### Purpose of Policy:
This policy is intended to ensure that any animal that may experience more than momentary or slight pain or distress be provided appropriate sedation, analgesia or anesthesia unless there is scientific justification for withholding such agents.

### Policy Information:
The Animal Welfare Act, the Guide for the Care and Use of Laboratory Animals and Public Health Service Policy Sec. 495(a)(2)(A) and (B) each require that animals be provided appropriate relief from procedures that cause more than momentary or slight pain or distress.

Pain is defined by The International Association for the Study of Pain (IASP) as “An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.” The IASP also notes that “Pain is always subjective.”

In keeping with the U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research and Training, the Animal Welfare Act and other regulatory and advisory bodies, the following policies will be in effect:

- It should be assumed that, in the absence of evidence to the contrary, procedures that cause pain or distress in humans also cause pain or distress in other animals.
- The Attending Veterinarian has the authority to ensure the provision of adequate sedation, analgesia or anesthesia.
- Procedures that cause more than momentary or slight pain or distress should be performed with appropriate sedation, analgesia or anesthesia.
- A detailed description of how pain or distress will be assessed and how it will be mitigated must appear in the animal care and use protocol application and be approved by the Institutional Animal Care and Use Committee (IACUC).
- For survival surgery, provision of post-operative analgesia is required unless there is evidence that the agent would compromise the scientific aspects of the project. Withholding of post-operative analgesia must be approved by the IACUC.
• Neuromuscular blockers may not be used without anesthesia in procedures that may cause more than momentary or slight pain or distress (See IACUC Policy No. 2014-018; Use of Neuromuscular Blocking Agents).
• Animals that would otherwise suffer severe or chronic pain or distress that cannot be relieved should be painlessly euthanized at the end of or during the procedure.
• Personnel shall be properly trained for conducting procedures on live animals.
• Exceptions to the above must be approved by the IACUC.

WesternU’s IACUC has adopted the United States Department of Agriculture’s (USDA) pain level classification system described below. Investigators must indicate the pain level for the procedures described in an animal use protocol and rigorous justification must be provided for any animals in Pain Category E. Withholding of analgesia or anesthesia during or following any procedure that may cause more than momentary or slight pain or distress must be approved by the IACUC.

USDA Pain Categories with examples (not all inclusive)

Category C: No more than momentary or slight pain or distress and no use of pain-relieving drugs, or no pain or distress

Examples: 1. Handling, weighing, behavioral observation
2. injections and non-surgical fluid collection
3. ear punching, tattooing, ear notching
4. tail biopsy of mice less than 21 days old (maximum sample of 5 mm)
5. food and water restriction that does not significantly alter animal well-being
6. infections without objective signs of pain or distress
7. localized inflammatory conditions without systemic effects
8. subcutaneous tumors of small-moderate size that adhere to IACUC Policy No. 2014-017, Tumors in Rodents
9. oral gavage
10. tissue collection after euthanasia
11. pain models in which pain can be compensated for by behavioral modification

Category D: Pain or distress appropriately relieved with anesthetics, analgesics and/or tranquilizer drugs or other methods for relieving pain or distress

Examples: 1. Surgical procedures with appropriate anesthesia and analgesia
2. blood or tissue sampling with appropriate anesthesia
3. physical trauma under anesthesia
4. transcardial perfusion under anesthesia

Category E: Pain or distress or potential pain or distress that is not relieved with anesthetics, analgesics and/or tranquilizer drugs or other methods for relieving pain or distress

Examples: 1. Studies with death or significant mortality as an endpoint
2. procedures leading to a significant (> 10%) weight loss
3. inflammatory conditions and microbial infections with significant systemic effects, e.g. fever or shock
4. use of paralyzing agents or immobilizing drugs without anesthesia (See IACUC Policy No. 2014-018, Use of Neuromuscular Blocking Agents)
5. prolonged restraint in conscious animals (See IACUC Policy No. 2014-026, Prolonged Physical Restraint of Unanesthetized Animals)
6. cancer studies involving bones or internal organs
7. infliction of burns or trauma without anesthesia
8. noxious stimuli from which there is no escape
Survival surgery: If for scientific reasons post-operative analgesia cannot be provided, the animals must be listed in Pain Category E. To be effective, analgesics must be administered before the animal emerges from anesthesia. Thus, analgesia must be administered before surgery and as needed during surgery. Minor surgical procedures require at least 24 hours of post-operative analgesia and then as needed thereafter whereas major survival surgeries require at least 48 hours of post-operative analgesia and then as needed if the animal still appears to be in pain (See IACUC Policy No. 2014-025, Survival Surgery on Laboratory Animals). In some cases, multimodal analgesia may be required. Contact the Attending Veterinarian for guidance on the selection and use of analgesics.

