The University of Texas at Austin
Office of Research Support and Compliance
Office of the Vice President for Research

Guidelines for Analgesia Use in Rodents
The University of Texas at Austin Institutional Animal Care and Use

These guidelines have been written to assist faculty, staff, and students in performing vertebrate animal procedures in a humane manner and complying with pertinent regulatory requirements. Under some circumstances deviations from these procedures may be indicated but such variances must be approved in advance by the IACUC.

This document provides analgesia information to researchers who use rodents in research, teaching, or other purposes at the University of Texas at Austin. It is organized into six sections:

Section A – Background
Section B – Types of Analgesia and Recommendations
Section C – Administration Routes
Section D – Administering Analgesia in Drinking Water
Section E – Examples of Potentially Painful Procedures and Recommended Analgesic Protocols
Section F – References and Acknowledgements

Section A – Background

According to The Guide for the Care and Use of Laboratory Animals, "Pain is a stressor and, if not relieved, can lead to unacceptable levels of stress and distress in animals." To optimize animal well-being and decrease scientific variability associated with distress, analgesics and anesthetics are used to alleviate pain resulting from spontaneous illness or experimental manipulation. The proper dosing strategy for analgesics is imperative for the humane use of animals and scientific integrity.

Pain is difficult to assess in animals, so indirect signs are often used to identify pain, including abnormal posturing, vocalization, decreased appetite, and self-mutilation. Because of the difficulty in determining when an animal is in pain, animal welfare regulations require providing analgesia whenever a procedure is being performed or a condition is present that is likely to cause pain. In the absence of evidence to the contrary, it is assumed that something that is painful in humans will also be painful in animals. **If analgesia cannot be provided due to scientific reasons, the rationale should be described and approved by the IACUC in the Animal Use Protocol.**

The current guiding principles of pain management include preemptive (preventative) analgesia, multimodal analgesia (using different classes of drugs simultaneously to interrupt the pain pathway at various points), and appropriate follow-up analgesia. Administration of pain-relieving drugs BEFORE pain circuits begin to activate due to surgical trauma has been shown to prevent "wind- up" pain and provide better analgesic outcomes in both human and animal surgery. As such, analgesia is best provided prior to the painful procedure, rather than after observing clinical signs of pain. Advantages of pre-emptive use of analgesics include 1) Reduces the intensity of painful stimulation, 2) Improves the animal's comfort level after surgery, 3) Decreases the amount of anesthesia required to maintain a surgical plane, 4) Results in a smoother recovery.

The Animal Resource Center's (ARC) Rodent Anesthesia Record template contains a Post-Procedural Recovery / Analgesic Administration Log. The template may be adapted for your laboratory's use or the information contained in this template should be recorded in your study records.

Section B – Types of Analgesia and Recommendations

This section describes three types of analgesia: opioids, NSAIDS, and local analgesia. Section E of this guideline describes recommended analgesic protocols based on the pain or discomfort an animal is expected to feel with various procedures.

Opioids

- Examples include buprenorphine HCL and SR
- Opioids exert their effects on the opiate receptors in the central nervous system. Opioids are effective for acute, deep, or visceral pain.
- The most commonly used opioid in laboratory animal medicine is buprenorphine, which manages mild to moderate pain. Potential side effects include respiratory depression, nausea, vomiting, pica (rats), and constipation. Sustained-release buprenorphine has been associated with dermatitis and ulceration at the site of administration in rats and mice.
- All opiates are controlled substances, and their use requires special record keeping.

