Arizona State University
Institutional Animal Care and Use Committee
STANDARD INSTITUTIONAL GUIDELINE

ANALGESIA

It is the policy of the IACUC that appropriate analgesic agents will be administered to animals utilized in approved research and teaching protocols. The analgesics listed in this SIG are guidelines from the DACT veterinary staff. We strongly recommend you discuss analgesic choices with the DACT veterinarians prior to submitting your protocol to determine the most effective analgesic regime for your project.

General Information

1. The process of pain stimulation, transmission, perception, and reaction is complex and varies greatly between species and even on an individual basis. Neuroanatomy and physiology is similar among most mammals. While the data for non-mammalian vertebrates is limited, it is best to assume that these species can also experience pain in a similar manner.
2. DACT veterinarians are available for consultation and training on proper analgesic usage and techniques.
3. According to the *Animal Welfare Act* (AWA), which covers mammals other than laboratory rats and mice, a painful procedure is defined as "...any procedure that would reasonably be expected to cause more than slight and momentary pain or distress in a human being to which that procedure was being applied." The Office of Laboratory Animal Welfare's (OLAW's) *Public Health Service Policy on Humane Care and Use of Laboratory Animals,* which can cover all vertebrates, states that "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." Many species of animals may not show obvious responses to painful stimuli, and the interpretation of the lack of such responses is difficult. Thus, it is best to use a generous assessment of the potential for a procedure to cause pain and to use analgesics when the presence of pain is uncertain.
4. Withholding the use of analgesic agents for procedures known or reasonably suspected to cause pain must be scientifically justified and approved by the IACUC. Even in cases where a scientific justification is provided and accepted by the IACUC, the experimental protocol that induces the pain and distress should be revisited on an annual basis to ascertain whether alternative approaches, drugs, or endpoints can be developed and implemented.

Choice of Analgesic Agents

1. The recommended analgesic agents, dosages, and routes of administration originate from a number of different sources including:

Carpenter, J. W. 2018. *Exotic Animal Formulary, 5th ed.*, Elsevier, St. Louis, MO.

Plumb, D. C. 2018 *Veterinary Drug Handbook, 9th ed*.. Wiley-Blackwell Publishing, Ames, IA.

Hubbell, J. A. E., and Muir, W. W. 1996. Evaluation of a survey of the diplomats of the American College of Laboratory Animal Medicine on use of analgesic agents in animals used in biomedical research, *Journal of the American Veterinary Medical Association* 209: 918-921.

Fish, R. E., Brown, M. J., Danneman, P. J., and Karas, A. Z. 2008. *Anesthesia and Analgesia in Laboratory Animals, 2nd ed.*, Elsevier, St. Louis, Mo.

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2. The tables below identify the analgesic agents (along with appropriate dosages, routes of administration, and duration of effect) recommended for the various species used in research/teaching protocols at ASU. Categories of analgesic agents include:

   A. Narcotics (work at the level of the brain and spinal cord)
      a. opioid agonists
         i. provide substantial analgesia
         ii. depress cardiovascular and respiratory activity
      b. opioid agonist-antagonists
         i. provide moderate to substantial analgesia
         ii. do not depress cardiovascular and respiratory activity

   B. Non-steroidal anti-inflammatory drugs (NSAIDs)
      a. provide mild to moderate analgesia
      b. may have antipyretic effects
      c. decrease inflammation

   C. Local analgesics (works at the site of administration)
      a. Provides analgesia only at the site administered (unless used as a regional nerve block)

Note – because analgesics can work at different sites of the pain pathway (locally, spinal cord, brain), concurrent use of drugs acting at different sites (i.e., multi-modal analgesia) is highly recommended.

