

**UNIVERSITY OF CALIFORNIA SAN DIEGO
INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE**

**Policy and Guidelines on Minimizing Pain and Distress in Animals
and Determination of Reportable Pain Categories**

The UCSD policy is adopted from the U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training:

- Proper use of animals, including the avoidance or minimization of discomfort, distress, and pain when consistent with sound scientific practices, is imperative. Unless the contrary is established, investigators should consider that procedures that cause pain or distress in human beings may cause pain or distress in other animals.
- Procedures with animals that may cause more than momentary or slight pain or distress should be performed with appropriate sedation, analgesia, or anesthesia. Surgical or other painful procedures should not be performed on unanesthetized animals paralyzed by chemical agents.
- Animals that would otherwise suffer severe or chronic pain or distress that cannot be relieved should be painlessly killed at the end of the procedure or, if appropriate, during the procedure.
- The living conditions of animals should be appropriate for their species and contribute to their health and comfort. Normally, the housing, feeding, and care of all animals used for biomedical purposes must be directed by a veterinarian or other scientist trained and experienced in the proper care, handling, and use of the species being maintained or studied. In any case, veterinary care shall be provided as indicated.
- Investigators and other personnel shall be appropriately qualified and experienced for conducting procedures on living animals. Adequate arrangements shall be made for their in-service training, including the proper and humane care and use of laboratory animals.
- Where exceptions are required in relation to the provisions of these Principles, the decisions should not rest with the investigators directly concerned but should be made by an institutional animal care and use committee. Such exceptions should not be made solely for the purposes of teaching or demonstration.

Definitions

UCSD employs three Pain and Distress Categories C, D, and E (corresponding to the USDA reportable pain categories) as follows:

Category C includes only procedures that are considered to produce minimal, transient, or no pain or distress in animals when performed by a competent individual. The definition of USDA category C also emphasizes that protocols involve no more than momentary or slight pain or distress and no use of pain-relieving drugs.

Category D includes procedures that have the potential to produce pain or distress in animals, but which are performed using appropriate and adequate anesthetics, analgesics, or tranquilizers to alleviate the pain or distress.

Category E includes potentially painful or distressing procedures that are performed without appropriate and adequate anesthesia, analgesia, or tranquilizers; or are not followed with appropriate measures to alleviate pain or distress; or are not amenable to relief by therapeutic measures.

General approach to pain/distress categorization

Investigators and reviewers should employ the following two sets of questions and criteria:

1. Comparison with humans. What would be an equivalent or comparable procedure or state in humans, and would it cause more than minimal or transient pain or distress? If pain might be expected, would it be necessary to treat it and how? What would the consequences be of not treating the pain? Animal procedures for which the human equivalent causes very transient, minor, or no pain or distress, or treatment is not necessary for the majority of individuals, should generally be classified as Category C procedures, unless animals show objective signs of pain or distress.
2. Objective signs of pain and distress in animals. Do animals develop objective signs of pain and distress following the procedure?

Such signs include, but are not limited to:

- Changes in activity level: reduced spontaneous motor activity, recumbent position, delayed response to handling, or observation of pacing, restlessness or lameness.
- Changes in appearance: hunched position, ruffled fur, decreased grooming, discharge around nose and eyes.
- Changes in temperament: increased aggression, guarding, reluctance to interact.
- Vocalizations: teeth-grinding, chattering, whining, whimpering.
- Changes in feeding behavior: decreased food and water consumption, reduction in body weight, urine, or stool output.
- Physiologic changes: heart rate, respiratory rate, blood pressure, body temperature, skin color.
- Appearance of surgical site: erythema, swelling or discharge, excessive licking or chewing.

Procedures that cause animals to exhibit objective signs of pain or distress spontaneously and to a significant extent should generally be categorized as Category E (or Category D if treated appropriately with analgesics or anesthetics) unless the investigator can justify variance. Importantly, the constellation of several parameters of pain and distress is given greater weight in evaluation than any one of these signs when observed in isolation.

Examples

The following examples illustrate the approach to assigning experimental procedures to categories:
(NOTE: These lists are examples and are not complete lists of every procedure; investigators may contact the IACUC for further guidance)

Examples for Category C

(procedures that are minimal, transient, or involve no pain or distress)

- a. Handling, weighing, behavioral observation
- b. Injections and non-surgical fluid collection of modest volumes (i.p., i.v., s.c.)
- c. Identification (ear punching, tattooing, ear notching)
- d. Tail clipping of mice less than 4 weeks old; less than 5 mm
- e. Food and water restriction without clinical health problems in closely monitored animals
- f. Mild to moderate ascites formation without systemic effects
- g. Infections without objective signs of pain or distress
- h. Inflammatory conditions without systemic effects (e.g. localized to skin)
- i. Cancer studies, limited to subcutaneous tumors of small - moderate size, which adhere to Policy
- j. Gavage
- k. Euthanasia followed by tissue collection
- l. Pain models in which animals can compensate for any potential pain by behavioral modification

Examples for Category D

(procedures with the potential to produce pain or distress in animals, but which are performed using appropriate and adequate anesthetics, analgesics, or tranquilizers to alleviate the pain or distress)

- a. Surgical procedures with appropriate and effective anesthesia and analgesia
- b. Blood or tissue sampling with appropriate anesthesia or tranquilizers
- c. Physical trauma under anesthesia
- d. Transcardial perfusion under anesthesia

