

DISTRESS AND PAIN CONSIDERATIONS

I. Background

- A. The Animal Welfare Act mandates that IACUCs oversee the care and use of animals covered by the Act. One of the provisions of the Animal Welfare Regulations requires that institutions provide an annual report indicating the number of covered species used in the following categories:
1. Category B – animals in which procedures caused no pain and distress
 2. Category C – animals in which pain and distress during procedures was appropriately relieved by pain- or distress-relieving drugs.
 3. Category D – animals involved in procedures which cause pain or distress that was not relieved by drugs for scientific reasons. Animal use reported in Category D must be accompanied by an explanation and justification as to why drugs to relieve pain and distress were withheld.
- B. Definitions
1. Pain has been defined in humans by the International Association for the Study of Pain as an unpleasant sensory and emotional experience associated with potential or actual tissue damage. While the ability of animals to feel pain is not completely understood, investigators should consider that procedures that cause pain or distress in humans may cause pain or distress in other animals.
 2. Distress has been defined by the National Research Council as the biological responses an animal exhibits in an attempt to cope with a threat to its homeostasis. When stressors are mild and/or of short duration, the animal may regain homeostasis without any lasting effects. However, stress results in distress to the animal when the stressor results in disruption of biological functions which are critical to the animal's well being. When normal function is disrupted, pathology may occur, threatening the animal's welfare, and the animal experiences distress.

II. Sources

- Kohn DF, Martin ME, Foley PL, et al. 2007. Guidelines for the Assessment and Management of Pain in Rodents and Rabbits. American College of Laboratory Animal Medicine. JAALAS 46:(2) 97-108.
- Recognition and Alleviation of Pain and Distress in Laboratory Animals Update (NRC 2009).
- Gaynor JS and Muir WW. 2009. Handbook of Veterinary Pain Management..
- NRC. (1996) Guide for the Care and Use of Laboratory Animals, Washington, DC: National Academy Press.
- NIH (2002) Public Health Service Policy on Humane Care and Use of Laboratory Animals, Bethesda, MD: Office of Laboratory Animal Welfare.

III. Policy

- A. The IACUC must assure that all aspects of the animal use protocol that may cause more than transient pain and/or distress are addressed, alternatives to painful or distressful procedures are considered, anesthetics and analgesics to minimize or eliminate pain and distress are included when these methods do not interfere with the research objectives, and that humane endpoints have been established for all situations where more than transient pain and distress cannot be avoided or eliminated. It is the responsibility of the animal care staff, the research staff, veterinarians and the IACUC to continue to monitor animals for pain, distress, illness, morbidity or mortality during the course of the research study. If unexpected pain or distress occurs, and is more than an isolated incident, the PI must submit an amendment explaining in detail the unexpected problems and stating their proposed resolution to the issue (i.e. administration of analgesics, lowering the dose of a drug that was administered, etc.).
- B. Animals should be monitored by trained individuals for pain and distress as appropriate for the species, condition, and procedure. It is most important to have the ability to distinguish between normal and abnormal animal behavior. Whenever more than transient pain or distress is anticipated preemptive measures should be taken to minimize or prevent the development of pain and/or distress. Following the implementation of such measures, animals must be monitored to ensure the efficacy of the measures taken and determine if or when additional treatment is necessary. Animals undergoing pilot studies or procedures new to the investigator or facility may also require a higher frequency of monitoring and a team approach. It is ultimately the responsibility of the PI and the personnel conducting the procedure to ensure the timely and adequate identification, monitoring, and documentation of the animals undergoing potentially painful or distressful procedures. Animals should be observed a minimum of once daily or more often based on professional judgment and the research being conducted. Observations and actions taken to relieve pain or distress must be documented. Documentation must be available to all personnel monitoring the cage or animal (i.e. IACUC, veterinarians, animal care staff, etc.).
- C. The relief of pain and distress in research animals is ethically sound, humane, and promotes good science. Strategies for the management of pain and distress may include non-pharmacological considerations (e.g. modified housing and husbandry practices, dietary modifications, desensitization and acclimation strategies, etc.), pharmacological interventions, or euthanasia. Preemptive measures should be taken to minimize or prevent the development of pain and/or distress. Mild pain may be successfully treated with the application of a local anesthetic or by the administration of a single dose of a non-steroidal anti-inflammatory agent or mixed narcotic agonist/antagonist, whereas moderate pain may require the repeated administration of the agent. The treatment of severe

pain often requires the frequent administration of pure narcotic agonists and may also benefit from a multimodal approach to pain management.

- D. Humane endpoints define when a study should end or the study design be changed due to animal pain, distress, and welfare considerations. Pilot studies may be utilized to determine appropriate endpoints. Good communication between researchers, veterinary staff, animal care staff, and the IACUC can help facilitate the determination of humane endpoints.