Recommended Analgesics by Species

Species	Drug Type	Drug Name	Dose	Route	Frequency
Mouse	Opioid	Buprenorphine	0.05-0.1 mg/kg	IP, SC	q6-12h
	Opioid	Buprenorphine ER	0.5-1 mg/kg	SC	Lasts 72 hrs
	Opioid	Buprenorphine ER (Ethiqa XR)	3.25 mg/kg	SC	Lasts 72 hrs
	NSAID	Meloxicam	1-5 mg/kg	SC, PO	q24h
	NSAID	Carprofen	2-5 mg/kg	SC, PO	q24h
	NSAID	MediGel CPF (carprofen)	5 mg/kg/day	oral	ad lib
	Local	Bupivacaine (Marcaine®) 0.25%	max of 2.5 mg/kg	topical, infiltrate	Onset 20-30 mins, lasts 3-5 hours
	Local	Lidocaine 2%	max of 2 mg/kg	topical, infiltrate	Onset 1-2 mins, lasts 1-2 hours
Rat	Opioid	Buprenorphine	0.02-0.1 mg/kg	IP, SC	q6-12h
	Opioid	Buprenorphine ER	1-1.2 mg/kg	SC	Lasts 72 hrs
	Opioid	Buprenorphine ER (Ethiqa XR)	0.65 mg/kg	SC	Lasts 72 hrs
	NSAID	Meloxicam	1-2 mg/kg	SC, PO	q24h
	NSAID	Carprofen	2-5 mg/kg	SC, PO	q24h
	NSAID	MediGel CPF	5 mg/kg/day	oral	ad lib

		(carprofen)			
	Local	Bupivacaine (Marcaine®) 0.25%	max of 2.5 mg/kg	topical, infiltrate	Onset 20-30 mins, lasts 3-5 hours
	Local	Lidocaine 2%	max 2 mg/kg	topical, infiltrate	Onset 1-2 mins, lasts 1-2 hours
Macaque	Opioid	Buprenorphine	0.01-0.03 mg/kg	SC, IM	q6-12h
	Opioid	Buprenorphine ER	0.2 mg/kg	SC	Lasts 72 hrs
	Opioid	Oxymorphone	0.15 mg/kg	SC, IM, IV	q4-6h
	Opioid	Hydromorphone	0.05-0.2 mg/kg	SC, IM, IV	q4-6h
	Opioid-like	Tramadol	2 mg/kg	PO	q12h
	NSAID	Meloxicam	0.2 mg/kg once, then 0.1 mg/kg	SC, PO	q24h
	NSAID	Meloxicam ER	0.6 mg/kg	SC	Lasts 72 hrs
	Local	Bupivicaine (Marcaine®) 0.25%	1 mg/kg (max of 2.5 mg/kg)	topical, infiltrate	N/A
Marmoset	Opioid	Buprenorphine	0.005-0.02 mg/kg	SC, IM	q6-12h
	NSAID	Meloxicam	0.2 mg/kg once, then 0.1 mg/kg	SC, PO	q24h
	Local	Bupivacaine (Marcaine®) 0.25%	1 mg/kg (max of 2.5 mg/kg)	topical, infiltrate	N/A
Rabbit	Opioid	Buprenorphine	0.01-0.05 mg/kg	SC, IM, IP, IV	q6-12h
	Opioid	Butorphanol	0.1-0.5 mg/kg	SC, IM, IV	q4-6h
	NSAID	Meloxicam	0.2-0.3 mg/kg	SC, PO	q24h
	Local	Bupivacaine (Marcaine®) 0.25%	1 mg/kg (max 2.5 mg/kg)	topical, infiltrate	N/A
Guinea Pig/Chinchilla	Opioid	Buprenorphine	0.05-0.1 mg/kg	SC	q6-12h
	NSAID	Meloxicam	0.5 mg/kg	SC, PO	q24h
	Local	Bupivacaine (Marcaine®) 0.25%	max of 2.5 mg/kg	topical, infiltrate	N/A
Cat	Opioid	Buprenorphine	0.01-0.03 mg/kg	IM	q6-8h
	Opioid	Buprenorphine ER	0.12 mg/kg	SC	Lasts 72 hrs
	Opioid	Hydromorphone	0.05-0.1 mg/kg	SC, IM, IV	q4-6h
	NSAID	Meloxicam	0.3 mg/kg	SC	Once
*Bird	Opioid	Butorphanol	0.5-4 mg/kg	IM	q1-4h
	NSAID	Meloxicam	0.1-0.2 mg/kg	IM, PO	q24h
	Local	Lidocaine gel	2%	topical	N/A
**Amphibians	Opioid	Butorphanol	0.2-0.4 mg/kg	IM	q4-6h; efficacy

