CCAC TRAINING MODULE ON:
LABORATORY ANIMALS USED IN BIOMEDICAL RESEARCH
This training module is relevant to all animal users working with animals housed in vivaria (enclosed areas such as laboratories) in biomedical research.

This training module covers the following animals housed in vivaria:

- rodents
- rabbits
- birds
- amphibians
- reptiles
- non-human primates
- other mammals

Photo courtesy of Dr. S. Craig
Training Module Goals

- Understand the differences in the types of animal models used in biomedical research and the importance of their selection
- Recognize the importance of accounting for and controlling the variables in the experimental design
- Develop a checklist of the variables that can affect research programs
- Describe and accept responsibility for ensuring the successful conduct of an experiment
Use and selection of animal models in biomedical research

Variables influencing the response of an animal model to an experiment:
- animal related factors
- physical and environmental factors
- husbandry, animal care and handling factors
- experimental manipulation factors

Responsibilities of team members involved with a research project:
- principal investigator
- graduate students, post-doctoral students and research technicians
- facility manager
- animal care staff
- laboratory animal veterinary staff
Animal models are used in biomedical research to study:

- biology
- behaviour
- spontaneous or induced pathological processes
- phenomenon that resembles those in humans
1. **Spontaneous or “natural” models**
   • naturally occurring animal disease/condition that corresponds to the same disease/condition in humans
     ○ (i.e., diabetes, arthritis)

2. **Experimental models**
   • disease/condition is reproduced by the investigator
     ○ (i.e., cancer, stroke)
3. Genetically-engineered models
   - manipulation of animal’s genetic code to produce the disease/condition

4. Negative models
   - animals that are resistant to a particular disease/condition

5. Orphan models
   - animal disease/condition for which there is no known human counterpart
Before an animal model is chosen, investigators must consider alternatives to the use of live animals (Three Rs).

Investigators must consider all factors when selecting the best model for research.

See the CCAC training module on: the Three Rs of humane animal experimentation (2003) and visit the CCAC Three Rs microsite at www.ccac.ca/en/alternatives for further information on this topic.
Factors that Influence Animal Research

Husbandry, Animal Care & Handling Factors

Research Manipulation Factors

Physical & Environmental Factors

Animal Related Factors

- Age, Sex, Reproductive Status
- Genetic Make-up
- Microbial Flora
- Biological Rhythms

Transportation Stress
- Relative Humidity
- Ventilation
- Lighting

Housing Stress
- Room Temperature
- Bedding
- Noise

Animal Stress
- Time and Duration of Manipulation
- Experimental Stressors
- Feed and Water
- Pain

Microbial Flora

Biological Rhythms

Photo courtesy of Dr. S. Craig
The non-experimental factors that can influence the response of the animal model (and affect the outcome of the study) can be grouped as:

- animal related factors
- physical and environmental factors
- husbandry, animal care and handling factors
- research manipulation factors
Animal Related Factors
1. Age, sex and reproductive status
   - responses vary with age and gender of animal
   - hormone and physiological variations can also influence responses of females and males

2. Genetic make-up
   - inbred (genetically identical) vs. outbred
   - genetic manipulation can affect phenotype
3. Microbial flora

- most animals carry microbes that can be a source of variability in research

4. Biological (circadian) rhythms

- metabolism varies with time of day
  - i.e., rodent metabolic rates are higher at night
- they can cause drugs to have variable effects depending on time of day they are administered
  - important to perform manipulations at the same time of day for all animals
5. Disease

Clinical disease: disease is apparent in the animal

Subclinical disease: animal appears healthy despite presence of infectious organisms

Fur mite infestation in a mouse

Immune deficient or immune compromised models are very susceptible to ordinarily non-pathogenic organisms

How can you be sure that this rabbit is not harbouring a virus, bacteria or parasite that will interfere with your research results?