Post-Procedural Pain Potential

Minimal to Mild	Mild to Moderate	Moderate to Severe
Catheter implantation	Minor laparotomy incisions	Major laparotomy/organ incision
Tail Clipping	Thyroidectomy	Thoracotomy
Ear Notching	Orchidectomy	Heterotopic organ transplantation
Subcutaneous transponder placement	C-section	Vertebral procedures
Superficial tumor implantation	Hypophysectomy	Burn procedures
Rodent embryo transfer	Embryo transfer in non-rodents	Orthopedic procedures
Multiple injections	Bone marrow collection	Trauma models
Non-corneal ocular procedures	Corneal procedures	Collection of ascetic fluid
Intracerebral electrode implantation	Thymectomy	Production of genetic defects (muscular dystrophy, hemophilia)
Vasectomy	Use of casts (Plaster of Paris)	Prolonged deprivation of food, water, or sleep
Vascular access port implantation		Carcinogenicity research with tumor induction
Craniotomy (periosteal pain)	Immobilization/restraint (primate chairs, inhalation chamber)	Application of painful stimuli, induction of convulsions
Superficial lymphadenectomy	Skin transplantation	Organ transplant procedures
Venipuncture	Immunization with incomplete Freund's adjuvant or substitute	Immunization of footpad or with complete Freund's adjuvant
Rectal examination	Moderate food, water deprivation	
Vaginal smear sampling		
Force-feeding of innocuous substances		
Radiography of unanesthetized animals		
Immunization with		

adjuvant		
Short-term mechanical or manual restraint		
EEG, EKG, EMG administration		
Short-term aversive stimuli		

IV. Species-Specific Signs of Distress and Pain

- A. Dogs: With severe pain, dogs are less alert, quieter, have stiff body movements, or unwillingness to move or to lie down or stand up. In less severe pain, dogs are restless and alert. Other signs are reduced barking, inappetence, shivering, and increased respiration and panting, whimpering, howling, or growling. They may bite, scratch, guard, or attend painful regions.
- B. Cats: Cats in pain are generally quiet and have an apprehensive facial expression (forehead creased). They may be inappetent, will vocalized if approached or moved, and will isolate themselves from other cats. The posture may be stiff and abnormal. Cats with generalized pain may crouch and hunch, or extend the body. Incessant licking of one place may indicate localized pain. Painful limbs are held up, and palpation of a painful area can produce an aggressive reaction.
- C. Rabbits: Rabbits in distress or pain appear apprehensive, anxious, dull, inactive, have a hunched posture, hide, and may squeal or cry, or be aggressive with increased scratching. Abdominal pain may cause teeth grinding and excessive salivation. An increased respiratory rate +/- open-mouth breathing, inappetence, cannibalism of young, self-mutilation and tonic in mobility are other signs.
- D. Rodents: Rodents with distress and pain are less active, hunched, have erect body hair, squint, lick, scratch, often self-mutilate, and have rapid, audible, respiratory sounds. Pupils dilate and red tears may appear. Rodents in pain or anticipating pain may vocalize and can be more aggressive. Rodents may become immobile (as do prey species) or may stampede wildly. Sick rodents usually have dull eyes with reddened and swollen eyelids.
- E. Horses: Horses in distress or pain are reluctant to be handled and may show other signs, including restlessness, interrupted feeding, anxiety with dilated pupils, sweating, increased respiratory and heart rates, and a rigid stance. In chronic pain, horses may be depressed and have a lowered head. Skeletal fractures lead to reluctance to move, unusual limb postures, and holding head and neck in a fixed position. Abdominal pain produces looking at, biting, or licking the abdomen; rising and lying frequently, walking in circles, rolling, and eventually progressive mucosal cyanosis and prolonged capillary filling time.
- F. Cattle: Distress and pain in cattle cause them to lower their heads and become refractory to surroundings. They eat less if at all, lose weight, and decrease milk yield. Respiration is rapid and shallow. They may react violently to handling or become immobile, grunt, and grind their teeth, and

lick or kick at the offending area. In acute abdominal conditions, cattle place one hind foot directly in front of the other.

- G. Sheep and Goats: Signs in these species resemble those in cattle except that sheep especially can tolerate (or seem to) severe injury without or with few overt signs of distress or pain. Changes in posture and movement and facial expressions change. Affected animals are reluctant to move and goats in pain may vocalize. Small ruminants in pain may grunt, grind teeth, stand and lie, tail wag, extend the neck, curl lips, kick, and roll.
- H. Swine: Pigs in distress or pain show changes in social behavior, gait, posture, bed making, and sleeping location. Pain produces squealing, hiding, reluctance to move, and increase aggression.
- I. Birds: Birds in distress or pain try to escape handling, vocalize, move excessively, show increased heart and respiratory rates. Eyes may be closed partially, wings held against the body, and necks retracted. Birds may become immobile or show few if any signs of ongoing distress or pain.
- J. Fish: Fish in pain have pronounced responses to acute injury but little response to chronic stimuli. Even fish with severe wounds may behave and feed normally. Reactions to sharp pain result in strong muscular movements. Abnormal swimming, discoloration, rapid opercular movements, and abnormal postures (tail or head up) are also signs.

V. **Alleviation of Pain**

Anesthetics and analgesics must be used appropriately unless their effects compromise the integrity of a study. Non-drug methods of relieving pain and/or distress must be considered also and include:

1. Use of socializing and gentle handling.
2. Enriching an animal's environment can distract the animal's attention from its pain, as will a familiar environment or a familiar scent.
3. Removal of environmental stressors, such as other animals, strange people, excessive light, noise, cold, or heat may reduce distress and pain.
4. Use of conditioning procedures so animals associate acute pain with pleasure – giving stimuli such as petting, feeding, and eye contact may reduce pain or distress.
5. Tonic immobility is a natural response of some animals to gentle neck traction. Such relaxation facilitates reduced stress and pain during physical examination, deep palpation, and eye examination.
6. Acupuncture
7. Hypothermia may be used for hairless neonates that have not developed effective thermoregulatory mechanisms.