Animal Bytes examines biosafety challenges posed when conducting work with animals and provides solutions that promote both safe and responsible research. Good safety and animal husbandry are essential for good science. Learn about best practices when working with animals and applied safety information that can be used every day. Please e-mail your comments, questions, and insights to barbara_johnson@verizon.net or Co-Editor Karen B. Byers at karen_byers@dfci.harvard.edu.

Use of Humane Endpoints in Research

Although implementation of humane endpoints is generally not considered a component of animal biosafety, many biosafety professionals serve on institutional animal care and use committees (IACUC) where humane endpoints are often a point of intense discussion. This is especially important for studies involving infectious disease and toxins that may result in the progression of the animal’s condition and death if allowed to continue with no intervention. In many animal welfare circles, death as an endpoint is generally not acceptable unless explicitly justified scientifically. As such, the implementation of humane endpoints represents a significant humane refinement for these types of studies and a necessary topic of awareness for biosafety professionals.

Replacement, reduction, and refinement, commonly known as the three Rs (Russell & Burch, 1959) provide an important ethical backbone when planning to conduct work with animals in research. As described by the authors, replacement is the use of non-sentient organisms rather than higher animals for experiments. Reduction entails designing experiments and statistics to obtain the highest quality and most precise information with the smallest number of animals. This results in the added benefit of not repeating an experiment due to poor or omitted data. Refinement refers to all changes in protocols that can reduce the incidence or severity of distress experienced by laboratory animals. The use of humane endpoints is a form of refinement. The term “humane endpoint” can be defined as the point at which an experimental animal’s pain and/or distress is terminated, minimized, or reduced by taking actions such as euthanizing the animal humanely, terminating a painful procedure, or giving treatment to relieve pain and/or distress (Canadian Council on Animal Care, CCAC, 1998).

Humane endpoints are those physiological, behavioral, and appearance-based indicators that are reliably predictive of the scientific outcome of the experiment that can be identified at the soonest possible time prior to (moderate/severe) pain, distress, or death. They are implemented when suffering cannot be morally justified; clinical signs directly support a certain outcome; the objective of the experiment is achieved, or the animal is no longer scientifically useful in the experiment (Hendriksen & Morton, 1999; Richmond, 2000; van der Meer et al., 2001). A recent report “outlines the need for the development of humane endpoints and biomarkers, for the administration of supportive clinical care, and for the alleviation of pain and distress” in research involving bioterrorism agent countermeasures (National Academies of Sciences, 2011). In establishing humane endpoints, early clinical signs that are predictive of later clinical outcomes are carefully validated before they can be used as reliable endpoints. The attending veterinarian plays a key role in determining humane endpoints. The IACUC reviews humane endpoints as part of the process for approving projects involving animals.

Validating Humane Endpoints

In developing endpoints it is important to understand that it is not always necessary for an animal model to progress to the final disease state or condition as would occur in a human. For example, using animals to study arthritis and preventative medications may not require the research to proceed to a point where the animals suffer chronic, painful joint disease; rather, it may be possible to collect data on increased or decreased urinary cartilage breakdown products before moderate pain occurs. The humane scientific endpoint is the change seen in cartilage breakdown products, which are used as a surrogate for the human endpoint of joint disease (The National Centre for the Replacement, Refinement and Reduction of Animals in Research, 2012). The Canadian Council on Animal Care (CCAC) has recommended that pilot studies using small numbers of animals be run to determine the onset and progress of adverse effects and identify these types of early scientific and humane endpoints. This approach has been widely adopted, and several resources have compiled studies and papers that describe the establishment of humane endpoints, specifically define endpoints, or provide score sheets to measure progression to endpoints (Morton & Hau, 2011; ILAR Journal, 2000; USDA, 2012).

Score Sheets

Score sheets provide a methodical and objective way to record clinical signs or changes in behavior that would most likely be seen after a given procedure in an individual.
species, breed, or strain. Because procedures differ on how they may affect the animal, score sheets must be specific for the procedure (i.e., the clinical signs displayed following the failed treatment for chronic arthritis will differ from those seen in a failed rabies vaccine trial). The list of key clinical signs is initially developed during pilot studies by carefully observing the animal’s behavior while unprovoked, then close-up during handling. Physiological responses are also measured. Observations and measurements are taken before the procedure, at regular intervals during the procedure, and at key points following the procedure by a team comprised of animal caretakers with knowledge of the species and training in animal observation and measurement procedures, and by the veterinarian.

Clinical signs are often reduced to the level of present (+) or absent (-) to reduce observer error and variation. A score of (+/-) indicates the observer is uncertain. Normalcy is recorded by (-) signs. Increases in the number of (+) signs indicate the animal is increasingly deviating from normal health and well-being. Examples of descriptors may include nasal/ocular discharge, lethargic, unresponsive, not drinking, not inquisitive, lameness, diarrhea, etc. It is also possible to use a scaled rating approach; for example, scoring factors related to an animal’s appearance, such as the degree to which posture is hunched or a coat appears scruffy, could range from 0-3, with 0 being normal and 3 being severe. A scaled rating approach requires a high level of training and very thoughtfully and well defined criteria to maintain consistency from day to day and among raters. Applicable clinical measurements, such as body weight, temperature, respiratory rate, blood test results, urinalysis, etc., may also be recorded. The score sheet typically includes guidelines for scoring, animal husbandry procedures, the criteria for a humane endpoint, and other actions to be taken following euthanasia (Morton, 2000). Several examples of score sheets by D. B. Morton can be accessed from the following sites:

- www.nus.edu.sg/iacuc/iacuc_forms/Research/awsh.pdf
- http://dels-old.nas.edu/ilar_n/ilarjournal/41_2/Systematic.shtml

It is important that individuals making observations are trained and competent in evaluating the normal physiology, behavior, and body condition of the species of animal under observation. Roles, responsibilities, and the reporting chain should be established and clearly communicated for all individuals involved in the animal’s care. When animals exhibit pain, distress, or unanticipated adverse effects, the veterinarian should be promptly notified. Once humane endpoints have been defined, it is important that they be implemented properly by the authorized individual. With new technology and improved technique, we have the opportunity to refine experimental protocols and allow for the incorporation of the earliest humane endpoints.

References


