific, regulatory and animal welfare communities disagree with respect to a universally accepted definition of distress.

Most definitions of distress characterize it as an aversive, negative state in which an animal’s coping and adaptation responses fail to return the animal to a state of normal physiological and/or psychological well being. However, there are philosophical differences as to whether or not emotions and feelings should be taken into consideration when evaluating the status of an animal’s well-being. The report proposes that even if a universally accepted definition existed, it could not be applied across all species and all conditions because many other factors—such as strain, age, gender, genetic background, and environment—must also be considered.

Often, a diagnosis of unintended distress is made when an animal’s abnormal behavior or clinical signs cannot be explained only by illness or by the scientific experiments being conducted.

Clinical signs interpreted through relevant animal behavior and physiological states are the most reliable distress measures. Although the knowledge of distress is incomplete, measures can be taken to reduce the possibility of an animal experiencing distress.

Evaluation and Treatment of Stress and Distress

The evaluation and treatment of an animal for distress needs to be a team effort. Evaluating distress is crucial when research animals are purposefully exposed to stressful conditions as part of the experimental protocol or when animals appear distressed unexpectedly. The assessment and subsequent interventions should involve researchers, veterinarians, and technicians, and the team should continue its collaboration to develop an intervention strategy once the assessment is completed. Well-trained, competent, and attentive research and animal care personnel, who are crucial in providing distress relief, should have adequate time and contact on a daily basis with the animals to properly evaluate their well-being. In addition to such observable behavioral and physical changes, such as weight loss or lack of grooming, clinical judgment is vital to effective assessment and treatment of stress and distress.

Avoiding, Minimizing, and Alleviating Distress

The mission of the National Research Council’s Institute for Laboratory Animal Research (ILAR), which convened the committee that wrote this report, is to evaluate and disseminate information on issues related to the scientific, technological, and ethical use of animals and related biological resources in research, testing, and education. The underlying principle on which ILAR relies to ensure ethical animal care and use is that of the “Three Rs;” Refinement of procedures to reduce or eliminate pain and distress, Reduction in the number of animals being used, and Replacement of animals with other reliable models.

The Three Rs should be the standard for alleviating, avoiding, and minimizing most causes of distress in laboratory animals. Although scientific research on the state of distress itself

and the development of treatments for alleviating distress (e.g., the development of anesthesia or analgesia) may unavoidably cause animal suffering, the optimum goal of research and veterinary teams should be to reduce and alleviate distress in laboratory animals to the minimum necessary to achieve the scientific objective. The report urges investigators, veterinarians and IACUCs to embrace The Three Rs and through those criteria to act in the best interest of the animals while safeguarding the integrity of the research process.

Recommendations for implementing the Three Rs include consideration of the following:

Housing – Potential environmental stressors that may lead to stress and distress such as levels of ambient light, noise, vibrations, temperature, and disturbances from operation of facilities should be kept to a minimum.



Husbandry – Investigators should handle animals in a consistent and gentle manner. Many techniques that minimize stress in husbandry, such as combining husbandry handling with habituation and handling for research purposes, acclimation to new environments, positive reinforcements, operant conditioning, and well-trained staff can be helpful tools for the overall reduction of stress and distress.

Enrichment – Environmental enrichment can improve animal welfare, reduce stress, and improve the quality of data obtained from the animals in situations where it does not compromise the anticipated research outcomes by introducing uncontrolled or unanticipated variables.

Socialization – It is generally preferable to house animals that are social by nature (such as rats, mice, dogs, primates) in groups unless there are scientific or welfare reasons not to do so. Overall, social housing among compatible individuals is neither stressful nor harmful. Furthermore, evidence indicates that housing naturally sociable animals in solitary conditions can result in distress and harm. It is therefore important to provide thorough scientific rationale for solitary housing.

Refining experimental design – When possible, the experiment should be designed to arrive at a research objective while avoiding or minimizing animal distress. Some strategies to accomplish this include a thorough literature review, using a less invasive or non-invasive data gathering method, and avoiding repeated exposures to stress. For example, the use of minimally invasive imaging technologies makes it possible to measure tumors so precisely that an animal may be euthanized before any clinical signs arise.

Humane endpoints – The choice and use of humane endpoints should be part of the experimental protocol whenever possible. For example, measurements or sample collections could be taken from animals before the appearance of clinical signs or abnormal behaviors, especially if the signs themselves are not the study's focus.

The value of statistics – planning experiments by using appropriate statistical methods may reduce the number of animals used in an experiment while still retaining scientific validity and statistical power. Not all methods will work in all situations. Each individual experiment should be evaluated to determine whether these methods would be effective. In some cases, a pilot study with fewer animals can be performed before seeking approval for the use of more animals. These studies are beneficial to establish proof-of-concept, provide preliminary data, and identify unanticipated adverse effects and opportunities for refinement. Experiments should be designed with at least an 80% probability of detecting a difference between experimental groups. This ensures that this difference will have both scientific validity and statistical significance. After calculating sample size, researchers should consider additional ways to further reduce it.

Communication

Animal welfare scientists and researchers and scientists who use animal models should communicate with each other more frequently to compare objectives and progress and to identify opportunities for collaboration. There should be a clearing house (or some other venue such as a website or a specialized peer reviewed journal) for publication of research on the effects of enrichment strategies on parameters such as physiology, distress, and endpoints for all laboratory animals, as the highly specialized nature of the field makes it difficult for the larger scientific community to remain informed about recent advances and ongoing debates. Biomedical research journals should be more open to submissions from scientists whose research focuses on animal welfare issues so that concerns about research interference or unjustified expenses can be debated on scientific as well as ethical or regulatory grounds.

Future Opportunities

Obtaining funding for welfare research is often difficult, especially when project applications compete against other fields of science due to lack of an appropriate and separate research oversight body. Given the impact of improved animal welfare on science as well as the growing public interest in the treatment of laboratory animals, federal agencies and foundations that support biomedical and behavioral research should make funds available specifically for research on animal welfare, stress and distress of laboratory animals.

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This report brief was prepared by the National Research Council based on the committee's report. For more information or copies, contact the Institute for Laboratory Animal Research at (202) 334-2590 or visit <http://dels.nas.edu/ilar>. Copies of *Recognition and Alleviation of Distress 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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