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					uncertain
	Local	Lidocaine gel	2%	topical	N/A
**Reptiles	Local	Bupivacaine (Marcaine®) 0.25%	1-2 mg/kg (max of 4 mg/kg)	topical, infiltrate	N/A

* There is wide variation in drug dosages depending on different bird species. Consult with the DACT veterinarians for dosages specific to your project.

**The effectiveness of analgesics in amphibians and reptiles is poorly known, and many doses in the literature have limited, if any, evidence to support them as being safe and effective. Consult with the DACT veterinarians for the appropriateness of analgesics for your specific project.

Drug Enforcement Agency (DEA) schedule for controlled substances listed in the table:

Buprenorphine	schedule 3
Buprenorphine ER	schedule 3
Butorphanol	schedule 4N
Hydromorphone	schedule 2
Oxymorphone	schedule 2
Tramadol	schedule 4

Other drugs listed in the table are not DEA-controlled substances.

Grimace Scale for Mice, Rats, Rabbits

1. **Changes in facial expression is a reliable way to assess pain in various species. Researchers have demonstrated specific changes that occur in mice, rats, and rabbits to develop grimace scales for each species. More information can be found at https://www.nc3rs.org.uk/3rs-resources/grimace-scales.**

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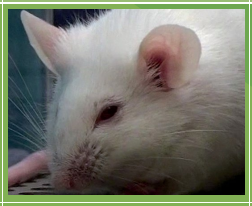
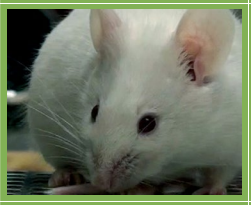
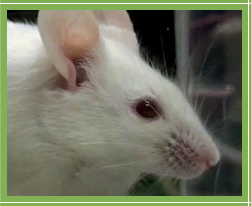
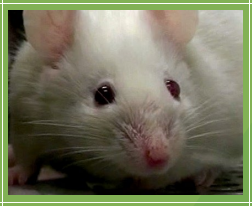
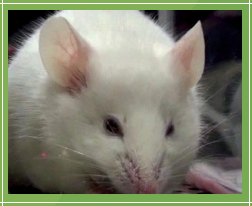
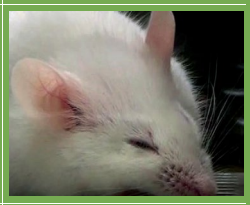
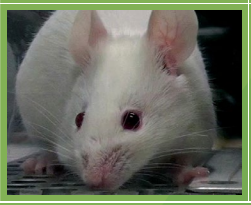
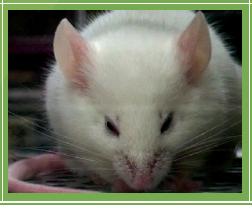
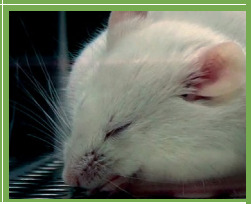
The Mouse Grimace Scale

Research has demonstrated that changes in facial expression provide a means of assessing pain in mice.

The specific facial action units shown below have been used to generate the Mouse Grimace Scale. These action units increase in intensity in response to post-procedural pain and can be used as part of a clinical assessment.

The action units should only be used in awake animals. Each animal should be observed for a short period of time to avoid scoring brief changes in facial expression that are unrelated to the animal's welfare.