	Mice	**Rats**	**Hamsters**	**Gerbils**
Buprenorphine-HCL	Dose: 0.05-0.1 mg/kg Recommended dose*: 0.1 when used alone; 0.075 when used in combination** Frequency: Every 6-8 hours. Frequency of dosing may be decreased to 9-12 hours if using multi-modal analgesia consisting of opioid, NSAID, and local analgesia. Route: Subcutaneous (SQ), intraperitoneal (IP)	Dose: 0.01-0.05 mg/kg Recommended dose*: 0.05 when used alone; 0.03 when used in combination*** Frequency: Every 6-8 hours. Frequency of dosing may be decreased to 9-12 hours if using multi-modal analgesia consisting of opioid, NSAID, and local analgesia. Route: Subcutaneous (SQ), intraperitoneal (IP)	Dose: 0.1-0.5 mg/kg Recommended dose*: 0.5 when used alone; 0.3 when used in combination Frequency: Every 6-8 hours. Frequency of dosing may be decreased to 9-12 hours if using multi-modal analgesia consisting of opioid, NSAID, and local analgesia. Route: Subcutaneous (SQ)	Dose: 0.05-0.2 mg/kg Recommended dose*: 0.5 when used alone; 0.3 when used in combination Frequency: Every 6-8 hours. Frequency of dosing may be decreased to 9-12 hours if using multi-modal analgesia consisting of opioid, NSAID, and local analgesia. Route: Subcutaneous (SQ), intraperitoneal (IP)
Buprenorphine SR (sustained release)	Dose: 1.0-2.0 mg/kg Frequency: Every 72 hours. Administer the first dose 2-4 hours prior to the painful procedure to ensure effective analgesia. Route: SQ	Dose: 1.0-1.2 mg/kg Frequency: Every 48-72 hours. Administer the first dose 2-4 hours prior to the painful procedure to ensure effective analgesia. Route: SQ		

*Recommended doses are a good starting point and may differ for procedures that are expected to elicit more/less pain than others

** One study suggests that 0.05 mg/kg may be more appropriate for analgesia specifically in female mice

*** One study suggests that 0.03 mg/kg may be more appropriate for analgesia specifically in female rats

Non-steroidal anti-inflammatory drugs (NSAIDs)

- Examples include carprofen, meloxicam
- Generally, the NSAID classification applies to drugs that inhibit one or more steps in the metabolism of arachidonic acid (AA). NSAIDs act primarily to reduce the biosynthesis of prostaglandins by inhibiting cyclooxygenase (COX).
- NSAIDs are effective for pain associated with inflammation. On their own, NSAIDs are effective against pain of mild to moderate intensity.
- Potential side effects include gastric or intestinal ulceration, disturbance of platelet function, and changes in renal function.

	Mice	Rats	Hamsters	Gerbils
Carprofen	Dose: 5-10 mg/kg Frequency: Every 12-24 hours Route: SQ, IP	Dose: 5 mg/kg Frequency: Every 24 hours Route: SQ, IP	Dose: 5 mg/kg Frequency: Every 24 hours Route: SQ	Dose: 5 mg/kg Frequency: Every 24 hours Route: SQ
Meloxicam	Dose: 5-10 mg/kg Frequency: Every 12 hours Route: SQ, PO	Dose: 1-2 mg/kg Frequency: Every 24 hours Route: SQ	Dose: 1-2 mg/kg Frequency: Every 24 hours Route: SQ	Dose: 1-2 mg/kg Frequency: Every 24 hours Route: SQ
Meloxicam SR*	Dose: 6 mg/kg Frequency: Every 24 hours* Route: SQ	Dose: 4 mg/kg Frequency: Every 24 hours* Route: SQ		

* Meloxicam-SR is a product which claims 72 hours of duration in some species. Independent studies have not demonstrated efficacy beyond 24 hours post-administration in rodents. Use of this product requires close monitoring for signs of pain if expected effect is greater than 24 hours.

Local analgesia

- Examples include lidocaine, bupivacaine, or 50:50 lidocaine bupivacaine block
- Local analgesics may be administered by several techniques. Anesthetic effects are seen within 15 minutes of administration and may last from 45 minutes to several hours, depending on the drug used.
    i. Infiltration or infusion: Injection beneath the skin and other tissue layers along the site of an incision before or after a procedure.
    ii. Field block, ring block: Injection into soft tissues distant from the actual incision in a pattern that intersects the nerve supplying the surgical site.
    iii. Nerve conduction block: Infusion of a small amount of drug or directly adjacent to the sheath of a nerve supplying the surgical site.
    iv. Topical local anesthetics, such as lidocaine jelly, may be useful for some surgical wounds.

