Institutional Animal Care and Use Committee		UNTHSC
Title: Analgesics and Anesthesia in Laboratory Animals at UNTHSC		
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A. BACKGROUND INFORMATION

a. In general, procedures which cause pain in humans should be expected to cause pain in animals.
b. Appropriate analgesics must be used unless withholding such agents is scientifically justified in the animal use protocol.

B. RESPONSIBILITIES

a. It is the responsibility of the Principal Investigator (PI):
    i. To list appropriate analgesics when performing potentially painful procedures on animals. The PI must consult with the Attending Veterinarian for information on which analgesic(s) to use if the PI is unsure.
    ii. To procure the analgesics listed on an approved protocol unless arrangements are made with DLAM (Department of Laboratory Animal Medicine) ahead of time. Some analgesics are controlled substances and will require a DEA license. It is the responsibility of the PI to have this license.
b. It is the responsibility of the Principal Investigator and other research personnel who will administer analgesics to have completed the applicable CITI training module.
c. It is the responsibility of the Principal Investigator or designated lab staff and/or students to administer the analgesics listed in the approved protocol unless arrangements are made ahead of time for DLAM staff to do so.
d. It is the responsibility of IACUC to assure that this SOP is followed.

C. PROCEDURES

a. Determining which procedures require analgesia and which ones may be useful, several factors should be considered:
    i. The invasiveness of the procedure that was performed:
        1. Are body cavities invaded?
        2. Are especially sensitive tissues involved (e.g. bones or teeth)?
        3. Is significant tissue destruction or inflammation produced?
    ii. The degree or severity of pain that is expected:
        1. Comparison to similar procedures in people: would a reasonably stoic human be able to tolerate the postoperative period without analgesics?
        2. Behavior of the animal during postoperative period; e.g., level of activity, appetite, etc. when compared to sham (anesthetized) control animals.
    iii. Duration of the postoperative pain or discomfort expected:
        1. Postoperative analgesia is desirable for most surgical procedures involving penetration deeper than the skin and subcutaneous tissues.

2. For procedures involving invasion of bones, joints, teeth or significant destruction or inflammation in other tissues, it is the responsibility of the PI to make sufficient justification in their animal use protocol is postoperative analgesics cannot be used.

b. **No post-operative analgesia required**:
   i. Injections that will cause mild or no pain or discomfort. Examples such as injections of low irritation potential substances, non-invasive catheter or electrode placement, skin incisions, or sutures.

c. **Short-term postoperative analgesia desired:**
   i. Procedures likely to cause mild to moderate pain or discomfort of short duration (12-24 hours). Examples include:
      1. Castrations, including ovariectomies
      2. Invasive electrode or catheter placement
      3. Adrenalectomy and hypophysectomy in rodents
      4. Extraocular surgery

d. **Prolonged postoperative analgesia required:**
   i. Procedures likely to result in severe or prolonged pain or discomfort. Examples include:
      1. Extensive dissection of soft tissues
      2. Major entry into the pleural or peritoneal cavity
      3. Intraocular surgery
      4. Orthopedic or dental surgery

e. **Types of analgesics:**
   i. Opioids - These are controlled substances. The Principal Investigator must have a DEA license.
   ii. NSAIDs - Non-steroidal anti-inflammatory drugs. These are not controlled substances.
   iii. Local analgesics – act only at the site of application

f. **Points to remember when using analgesics:**
   i. Always use the analgesic that is listed in protocol.
   ii. Calculate the dose by body weight.
   iii. Drugs under the control of the Drug Enforcement Agency (DEA) must be stored in a locked cabinet in a secure area.
   iv. A written record is required when controlled drugs under the control of the DEA are used (how much of the drug you have, how much was used and for what purpose).
   v. An inventory list of analgesics should be kept.

g. The following listings of analgesics and the corresponding doses for each species must be considered for use by the Principal Investigator. If another drug not on this list is to be used, the Attending Veterinarian must be consulted.

