# Pain and Distress in Mice, Rats and Rabbits: Responsibilities, Recognition and Alleviation

## Introduction

Animals can experience pain and distress. It is the ethical and legal obligation of all personnel involved with the use of animals in research to reduce or eliminate pain and distress in research animals whenever such actions do not interfere with the research objectives. The Institutional Animal Care and Use Committee (IACUC) has the delegated responsibility and accountability for ensuring that all animals under their oversight are used humanely and in accordance with a number of Federal Regulations and policies [1-5]. Key to fulfilling the responsibilities for both the principal investigator (PI) and the IACUC are:

- ***understanding the legal requirements,***
- ***being able to distinguish pain and distress in animals from their normal state, and***
- ***to relieve or minimize the pain and distress appropriately.***

## Regulatory Requirements

The IACUC must assure that all aspects of the animal study proposal (ASP) that may cause more than momentary pain and/or distress are addressed; alternatives to painful or distressful procedures are considered; and that methods, anesthetics and analgesics to minimize or eliminate pain and distress are included when these methods do not interfere with the research objectives. A written scientific justification is required to be included in the ASP for any painful or distressful procedure that cannot be relieved or minimized.

The obligation to reduce pain and distress ***does not end*** with the review of the ASP. It is the responsibility of the animal care staff, the research staff, the IACUC, and veterinarians to continue to monitor animals for pain, distress, illness, or mortality during the course of the research study. Animals should be monitored for evidence of pain or distress, and should be administered analgesics or have procedures instituted to relieve it, unless scientifically justified. Observations and actions taken to relieve pain or distress must be documented. The animals should be observed a minimum of once daily or more often based on professional judgment. ***These documents must be available to the IACUC, veterinarians, and animal care staff.*** If it is necessary to make significant changes in the ASP procedures (see http://oacu.od.nih.gov/ARAC/FinalASPChanges.0703.pdf), the PI must submit an amendment to the IACUC and receive approval prior to initiation.

## Recognition of Pain and Distress

Animals should be monitored for pain and distress as appropriate for the condition, procedure and degree of invasiveness. Critical to the assessment of the presence or absence of pain or distress is having the ability to distinguish between normal and abnormal animal behavior. This is especially true when dealing with rodents and rabbits that often exhibit pain and distress with only subtle changes in their behavior (see Table 1).

## Examples of Analgesics

The choice of analgesic varies with rodents and rabbits with the procedure being performed,

duration of action needed, route of administration preferred, and type of analgesia needed. It is strongly suggested that the PIs consult their IC veterinary staff prior to submission of the ASP. Reduction of research-associated pain/distress in animals can have an affect on the speed with which animals return to normal behavior following surgical procedures. It has been repeatedly demonstrated in humans that the provision of effective analgesia reduces the time taken for post-operative recovery[6]. A number of drugs and techniques are currently used within the NIH to reduce pain and distress in rodents and rabbits (Table 2).

**Summary**

The relief of pain and distress in research animals is ethically sound, humane, and promotes good science.

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## References


1. IRAC (Interagency Research Animal Committee). 1985. *U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research and Training*. Federal Register, May 20, 1985. Washington, D.C.: Office of Science and Technology Policy.

2. PHS (Public Health Service). 1996. *Public Health Service Policy on Humane Care and Use of Laboratory Animals.* Washington, D.C.: U.S. Department of Health and Human Services, 28 pp. [PL-99-158, Health Research Extension Act, 1985]

3. NRC (National Research Council). 1996. *Guide for the Care and Use of Laboratory Animals*. Washington, D.C.: National Academy Press.

4. Animal Welfare Act:
   Public Law 89-544, 1966, as amended, (P.L. 91-579, P.L. 94 -279 and P.L. 99-198) 7 U.S.C. 2131 et. seq. Implementing regulations are published in the Code of Federal Regulations (CFR), Title 9, Chapter 1, Subchapter A, Parts 1, 2, and 3.

