

Bio-research and the Beast



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NEAR EAST UNIVERSITY
RESEARCH CENTER OF
EXPERIMENTAL HEALTH
SCIENCES

Human - Animal Relationships



Use of animals by man

- Food
- Clothing
- Transport
- Sport
- Exhibition
- Pets
- Research





Why Do we Use Animals in Research?

- Primarily, so we don't use humans
- They provide us with a 'model' for:
 - Understanding physiology
 - Understanding gene function
 - Disease pathology
 - Treatment testing
 - Psychological and Behavioural studies
 - Toxicology - Protecting people, animals and the environment

Cont'd

The fantastic fruit fly

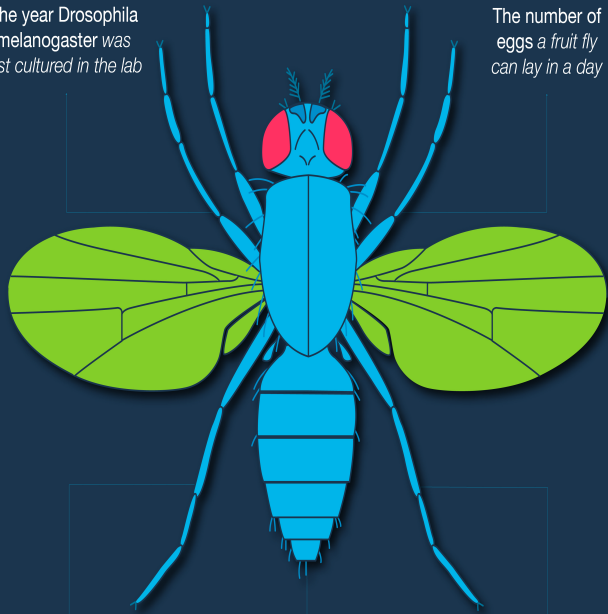
A laboratory's best friend

1901

The year *Drosophila melanogaster* was first cultured in the lab

100

The number of eggs a fruit fly can lay in a day



30 generations

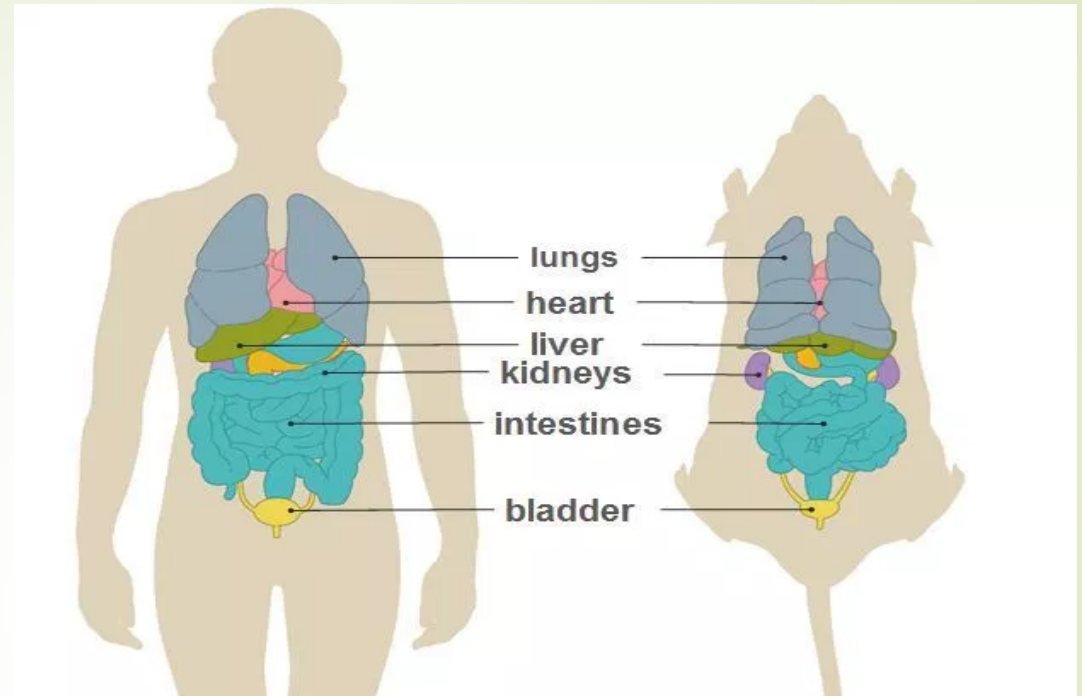
Can be grown a year due to the short egg-adult life cycle

3mm

The size of a fully grown fly, hatched from an egg the size of a grain of sand

6 Nobel Prizes

Won through research into the fruit fly (1933 – 2017)



Hemoglobin Comparisons Between Humans and Other Vertebrates

Species	Human	Gorilla	Rhesus monkey	Mouse	Chicken	Frog
Number of Amino Acids That Differ From a Human Hemoglobin Chain*	0	1	8	27	45	67

*Total chain length = 146 amino acids

Is this acceptable?



Huge diversity of opinion

Unadulterated Use  No Use



Clash of perspective regarding use of animals in research

Outcomes:

benefits can outweigh harms

Cf.

Intrinsic concerns:

animals are not means to ends



Comes down to Ethics and Necessity?