Mouse

Opioid Analgesia

Drug Name	Dose and Route	Frequency	Notes
Buprenorphine (Recommended)	0.05-0.1 mg/kg SC or IP	Pre-operatively for preemptive analgesia and post-operatively every 4 – 12 hours	When used as sole analgesic, typical regimen is: once at time of procedure, second dose will be administered 4-6 hours later. Additional doses every 8-12 hrs as needed. Consider multi-modal analgesia with NSAID and local analgesic.
Buprenorphine SR LAB	0.5-1.0 mg/kg SC	Give once for 72 hours	
Buprenorphine ER	3.25 mg/kg SC	Give once for 72 hours	
Oxymorphone	0.2-0.5 mg/kg SC	Give every 4 hours	
Morphine	1-2.5 mg/kg SC	Give every 2-6 hours	

Non-steroidal anti-inflammatory (NSAID) analgesia

Note that prolonged use may cause renal, gastrointestinal, or other problems.

Drug Name	Dose and Route	Frequency	Notes
Carprofen (Recommended)	2-5 mg/kg SC	Used pre-operatively for preemptive analgesia and post-operatively every 12-24 hour	Depending on the procedure, may be used as sole analgesic, or as multi-modal analgesia with buprenorphine.
Carprofen (50mg/ml) in Drinking Water	10 mg/kg - 0.12 ml carprofen in 89.88 ml of drinking water (0.067 mg/ml) stable x 7d. Start treatment 12-24 h prior to surgery		
Meloxicam	1-2 mg/kg SC, PO	Used pre-operatively for preemptive analgesia and post-operatively every 12-24 hour	Depending on the procedure, may be used as sole analgesic, or as multi-modal analgesia with buprenorphine.

Non-steroidal anti-inflammatory (NSAID) analgesia continued

Drug Name	Dose and Route	Frequency	Notes
Meloxicam	4 mg/kg SC, PO	Used pre-operatively for preemptive analgesia and post-operatively every 72 hour	Depending on the procedure, may be used as sole analgesic, or as multi-modal analgesia with buprenorphine.
Ketoprofen	2-5 mg/kg SC	Used pre-operatively for preemptive analgesia and post-operatively every 12-24 hour	Depending on the procedure, may be used as sole analgesic, or as multi-modal analgesia with buprenorphine.
Ketorolac	5-7.5 mg/kg ORAL or SC	Used pre-operatively for preemptive analgesia and post-operatively every 12-24 hour	Depending on the procedure, may be used as sole analgesic, or as multi-modal analgesia with buprenorphine.
Flunixin Meglumine	~2 mg/kg SC	Used pre-operatively for preemptive analgesia and post-operatively every 12-24 hour	Depending on the procedure, may be used as sole analgesic, or as multi-modal analgesia with buprenorphine.

Local anesthetic/analgesics

Lidocaine and Bupivacaine may be combined in one syringe for rapid onset and long duration analgesia

Drug Name	Dose and Route	Frequency	Notes
Lidocaine hydrochloride	Dilute to 0.5%, do not exceed 7 mg/kg total dose SC or Intra-Incisional	Use locally before making surgical incision, or before final skin closure	Faster onset than bupivacaine but short (<1 hour) duration of action
Bupivacaine	Dilute to 0.25%, do not exceed 8 mg/kg total dose SC or Intra-Incisional	Use locally before making surgical incision, or before final skin closure	Slower onset than lidocaine but longer (~ 4-8 hour) duration of action

Mouse / Rat

Lidocaine/Bupivacaine Pre-Operative Infiltration

Incision site and underlying tissues

1-2% lidocaine/0.25-0.5% bupivacaine (50/50) mix by volume. May need to dilute, especial for mice (e.g. 1/10 dilution). Epinephrine prolongs action

Local Anesthetic	Onset	Duration	Do not exceed (toxic dose)
Lidocaine (xylocaine)	1-3 minutes	20-40 minutes	10 mg/kg
Bupivacaine	~20 minutes	4-6 hours	6 mg/kg

Recommended Peri-Operative Analgesic Protocols for Mice and Rats

Mild Pain

Preemptive[1] (once)		Lidocaine/bupivacaine as local infiltration
Post-surgical	**Drug**	Buprenorphine, morphine or oxymorphone
	Frequency	Once

[1]Administration of analgesics prior to induction of pain.