Examples for Category E

(potentially painful or distressing procedures that are performed without appropriate and adequate anesthesia, analgesia, or tranquilizers because they would adversely affect the results or interpretation of data)

- a. Studies with significant mortality or death as an endpoint
- b. Procedures leading to clinically significant (>10%) weight loss
- c. Inflammatory conditions and microbial infections with significant systemic effects (e.g. fever, shock)
- d. Use of paralyzing agents or immobilizing drugs without anesthesia
- e. Prolonged restraint in conscious animals
- f. Cancer studies with involvement of bones or internal organs
- g. Infliction of burns or trauma without anesthesia
- h. Noxious stimuli from which there is no escape

Pain and distress in breeding colonies

Breeding of genetically altered animals raises special concerns as spontaneous phenotypes can occur in the absence of specific interventions. For example, an animal might be born healthy but then develop symptoms that would necessitate inclusion into Category E. In addition, the phenotype of a new mutation is often not known or predictable. Unexpected phenotypes which fall into Category E will require the Principal Investigator to submit an amendment to the applicable Animal Use Protocol.

Analgesia

All animals that undergo a painful procedure such as surgery and are likely to experience post procedural pain, should receive preemptive analgesic medication. The Principal Investigator in consultation with the ACP Veterinarian should use their professional judgment to determine the need for analgesic medication. Procedures for analgesic administration and a plan for postoperative care should be prepared in advance. Exceptions to this policy must be justified scientifically in writing and approved by the IACUC. Where doubt exists regarding the potential for interference with an experiment, consideration should be given to performing a pilot study designed to investigate the possibility of interference.

Note: Pain is more easily controlled by administration of analgesics before pain starts than after the animal is experiencing pain. Therefore, analgesics should be administered preemptively before the animal recovers from anesthesia.

Recognizing Pain

Anthropomorphic assessment of the degree of pain or discomfort experienced by an animal can be difficult and inaccurate. While the physiologic mechanisms of pain perception are similar in all mammalian species the ability to tolerate and cope with pain may be vastly different in different species. For example, prey species such as rodents have adapted to hide overt signs of pain to avoid signaling to a predator that they are ill and would be an easy meal. Therefore, a rodent that is experiencing mild to moderate pain may display no clinical signs associated with its discomfort. Moderate to severe pain in rodents frequently leads to changes in normal physiology or behavior. Accurate recognition of these changes requires that research personnel have some knowledge of normal behavior and physiology for the species they are using.

General clinical signs associated with pain in most species:

- Changes in activity level: reduced spontaneous motor activity, recumbent position, delayed response to handling, or observation of pacing, restlessness or lameness.
- Changes in appearance: hunched position, ruffled fur, decreased grooming, discharge around nose and eyes.
- Changes in temperament: increased aggression, guarding, reluctance to interact.
- Vocalizations: teeth-grinding, chattering, whining, whimpering.
- Changes in feeding behavior: decreased food and water consumption, reduction in body weight, urine, or stool output.
- Physiologic changes: heart rate, respiratory rate, blood pressure, body temperature, skin color.
- Appearance of surgical site: erythema, swelling or discharge, excessive licking or chewing.

Analgesic Drugs and Delivery Methods

There are many drugs and routes of administration available for alleviation of pain in all species. Some drugs, such as the opiates (example: buprenorphine or morphine), provide pain relief through their action on the central nervous system. Corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs), relieve pain by decreasing inflammation. Long acting local anesthetics such as bupivacaine, provide postoperative analgesia by their direct action blocking nerve conduction.

Common analgesics for rodents and rabbits are shown in the chart below. Check the ACP web site for the Recommended Dosage Chart for analgesics in many other species. For a consultation with the veterinary anesthesiologist about analgesia in rodents or other species please contact vetservices@acp.ucsd.edu.

Recommended Dosage Rates for Analgesic Drugs in Rodents and Rabbits			
Drug Name	Mouse	Rat	Rabbit
Bupivacaine local anesthetic; injected or dripped onto incision site	Maximum total dose of 4 mg/kg given once at the end of surgery	Maximum total dose of 4 mg/kg given once at the end of surgery	
Buprenorphine mild pain; longer duration of action	0.05-0.1 mg/kg SC every 8-12 hours	0.01-0.05 mg/kg SC every 8-12 hours	0.01-0.05 mg/kg IM, SC or IV every 6-12 hours
Butorphanol moderate pain; short duration of action	1.0-2.0 mg/kg SC every 4 hours	1.0 - 2.0 mg/kg SC every 2- 4 hours	0.1-0.5 mg/kg SC, IM,IV every 4 hours
Carprofen (Rimadyl)	5 mg/kg SC every 24 hours	5 mg/kg SC every 24 hours	4 mg/kg SC every 24 hours
Flunixin (Banamine)	2.5 mg/kg SC every 12-24 hours	2.5 mg/kg SC every 12-24 hours	1.0 mg/kg SC every 12 - 24 hours
Ketoprofen (Toradol)	5 mg/kg SC every 24 hours	5 mg/kg SC every 24 hours	3 mg/kg SC every 24 hours
Morphine moderate to severe pain; short duration	2 - 5 mg/kg SC every 4 hours	2 - 5 mg/kg SC every 4 hours	2 - 5 mg/kg SC, every 4 hours
Analgesic effectiveness must be evaluated in each animal due to variations in response between individuals and strains.			