	Mice	Rats	Hamsters	Gerbils
Lidocaine*	Dilute to 0.5%, do not exceed 7 mg/kg (1.4 ml/kg) total dose	Dilute to 0.5%, do not exceed 7 mg/kg (1.4 ml/kg) total dose	Dilute to 0.5%, do n ot exceed 4 mg/kg (0 .8 ml/kg) total dose	Dilute to 0.5%, do not exceed 7 mg/kg (1.4 ml/kg) total dose

	Route: Local infiltration	Route: Local infiltration	Route: Local infiltration	Route: Local infiltration
Bupivacaine*	Dilute to 0.25%, do not exceed 8 mg/kg (3.2 ml/kg) total dose Route: Local infiltration	Dilute to 0.25%, do not exceed 8 mg/kg (3.2 ml/kg) total dose Route: Local infiltration	Dilute to 0.25%, do not exceed 6 mg/kg (2.4 ml/kg) total dose Route: Local infiltration	Dilute to 0.25%, do not exceed 8 mg/kg (3.2 ml/kg) total dose Route: Local infiltration

*For rodent use, dilute 1-2% lidocaine to 0.5% and 0.5% bupivacaine to 0.25% to allow for feasible volumes to infuse at the incision site (1% solution is equal to 10 mg/mL).

Section C – Administration Routes

Direct routes of administration (e.g., parenteral) are strongly recommended for accurate dosing.

Mild pain or discomfort: For procedures that cause a mild persistent pain or discomfort, analgesics in the water may be utilized post-operatively, provided that an initial analgesic dose is administered via a direct route during or immediately after the procedure. Animals in pain may not adequately self-medicate using water administration because fluid intake is often decreased, so observation and assessment are important.

Moderate to severe pain: For procedures that cause moderate to severe pain, post-operative analgesics should be administered directly via parenteral injection or oral gavage. In most cases, a multi-modal regimen should be considered.

Sustained release (SR) formulations of opioid or non-steroidal anti-inflammatory drugs (NSAIDs) are available and may represent excellent options for decreasing stress associated with multiple injections. Animals requiring SR formulations of opioid or NSAIDs should be dosed 3-4 hours before the start of surgery to be effective. Consult with a UT Austin veterinarian to develop an appropriate analgesic plan or for more information on acquiring sustained release products. Note that many of the analgesic formulations are new and the optimal dosing regimens are still being developed for some species.

Section D – Administering Analgesia in Drinking Water

If analgesics will be administered via drinking water for procedures causing more than mild pain or distress, the Animal Use Protocol must include:

- A clearly stated scientific justification indicating why direct administration cannot be used for the study.
- A description of the methods used to ensure animals consume the appropriate amount of analgesic water and an outline of how clinical assessments of pain will be performed. It is the investigator's responsibility, in consultation with the area veterinarian, to determine the best methods to accomplish these tasks. Examples include:
    i. Monitoring fluid intake: Measure the volume or weight of the water bottle to ensure an acceptable amount of fluid displacement has occurred within the daily time period. In addition, weigh each animal every day to ensure appropriate fluid and food consumption.
    ii. Clinical assessment of pain: Include identifying signs such as hunched posture, decreased activity or hyperactivity, dehydration determined by a prolonged skin tent when scruffed, ruffled hair coat or lack of grooming, self-mutilation, altered mobility, decreased hindlimb-rearing behavior, decreased fecal output, or poor nest incorporation.

- A description of criteria for providing rescue analgesics (additional doses or routes of analgesia given) or euthanasia for any animals identified as having unexpected or unrelieved pain.
- An outline of procedures for replacing analgesic water when an empty water bottle is identified on weekends, nights, and holidays.