Mild to Moderate Pain – OPTION 1

Preemptive (once)		Lidocaine/bupivacaine as local infiltration
		AND
		Buprenorphine, morphine or oxymorphone
Post-surgical	**Drug**	Buprenorphine
	Duration	1-2 days

Mild to Moderate Pain – OPTION 2

Preemptive (once)		Lidocaine/bupivacaine as local infiltration
		AND
		Buprenorphine, morphine or oxymorphone
Post-surgical	**Drug**	Carprofen, ketoprofen or melixocam
	Duration	1-2 days

Moderate to Severe Pain

Preemptive (once)		Lidocaine/bupivacaine as local infiltration
		AND
		Buprenorphine, morphine or oxymorphone
Post-surgical	**Drug**	Buprenorphine
	Duration	2 days
		AND
	Drug	Meloxicam (use highest does)
	Duration	2-3 days
		AND
	Drug	Morphine for severe pain
	Duration	As needed

Examples of mild, moderate and severe post-surgical pain in mice and rats*

Mild:

- Subcutaneous pump or pellet implantation
- Tail clipping
- Intracerebral electrode implantation
- Simple laparoscopic biopsies
- Superficial lymphadenectomy
- Vascular access port implantation

Moderate:

- Vascular catheterization
- Embryo transfer
- Ovariectomy
- Craniotomy
- Thyroidectomy
- C-section
- Hypophysectomy
- Thymectomy
- Minor laparotomy incisions

Severe:

- Orthopedic procedures
- Thoractomy
- Organ transplantation
- Major laparotomy procedures
- Vertebral procedures

IMPORTANT CONSIDERATION: This is a guideline for classifying pain categories to common surgical procedures in mice and rats to aid the investigator, the Attending Veterinarian and the animal care committee in deciding an appropriate peri-operative analgesic protocol. This classification must be considered against other factors, such as length of procedure, extent of tissue dissection, degree of blood loss, materials implanted, unexpected surgical events, health status, age, strain, and surgeon's experience and skill.

Rat

Opioid Analgesia

Drug	Dose and Route	Frequency	Notes
Buprenorphine	0.01-0.05 mg/kg IM or SC	Pre-operatively for preemptive analgesia and post-operatively every 8-12 hours	Takes 1 h to be effective so should be given pre-emptively. Duration of effect is 4-6 h. NSAID is recommended for continued pari relief.
Buprenorphine SR LAB	1-1.2 mg/kg SC	Give once for 72 hours	
Buprenorphine ER	0.65 mg/kg SC	Give once for 72 hours	
Oxymorphone	0.2-0.5 mg/kg SC	Give every 4 hours	
Morphine	1-2.5 mg/kg SC	Give every 2-6 hours	

Non-steroidal anti-inflammatory analgesia (NSAID)

Note that prolonged use may cause renal, gastrointestinal, or other problems.

Drug Name	Dose and Route	Frequency	Notes
Ketoprofen	2-5 mg/kg SC	Give once every 24 hour	
Carprofen	2-5 mg/kg SC	Give once every 12-24 hour	
Meloxicam	1-2 mg/kg SC, PO	Give once every 12 hour	Depending on the procedure, may be used as sole analgesic, or as multi-modal analgesia with buprenorphine.
Rimadyl ®	Tablet	Give once every 24 hour	

Non-steroidal anti-inflammatory analgesia (NSAID) continued

Drug Name	Dose and Route	Frequency	Notes
Meloxicam	4 mg/kg SC, PO	Used pre-operatively for preemptive analgesia and post-operatively every 72 hour	Depending on the procedure, may be used as sole analgesic, or as multi-modal analgesia with buprenorphine.

Local anesthetic/analgesics

Lidocaine and Bupivacaine may be combined in one syringe for rapid onset and long duration analgesia

Drug Name	Dose and Route	Frequency	Notes
Lidocaine	Dilute to 0.5%, should not exceed 7 mg/kg. SC or intra-incisional.	Use locally before making surgical incision, or before final skin closure	Use as local anesthetic, fast onset but duration of action is less than 1 h.
Bupivacaine	Dilute to 0.25%, should not exceed a total dose of 8 mg/kg. SC or intra-incisional.	Use locally before making surgical incision, or before final skin closure	Use as a local anesthetic, slow onset but duration of action is 4-8 h. Do not give IV.

Hamster

Opioid analgesia

Drug Name	Dose and Route	Frequency	Notes
Buprenorphine	0.05-0.1 mg/kg SC	Every 8-12 hours	
Butorphanol	1-5 mg/kg SC	Every 2-4 hours	

Non-steroidal anti-inflammatory analgesia (NSAID)

Note that prolonged use may cause renal, gastrointestinal, or other problems.