5. NIH Policy Manual 3040-2, *Animal Care and Use in the Intramural Program*.

6. Smith, G. and B.G. Covino (1985). *Acute Pain*. Butterworths: London.

## TABLE 1

## POTENTIAL SIGNS ASSOCIATED WITH PAIN OR DISTRESS IN RATS, MICE AND RABBITS

| | Mice | Rats | Rabbits |
|---|---|---|---|
| Decreased Food and Water Consumption | X | X | X |
| Weight loss | X | X | X |
| Self-imposed isolation/hiding | X | X | X |
| Self-mutilation, gnawing at limbs | X | X | X |
| Rapid Breathing | X | X | X |
| Opened-Mouth Breathing | X | X | X |
| Abdominal Breathing | X | X | X |
| Grinding Teeth | | X | X |
| Biting/Growling/Aggression | | X | X |
| Increased/Decreased Movement | X | X | X |
| Unkempt Appearance (Erected, Matted, or Dull Haircoat) | X | X | X |
| Abnormal Posture/Positioning (e.g., Head-pressing, Hunched Back) | X | X | X |
| Restless Sleep | | | X |
| Tearing (including Porphyria), Lack of Blinking Reflex | | X | X |
| Dilated Pupils | | | X |
| Muscle Rigidity, Lack of Muscle Tone | X | X | X |
| Dehydration/Skin Tenting/Sunken Eyes | X | X | X |
| Twitching, trembling, tremor | X | X | X |
| Vocalization (Rare) | X | X | X |
| Redness or Swelling Around Surgical Site | X | X | X |
| Increased Salivation | | | X |

## TABLE 2

### Some Common Drugs and Techniques Currently Used to Reduce Pain and Distress in Rats, Mice and Rabbits at the NIH

| PROCEDURE | RAT | MOUSE | RABBIT |
|---|---|---|---|
| **LAPAROTOMY** | **Buprenorphine:** A) 0.01-0.05 mg/kg (SQ, IV), bid - tid<br>B) 0.1-0.25 mg/kg (PO), bid - tid<br>**Ketoprofen**: 5mg/kg po<br>**Flunixin**: 2.5 mg/kg (SC, IM), bid<br>**Carprofen**: 5 mg/kg (SQ, IM) q 4-5 hrs | **Buprenorphine**: 0.05 - 0.1 mg/kg (SQ) q 6-12 hrs<br>**Flunixin**: 2.5 mg/kg (SC, IM), bid<br>**Carprofen**: 5 mg/kg (SQ, IM) q 4-5 hrs | **Buprenorphine**: 0.02-0.1 mg/kg (SQ, IM), q 6-12 hrs<br>**Ketoprofen**: 1-3 mg/kg, (IM)<br>**Flunixin**: 1.1 mg/kg (SC, IM), bid<br>**Carprofen**: 1.5 mg/kg PO bid |
| **THORACOTOMY** | **Buprenorphine**: 0.01-0.05 mg/kg (SQ, IV), bid - tid<br>plus<br>**Bupivicaine**: Local infiltration along surgery site during closure | **Buprenorphine**: 0.01-0.05 mg/kg (SQ, IV), bid<br>plus<br>**Bupivicaine**: Local infiltration along surgery site during closure | **Buprenorphine**: 0.02-0.1 mg/kg (SQ, IM), q 6-12 hrs<br>plus<br>**Bupivicaine**: Local infiltration along surgery site during closure |
| **ORTHOPEDIC** | **Buprenorphine**: 0.01-0.05 mg/kg (SQ, IV), bid - tid<br>plus<br>**Bupivicaine**: Local infiltration along surgery site during closure | **Buprenorphine**: 0.01-0.05 mg/kg (SQ, IV), bid<br>plus<br>**Bupivicaine**: Local infiltration along surgery site during closure | **Buprenorphine**: 0.02-0.1 mg/kg (SQ, IM), q 6-12 hrs<br>plus<br>**Bupivicaine**: Local infiltration along surgery site during closure |
| **CUT-DOWN** | **Bupivicaine**: Local infiltration along surgery site during closure | **Bupivicaine**: Local infiltration along surgery site during closure | **Ketoprofen**: 1-3 mg/kg, (IM)<br>plus<br>**Bupivicaine**: Local infiltration along surgery site during closure |
| **CRANIOTOMY** | ***** **3% Lidocaine gel** on ear bars and infiltrate incision line<br>plus<br>**Ketoprofen Fluids** (SQ) bid or<br>**Flunixin Fluids** (SQ) bid | ***** **3% Lidocaine gel** on ear bars and infiltrate incision line<br>plus<br>**Ketoprofen Fluids** (SQ) bid or<br>**Flunixin Fluids** (SQ) bid | |
| **EMBRYO TRANSFER (Recipient)** | | **Bupivicaine or Ropivicaine**: 1-2 drops into muscle or local infiltration along surgery site during closure | |

*For additional advice on analgesic selection or use, please consult your institutional veterinarian and/or the Animal Use Training Handbook - Anesthesia/Analgesia Formulary (http://oacu.od.nih.gov/ARAC/tablesbyspecies.pdf).