	Not present "0"	Moderately present "1"	Obviously present "2"
Orbital tightening ▪ Closing of the eyelid (narrowing of orbital area) ▪ A wrinkle may be visible around the eye			
Nose bulge ▪ Bulging on the bridge of the nose ▪ Vertical wrinkles on the side of the nose			
Cheek bulge ▪ Bulging of the cheeks			
Ear position ▪ Ears rotate outwards and/or backwards, away from the face ▪ Ears may fold to form a 'pointed' shape ▪ Space between the ears increases			
Whisker change ▪ Whiskers are either pulled back against the cheek, or pulled forward to 'stand on end' ▪ Whiskers may clump together ▪ Whiskers lose their natural 'downward' curve			

Read the original paper:
Langford DJ, Bailey AL, Chanda ML, Clarke SE, Drummond TE, Echols S, Glick S, Ingrao J, Klassen-Ross T, LaCroix-Fralish ML, Matsumiya L, Sorge RE, Sotocinal SG, Tabaka JM, Wong D, van den Maagdenberg AMJM, Ferrari MD, Craig KD, Mogil JS. 2010. Coding of facial expressions of pain in the laboratory mouse. Nature Methods 7(6): 447-449. doi:10.1038/nmeth.1455

For guidance on using the Mouse Grimace Scale, research papers that underpin this technique, and for grimace scales in other species, visit: www.nc3rs.org.uk/grimacescales
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Images kindly provided by Dr Jeffrey Mogil, McGill University

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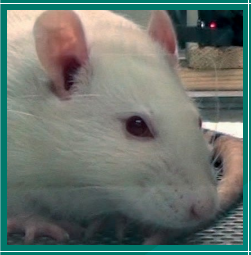
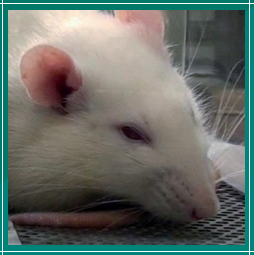
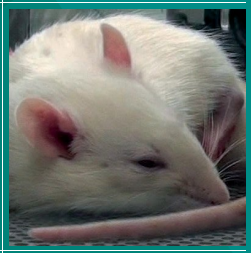
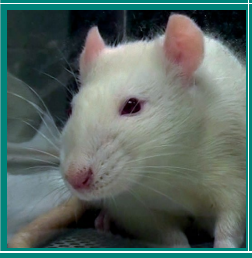
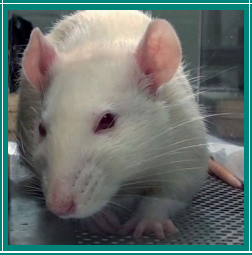
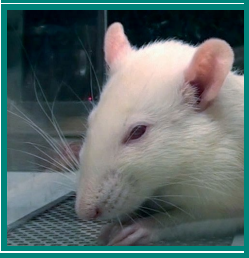
The Rat Grimace Scale

Research has demonstrated that changes in facial expression provide a means of assessing pain in rats.

The specific facial action units shown below have been used to generate the Rat Grimace Scale. These action units increase in intensity in response to post-procedural pain and can be used as part of a clinical assessment.

The action units should only be used in awake animals. Each animal should be observed for a short period of time to avoid scoring brief changes in facial expression that are unrelated to the animal's welfare.