Drug Name	Dose and Route	Frequency	Notes
Aspirin	240 mg/kg PO	Every 24 hours	
Flunixin	2.5 mg/kg SC	Every 12 – 24 hours	Consult with Vet regarding repeated administration

Local anesthetic/analgesics

Lidocaine and bupivacaine may be combined in one syringe for rapid onset and long duration analgesia.

Drug Name	Dose and Route	Frequency	Notes	
Bupivacaine	1-2mg/kg max dose, mixed with Lidocaine at 1-4 mg/kg Lidocaine	Before incision is made	Use as a local anesthetic, slow onset but duration of action is 4-8 h. Do not give IV.	
Lidocaine	1-4 mg/kg max dose, mixed with bupivacaine at 1-2 mg/kg bupivacaine	Before incision is made	Use as local anesthetic, fast onset but duration of action is less than 1 h.	

Rabbit

Opioid analgesia

Drug	Dose and Route	Frequency	Notes
Recommended: Buprenorphine	0.05 – 0.1 mg/kg SC or IP	Used pre-operatively for preemptive analgesia and post-operatively every 4-12 hrs	When used as sole analgesic, typical regimen is: once at time of procedure, second dose will be administered 4-6 hours later. Additional doses every 8-12 hrs as needed. Consider multi-modal analgesia with NSAID and local analgesic.
Buprenorphine SR	1.0-2.0 mg/kg SC	Give once for 72 hours	

Non-steroidal anti-inflammatory analgesia (NSAID)

Note that prolonged use may cause renal, gastrointestinal, or other problems.

Drug	Dose and Route	Frequency	Notes
Recommended: Carprofen	4-5 mg/kg SC	Used pre-operatively for preemptive analgesia and post-operatively every 12-24 hours	Depending on the procedure, may be used as sole analgesic, or as multi-modal analgesia with buprenorphine.
Meloxicam	0.1-0.3 mg/kg PO, IM or SC	Used pre-operatively for preemptive analgesia and post-operatively every 24 hour for up to 4 days	Depending on the procedure, may be used as sole analgesic, or as multi-modal analgesia with buprenorphine.

Non-steroidal anti-inflammatory analgesia (NSAID) continued

Drug	Dose and Route	Frequency	Notes
Ketorolac	0.3-0.5 mg/kg PO or SC	Used pre-operatively for preemptive analgesia and post-operatively every 12-24 hour	Depending on the procedure, may be used as sole analgesic, or as multi-modal analgesia with buprenorphine.
Ketoprofen	2-5 SC	Used pre-operatively for preemptive analgesia and post-operatively every 12-24 hour4-8 hour) duration of action	Depending on the procedure, may be used as sole analgesic, or as multi-modal analgesia with buprenorphine.

Local anesthetic/analgesics

Lidocaine and bupivacaine may be combined in one syringe for rapid onset and long duration analgesia.

Drug	Dose and Route	Frequency	Notes
Lidocaine Hydrochloride	Dilute to 0.5%, do not exceed 7 mg/kg total dose, SC or intra-incisional	Use locally before making surgical incision	Faster onset than bupivacaine but short (< 1 hour) duration of action
Bupivacaine	Dilute to 0.25%, do not exceed 8 mg/kg total dose, SC or intra-incisional	Use locally before making surgical incision	Slower onset than Lidocaine but longer (˜ 4/8 hour) duration of action

Swine

Opioid analgesia

Drug	Dose and Route	Frequency	Notes
Recommended: Buprenorphine	0.005 – 0.1 mg/kg SC (Usually use .05 – 0.1 for major surgery)	Used pre-operatively for preemptive analgesia and post-operatively every 4-12 hrs	When used as sole analgesic, typical regimen is once at time of procedure, second dose will be administered 4-6 hours later. Additional doses every 8-12 hrs as needed. Consider multi-modal analgesia with NSAID and local analgesic.