See the CCAC training module on: infectious diseases (2010) for further information on this topic
Physical & Environmental Factors

1. Room temperature

- Temperature variations can cause changes in:
  - behaviour (huddling, shivering)
  - metabolic rate (higher food consumption for body heat production)

- Temperature fluctuations should be:
  - monitored
  - limited to +/- 2°C as these changes can affect metabolic processes including drug metabolism
2. Relative humidity (RH)

• RH can affect:
  ○ thermoregulation
  ○ food consumption
  ○ activity level
  ○ disease transmission

• most species do well with RH levels between 40 and 60%:
  ○ level should be appropriate for species and kept consistent (+/- 5%)
3. **Ventilation**
   - animal housing requires high air exchange rates to remove heat, ammonia, carbon dioxide and airborne particles

4. **Lighting**
   - day/night cycle
     - consistent diurnal rhythms are necessary
   - intensity of lights
     - light intensities of greater than 300 lux can cause retinal damage to albino rodents
   - wavelength
     - influences organ weights and estrus cycle length in mice
5. Noise

- May induce seizures in young rodents and can affect:
  - food and water consumption
  - reproduction
  - blood pressure
  - immune response
  - white blood cell count
  - plasma cholesterol levels
  - learning abilities
6. **Feed and water**
   - animals should be given a consistent and reproducible diet that meets nutritional needs
   - provided with water to meet the standards set for human consumption

7. **Bedding**
   - regular bedding materials should be provided to animals
Husbandry, Animal Care & Handling Factors

1. Transportation
   - animals should be allowed sufficient time to acclimate to the research facility upon arrival
   - a minimum of one week is recommended

2. Housing
   - caging
     - space per animal and number of animals per cage should remain consistent within a study
     - significant differences in temperature, humidity and air quality, noise and vibration levels between different types of cages
2. Housing (continued)

- environmental enrichment
  - can improve animal well-being
  - should be uniformly and consistently provided for the duration of the experiment

Hammocks can be used in cages to make them more interesting and stimulating to ferrets

Toys and chewable objects allow the expression of species-typical postures and activities

See the CCAC training module on: environmental enrichment (2003) and the CCAC Three Rs microsite at www.ccac.ca/en/alternatives for further information on this topic.
3. **Routine care, husbandry and handling**

- All animals should be handled the same way at the same time of day.
  - If not possible, randomize design.

- Handling must be gentle and consistent to minimize variability.

- The kind of handling an animal receives may alter behaviour or physiology, thereby affecting its response in a study.
Experimental Manipulation Factors
1. **Time and duration of manipulation**
   - efforts should be made to:
     - take repeated samples as the same time of day everyday
     - keep duration of manipulation consistent

2. **Experimental stressors**
   - familiarizing an animal to manipulation before a project starts is important to reduce stress

It is recommended that Standard Operating Procedures (SOPs) be written & observed to standardize each and every animal manipulation
3. Pain

- untreated pain can affect biology and physiology
- amount of pain will depend on:
  - the dose and time of administration of analgesics
  - handler’s skills
  - previous experience of animal
  - the added presence of fear or stress

See the CCAC training module on: pain, distress and endpoints (2010), the CCAC training module on: analgesia (2003), and the CCAC training module on: anesthesia (2003) for further information on these topics
Responsibilities of Research Team Members

All play a role in limiting the effects of both non-experimental and experimental variables
Considers and outlines all pertinent variables

Consults and observes SOPs to:

- ensure that all experimental variables are controlled
- ensure monitoring/recording of controls of variables
- limit disease introduction

Ensures animal health quality before, and regular health monitoring after purchase
Monitor and record controls on all variables

Employ skilled animal handling and manipulation techniques

Consult and observe SOPs to:
  - limit disease introduction
  - conduct all experimental procedures accordingly
Ensure consistent facility environmental operations

Ensure high level of animal care training and expertise

Implement SOPs for all animal facility operations

Ensure animal health before purchase and health monitoring after
Animal Care Facility Staff

- Conduct daily animal facility routines according to SOPs
- Conduct all animal care handling and manipulations in a way that is:
  - consistent
  - gentle
  - humane
Laboratory Animal Veterinary Staff

- Advise on and ensure health status of all animals
- Effect procedures that will maintain animal health quality
Animal models must be carefully selected with the Three Rs in mind.

Animals are influenced by the many different factors that can affect experimental results:

- animal related factors
- physical factors
- husbandry/handling factors
- experimental manipulation factors

All members of the research and animal care teams have a role to play in recognizing and controlling these variables.

Quality Animal Care = Quality Science