Local anesthetics might be indicated in addition to systemic analgesia for procedures that significantly disrupt the skin, e.g. placement of Alzet pumps and catheter exteriorization. However, local anesthetics are not to be used in lieu of systemic analgesics unless scientifically justified and approved by the IACUC.

Pain and Distress in Breeding Colonies: Breeding of genetically altered animals can unexpectedly give rise to phenotypes that appear to be born healthy but later develop symptoms that would require the animals to be placed in Pain Category E. In such cases, the Principal Investigator must submit an amendment to their animal use protocol for evaluation by the IACUC.

Objective Signs of Pain and Distress include, but are not limited to:

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

Choice of Pain Medication

There are multiple pain pathways with specialized fibers that relay information about specific types of pain. For example, acute, sharp, piercing pain, such as occurs with inflammation, is carried mainly by thinly myelinated Aδ fibers whereas dull, burning, throbbing pain is carried mainly by unmyelinated C fibers. Thus, the type of pain will influence the choice of analgesic. Opioids exert their analgesic effect through actions on the central nervous system and are most effective against dull, burning, throbbing pain although a high enough dose will mitigate pain from almost any cause. However, the risk of undesirable effects, including animal death, increases significantly with higher doses.

Corticosteroids and non-steroidal antiinflammatory drugs (NSAIDS) exert their effects peripherally on various cytokines and eicosanoids and are more effective against pain due to inflammation. Local anesthetics provide pain relief by blocking fast sodium channels and thus nerve conduction. Thus, the type of pain will influence the choice of analgesic.

Commonly Used Analgesics (Contact the Attending Veterinarian for options, dose and regimen recommendations)

- Acetaminophen (APAP; acetyl-p-aminophenol) has analgesic and antipyretic activity but does not have clinically useful antiinflammatory effects. It is effective for low to moderate pain and
is recommended only for minor surgical procedures. It is available in solid and liquid dosage forms.

- **NSAIDS**, by definition, have antiinflammatory activity in addition to their analgesic and antipyretic effects. Their therapeutic and adverse effects are due to inhibition of cyclooxygenase (COX) thus inhibiting prostaglandin synthesis. Most NSAIDS have GI side effects and can cause ulceration. They can also alter platelet function and bleeding time. Unlike corticosteroids, they do not suppress the immune system. There are several different chemical classes of NSAIDS used in veterinary medicine.
  
  - **Propionic acid derivatives** include ibuprofen, ketoprofen and carprofen. All three products are available in oral and parenteral dosage forms.
  
  - **Oxicams**: The most commonly used drug in this class by veterinarians is the selective COX-2 inhibitor meloxicam which is available for parenteral use and in solid and liquid oral dosage forms. It is as effective an analgesic as the opioid buprenorphine for post-operative pain due to soft tissue surgery.

  - **Nicotinic acid derivatives** include flunixin meglumine which is available in oral and parenteral dosage forms. When given parenterally, its analgesic activity is comparable to that of ketoprofen and carprofen.

- **Opioids** are the most effective analgesics for the systemic treatment of pain in most species. They alter not only the transmission of pain but also the perception of pain. They exert their therapeutic and adverse effects at one or more of three major types of opioid receptors (mu, delta, kappa). Although their analgesic effects are due to actions within the central nervous system, many of their side effects are due to peripheral actions. The most common side effects include respiratory depression, constipation, sedation, euphoria, dysphoria and pica (abnormal craving for and eating of non-food substances).

  - **Buprenorphine** is a partial mu opioid agonist and a kappa opioid antagonist that is widely used in laboratory animal medicine because of its relatively long duration of action and its lesser effect on respiratory depression.

- **Local Anesthetics**: Bupivacaine (Marcaine®) is longer acting than lidocaine and is generally given by local infiltration around a surgical site. Local anesthetics are often used in addition to systemic analgesics for procedures that will result in significant disruption of the skin to block the onset of the pain cascade due to disruption of the skin.