Opioid analgesia continued

Drug	Dose and Route	Frequency	Notes
Butorphanol	0.1 – 0.5 mg/kg SC	Used pre-operatively for preemptive analgesia and post-operatively every 4-6 hour	For major procedures, require more frequent dosing than 12 hour intervals. Consider multi-modal analgesia with a NSAID
Oxymorphone	0.01 – 0.2 mg/kg	Used pre-operatively for preemptive analgesia and post-operatively every 3-4 hour, or for 'rescue analgesia' when buprenorphine is not potent enough	More potent but shorter duration than buprenorphine or butorphanol.
Fentanyl patch	50 ug/hr	Place patch 24 hours in advance of surgery and maintain for up to 3 days	When severe post-surgical pain is anticipated. Should not be used as sole analgesic.

Non-steroidal anti-inflammatory analgesia (NSAID)

Note that prolonged use may cause renal, gastrointestinal, or other problems.

Drug	Dose and Route	Frequency	Notes
Recommended: Carprofen	2 – 4 mg/kg SC or PO	Used pre-operatively for preemptive analgesia and post-operatively every 24 hours for up to 4 days (Page 2)	Depending on the procedure, may be used as sole analgesic, or as multi-modal analgesia with buprenorphine.
Ketoprofen	10. – 2.0 mg/kg SC	Used pre-operatively for preemptive analgesia and post-operatively every 24 hour for up to 4 days	Depending on the procedure, may be used as sole analgesic, or as multi-modal analgesia with buprenorphine.

Non-steroidal anti-inflammatory analgesia (NSAID) continued

Drug	Dose and Route	Frequency	Notes
Ketorolac	5 – 1.0 mg/kg SC	Used pre-operatively for preemptive analgesia and post-operatively every 24 hour for up to 4 days	Depending on the procedure, may be used as sole analgesic, or as multi-modal analgesia with buprenorphine.

Local anesthetic/analgesics

Lidocaine and bupivacaine may be combined in one syringe for rapid onset and long duration analgesia.

Drug	Dose and Route	Frequency	Notes
Lidocaine Hydrochloride	May dilute to 0.5 – 1% (=10mg/ml). May be mixed in same syringe with bupivacaine SC or intra-incisional	Use locally before making surgical incision	Faster onset than bupivacaine but short (< 1 hour) duration of action
Bupivacaine	May dilute to 0.25-0.5%, May be mixed in same syringe with lidocaine. SC or intra-incisional	Use locally before making surgical incision	Slower onset than Lidocaine but longer (˜4-8 hour) duration of action.

MOUSE FORMULARY

Note that all of these doses are approximations and must be titrated to the animal's strain, age, sex and individual responses. Significant departures from these doses should be discussed with a veterinarian. Doses will also vary depending on what other drugs are being administered concurrently.

All doses are listed as milligrams per kilogram (mg/kg) unless otherwise noted. Dilution of injected drugs allows more precise dosing, but may shorten the shelf-life of the compound. (UNTHSC-DLAM standard: diluted drugs should be labeled, then discarded after 21 days).

Inhalation Anesthetics

Drug Name	Dose and Route	Frequency	Notes
Isoflurane	1-3% to effect (up to 5% for induction) INH	Whenever general anesthesia is required	Must use precision vaporizer – survival surgery requires concurrent preemptive analgesia
Sevoflurane	1-3% to effect (up to 8% for induction) INH		
Nitrous oxide (N2O)	Up to 60% with oxygen INH	Whenever deep sedation or general anesthesia is required	Not acceptable for surgery as sole agent – usually used with inhalant anesthetic to potentiate effect and lower required dose
Carbon dioxide	To effect (cannot determine percentage) INH	Once, at time of euthanasia	May be used for fast terminal procedure followed by euthanasia

Ketamine Combinations

Drug Name	Dose and Route	Frequency	Notes
Ketamine-Xylazine-Acepromazine	70-100 (K) + 10- 20 (X) + 2-3 (A) (in same syringe)	As needed	May not produce surgical-plane anesthesia for major procedures. If redosing, use ketamine alone. May be partially reversed with Atipamezole (better option) or Yohimbine

Ketamine Combinations continued

Drug Name	Dose and Route	Frequency	Notes
Ketamine-Medetomidine	50-75 + 0.5 -1 IP (in same syringe)	As needed	May not produce surgical-plane anesthesia for major procedures. If redosing, use ketamine alone. May be partially reversed with Atipamezole
Ketamine-Xylazine	80-100 + 5-10 IP (in same syringe)		May not produce surgical-plane anesthesia for major procedures. If redosing, use ketamine alone. May be partially reversed with Atipamezole or Yohimbine
Ketamine-Xylazine	80-100 + 5-10 IP (in same syringe)		
Ketamine-Midazolam	80-100 + 4-5 IP (in same syringe)		May not produce surgical-plane anesthesia for major procedures, but may be useful for restraint.
Ketamine alone	100-200 IP		Deep sedation, but not surgical anesthesia. Not often used alone.