Lab personnel must do the following if analgesics will be administered via drinking water for procedures causing more than mild momentary pain or distress:

- Provide water bottles containing analgesics at least 12-24 hours before the painful procedure. Rodents are neophobic, and they may initially decline to consume water that contains new substances.
- Document in post-operative records that a daily assessment for the presence or absence of signs of pain was performed.
- Maintain appropriate identification of cages receiving medicated water by properly labeling bottles and provide signage on the cage stating the analgesic used, the date the bottle was made, and the dose of the drug.

Section E – Examples of Potentially Painful Procedures and Recommended Analgesic Protocols

The tables below describe examples of potentially painful procedures and recommended analgesic protocols for each. Contact a UT Austin veterinarian for assistance in developing an appropriate analgesia plan for rodents on your studies.

Mild and Momentary Pain or Discomfort

Examples of Potentially Painful Procedures	Recommended Analgesic Protocols
Percutaneous blood draw	Analgesia may not be indicated.
Ear notch	
Superficial tumor inoculation (SQ or similar)	
Multiple injections	
Tail snipping (neonatal rodents) – see IACUC Guidelines for Tail and Toe Clipping Rodents	

Mild and Persistent Pain or Discomfort

Examples of Potentially Painful Procedures	Recommended Analgesic Protocols
Tail snipping (adult rodents) – see IACUC Guidelines for Tail and Toe Clipping Rodents	Use any one of the three types of analgesia in Section B. Give a single dose of injectable analgesia on the day of the procedure.
Subcutaneous pump or pellet implantation	
Enucleation	

Moderate Pain

Examples of Potentially Painful Procedures	Recommended Analgesic Protocols
Embryo transfer (surgical)	Use a combination of at least 2 of the 3 types of analgesia in Section B. For example: • NSAID + opioid
Ovariectomy/ Orchidectomy	

Tail amputation	• NSAID + local Give a single dose of injectable analgesia on the day of the procedure. Additional doses to be provided via injection for at least 1-2 days following the procedure. Additional or rescue analgesia doses to be provided as needed based on clinical pain evaluation.
Craniotomy	
Minor laparotomy with minimal organ manipulation	

Severe Pain

Examples of Potentially Painful Procedures	Recommended Analgesic Protocols
Orthopedic procedures	Use all 3 types of analgesia in Section B. Where possible, preempt the painful event by starting NSAIDs and/or opioids in advance. At least 3-5 days of injectable analgesia to be given. *Analgesia in the drinking water is not a reliable source.*
Thoracotomy	
Organ transplant	
Major laparotomy with organ manipulation	
Burns	
Trauma models	

Section F – References and Acknowledgements

This document contains content that was adapted from

- University of Colorado Denver Veterinary Anesthetic and Analgesic Formulary: https://www.colorado.edu/researchinnovation/sites/default/files/attached-files/CU%20Denver%20Analgesic%20%26%20Anesthetic%20Drug%20Formulary.pdf
- University of Iowa Analgesia Guideline: https://animal.research.uiowa.edu/iacuc-guidelines-analgesia
- University of Minnesota Analgesia Guidelines: https://www.researchservices.umn.edu/services-name/research-animal-resources/research-support/guidelines/analgesia
- Recognition and Alleviation of Pain and Distress in laboratory animals https://www.nap.edu/read/12526/chapter/1
- Guidelines for the assessment and management of pain in rodents and rabbits https://www.aclam.org/media/0472274f-1d17-4957-b01b-4076d73e6d5a/qimOxQ/ACLAM/About%20Us/Position%20Statements/position_pain-rodent-rabbit.pdf
- Ramirez et al., J Am Assoc Lab Anim Sci. 2015 Jul;54(4):426-32
- Clinical Management of Pain in Rodents. 2019. Comp Med (V69), pg468

Approval Date	Change(s) Approved
09/14/2020	• Section B – Types of Analgesia and Recommendations: ▪ [NSAID table] Mice carprofen and meloxicam dose, frequency, and routes updated ▪ [NSAID table] Meloxicam SR added for mice and rats ▪ [Local Analgesia table] Lidocane/ bupivacaine mixture removed
03/08/2021	• Section B – Types of Analgesia and Recommendations:

	▪ [Opiod table] Frequency for Buprenorphine-HCL updated for all species listed