	Not present "0"	Moderately present "1"	Obviously present "2"
Orbital tightening ▪ Closing of the eyelid (narrowing of orbital area) ▪ A wrinkle may be visible around the eye			
Nose/cheek flattening ▪ Flattening and elongation of the bridge of the nose ▪ Flattening of the cheeks (potentially sunken look)			
Ear changes ▪ Ears curl inwards and are angled forward to form a 'pointed' shape ▪ Space between the ears increases			
Whisker change ▪ Whiskers stiffen and angle along the face ▪ Whiskers may 'clump' together ▪ Whiskers lose their natural 'downward' curve			

Read the original paper:
Sotocinal SG, Sorge RE, Zaloum A, Tuttle AH, Martin LJ, Wieskopf JS, Mapplebeck JCS, Wei P, Zhan S, Zhang S, McDougall JJ, King OD, Mogil JS. 2011. The Rat Grimace Scale: a partially automated method for quantifying pain in the laboratory rat via facial expressions. Molecular Pain 7: 55. doi:10.1186/1744-8069-7-55

For guidance on using the Rat Grimace Scale, research papers that underpin this technique, and for grimace scales in other species, visit: www.nc3rs.org.uk/grimacescales
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Images kindly provided by Dr Jeffrey Mogil, McGill University

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National Centre for the Replacement Refinement & Reduction of Animals in Research

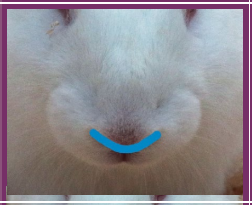
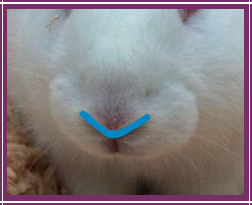
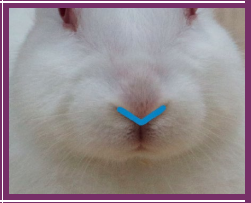
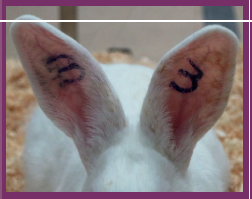
Newcastle University

The Rabbit Grimace Scale

Research has demonstrated that changes in facial expression provide a means of assessing pain in rabbits.

The specific facial action units shown below comprise the Rabbit Grimace Scale. These action units increase in intensity in response to post-procedural pain and can form part of a clinical assessment alongside other validated indices of pain.

The action units should only be used in awake animals. Each animal should be observed for a short period of time to avoid scoring brief changes in facial expression that are unrelated to the animal's welfare.

	Action units		
	Not present "0"	**Moderately present "1"**	**Obviously present "2"**
Orbital tightening ▪ Closing of the eyelid (narrowing of orbital area) ▪ A wrinkle may be visible around the eye			
Cheek flattening ▪ Flattening of the cheeks. When 'obviously present', cheeks have a sunken look. ▪ The face becomes more angular and less rounded			
Nostril shape ▪ Nostrils (nares) are drawn vertically forming a 'V' rather than 'U' shape ▪ Nose tip is moved down towards the chin			
Whisker shape and position ▪ Whiskers are pushed away from the face to 'stand on end' ▪ Whiskers stiffen and lose their natural, downward curve ▪ Whiskers increasingly point in the same direction. When 'obviously present', whiskers move downwards			
Ear shape and position ▪ Ears become more tightly folded / curled (more cylindrical) in shape ▪ Ears rotate from facing towards the source of sound to facing towards the hindquarters ▪ Ears may be held closer to the back or sides of the body			

Read the original paper: Keating SCJ, Thomas AA, Flecknell PA, Leach MC (2012) Evaluation of EMLA cream for preventing pain during tattooing of rabbits: Changes in physiological, behavioural and facial expression responses. PLOS ONE 7(9): e44437. doi:10.1371/journal.pone. 0044437

For guidance on using the Rabbit Grimace Scale, additional images of each action unit, research papers that underpin this technique, and for grimace scales in other species, visit: www.nc3rs.org.uk/grimacescales

To request copies of this poster, please email: enquiries@nc3rs.org.uk
The NC3Rs provides a range of 3Rs resources at www.nc3rs.org.uk/resources

Images kindly provided by Dr Matthew Leach, Newcastle University

The Rabbit Grimace Scale would not have been developed without the continuing work of the Pain and Animal Welfare Sciences Group (PAWS) at Newcastle University

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