Reversal Agents

Drug Name	Dose	Frequency	Notes
Atipamezole	0.1 - 1.0 SC or IP	Any time medetomidine or xylazine has been used	More specific for medetomidine than for xylazine (as a general rule, Atipamezole is dosed at the same volume as Medetomidine, though they are manufactured at different concentrations).
Yohimbine	1.0 – 2.0 SC or IP	Any time xylazine has been used	For reversal of xylazine effects

Other Injectable Anesthetics

Drug Name	Dose and Route	Frequency	Notes
Sodium pentobarbital (Nembutal)	40 – 50 IP	Recommended for terminal/acute procedures only, with booster doses as needed	Consider supplemental analgesia (opioid or NSAID) for invasive procedures

Other Injectable Anesthetics continued

Drug Name	Dose and Route	Frequency	Notes
Tribromoethanol (Avertin)	250-500 IP	May be used once for survival procedure (boosted as necessary during procedure) and once for terminal/acute procedure	Diluted Avertin Solution must be used within 30 days of initial preparation and be properly stored. Lower concentration (1.25%) less likely to cause peritonitis. See recipe below.
Propofol	12-26 IV	As needed	Only useful IV, so therefore limited usefulness in mice. Respiratory depression upon induction is possible.

Opioid Analgesia

Drug Name	Dose and Route	Frequency	Notes
Buprenorphine	0.05 - 0.1 SC or IP	Used pre-operatively for preemptive analgesia and post-operatively every 4-12hrs	When used as sole analgesic, typical regimen is: once at time of procedure, second dose will be administered 4-6 hours later. Additional doses every 8-12hrs as needed. Consider multi-modal analgesia with NSAID and local analgesic.

Non-Steroidal Anti-Inflammatory Analgesia (NSAID)

Note that prolonged use my cause renal, gastrointestinal, or other problems

Drug Name	Dose and Route	Frequency	Notes
Carprofen	5-10 SC	Used pre-operatively for preemptive analgesia and post-operatively every 12-24 hour	Depending on the procedure, may be used as sole analgesic, or as multi-modal analgesia with buprenorphine.

Drug Name	Dose and Route	Frequency	Notes
Meloxicam	~ 5-10 PO, IM or SC	Used pre-operatively for preemptive analgesia and post-operatively every 12-24 hour	Depending on the procedure, may be used as sole analgesic, or as multi-modal analgesia with buprenorphine.
Ketoprofen	2 – 5 SC		
Ketorolac	5 – 7.5 Oral or SC		
Flunixin meglumine	~ 2 SC		
Rimadyl ®	Tablet		

Avertin Recipe

100% stock avertin

Mix: add Tribromoethanol to Tertiary Amyl Alcohol and dissolve by heating and stirring. Add distilled water and continue until the solution is well mixed. Store wrapped in foil (light sensitive solution, ok to use brown glass bottle), 4° C.

Solution may have to be warmed to dissolve. Mixture should be clear.

- Warning! Decomposition can result from improper storage.
- 2.5% Diluted Avertin Solution must be used within 30 days of initial preparation and be properly stored. Be sure to label the container with the date of preparation.

For use in mice, dilute the 100% to 2.5% (1:40) using diluent, water or isotonic saline.

Diluent Recipe

0.8% NaCl

1mM Tris (pH 7.4)

0.25mM EDTA

Check the pH. Adjust to pH 7.4.

To make 50 ml 2.5% avertin, add 1.25 ml 100% to 48.75 ml liquid (diluent, water or saline)

Filter .22 micron

Store at 4° C, away from light in foil wrap or brown bottle

Dosage for mice may vary with different preparations of Avertin. Dosage should be redetermined each time a 100% stock is made up. Test for best effect in a few mice before choosing dose. Allow 5-10 min to take effect.

A. REFERENCES

a. The Guide for the Care and Use of Laboratory Animals (2011), National Academies Press, Washington, D.C.