Refinements in Minipig Inhalation Toxicology

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Refinements in Pig Inhalation Toxicology

Overview
- Why pigs?
- Challenges
- Refinements
  - Training
  - Physical environment
  - Safety monitoring
- Future
Inhalation Toxicology

Our capabilities:

• Acute to carcinogenicity
• Embryofetal to two-generation reproductive studies
• Studies with specific approaches and dosing up to 24 hours/day
• Cardiotoxicity to assessing anesthetic potential

• All work is performed in accordance with the Animals (Scientific Procedures) Act 1986 (amended in 2012 to conform with European Directive 2010/63/EU)
• Ethical review of all project licences by internal Animal Welfare and Ethical Review Body and UK government Animals in Science Regulation Unit

>80 compound classes | >1000 studies in 6 years
Why Minipigs?

Ethical factors
Scientific factors
Challenges

• Developing background data

• Pig welfare (and compliance)

• Equipment

• Pig safety
Developing Background Data

Respiratory plethysmography
Pig Welfare (and compliance)

• Working with conscious pigs is essential to allow 1 hour+, repeat dose inhalation exposure in large numbers of pigs
  - Welfare
  - Replication of intended dose routes
  - Efficiency

• Training

• Environment

• Equipment
Training

- 28 day+ training programme
  - Longer doses need longer training periods

- Socialisation in pen

- Harness and lead training

- Walking to dose suite, feeding treats from mask

- Bench restraint

- Mask with air
  - Slow escalation to eventual dose length
Key Training is Before Mask

Animals walk voluntarily to dosing suite

• Create positive associations with:
  • Staff
  • Harness
  • Dosing suite
  • Mask
Animals will voluntarily walk onto dosing “bench”
Physical Environment

- Transport
- Dose suite
- Mask
Dose Suite

Optimizing the room for pig dosing

- Consistent
- On floor
- Surface substrate
- Quiet but not silent
- Light levels
- In groups where possible
- Comfort bolsters
- Every pig is different
Computer-Aided Design and 3D Printing
Masks in Use
Safety Monitoring

• Constant supervision

• Behavioural scoring

• Capnography
0  No observation of aversive behaviours, e.g., trying to remove mask or leave bench

1  Occasional observation of aversive behaviours, e.g., trying to remove mask or leave bench

2  Occasional to intermittent observation of aversive behaviours, e.g., trying to remove mask or leave bench

3  Intermittent observation of aversive behaviours, e.g., trying to remove mask or leave bench

4  Intermittent to repeated observation of aversive behaviours, e.g., trying to remove mask or leave bench

5  Repeated observation of aversive behaviours, e.g., trying to remove mask or leave bench
Capnography provides real-time data about respiratory rate, depth and quality
Example Respiratory Data

- CO2 Inspired (mmHg)
- CO2 Expired (mmHg)
- Respirations
Future

- Constant cycle of refinement
  - Technician-led AWERB subgroups for dose route (inhalation) and species (minipig)

- Longer term studies

- Different study types, e.g., dose modalities
Thanks to all the staff at Labcorp Huntingdon who have collaborated on this project, including:

Dog & Minipig Toxicology team

Aerosol Technology team

Inhalation Engineering team

Cardiovascular Safety Pharmacology team

Study Management team

Animal Welfare & Veterinary Services team