- Most people agree that some level of research is required.
- Many countries require products and chemicals to be tested before release to the general public.

Why not use humans?

Human rights!!





Limitations of testing in patients

Ethical concerns with use of poorly tested protocols.

Practical concerns: organisation, recruitment and cost.

Requirement to do no harm which is in contrast to cell and animal studies.

What are human rights?

- **Human rights** refer to the "basic rights and freedoms to which all humans are entitled."
- Examples of human rights include:
 - civil and political rights
 - the right to life and liberty
 - freedom of expression and equality before the law
 - economic, social and cultural rights, including the right to participate in culture, the right to food, the right to work, and the right to education.

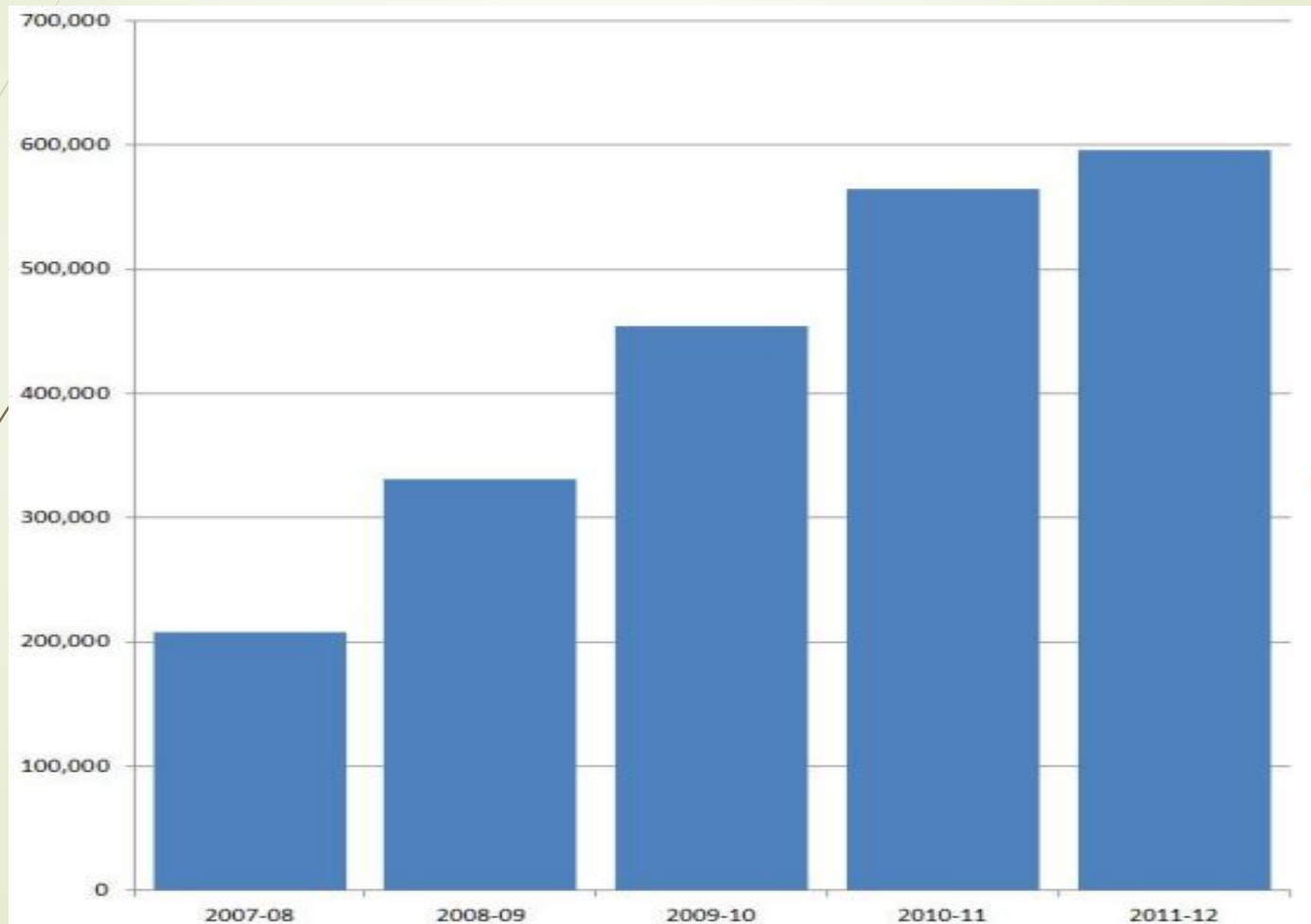
Human rights legislation

- Nuremburg Code (1947) - attempted to give Clear **rules** about what was legal and what was not when conducting **human experiments**.

Unethical examples

- Breaking and re-breaking of bones (to see how many times they could be broken before healing failed to occur) Nazi
- Patients had been injected with live cancer cells (Jewish Chronic Disease Hospital, NY, 1963)
- 400 men had been left to suffer with syphilis long after a cure (penicillin) was available. (Tuskegee, Alabama, 1932-72)
- Milgram's study sustained no physical harm, they suffered shame and embarrassment for having behaved inhumanely toward their fellow human beings.(1963)

Human clinical trials (UK)



Basic animal rights



South Cloisters of the main building of UCL

"The question is not, can they reason? nor, can they talk? but, can they suffer?"

Jeremy Bentham 1789
*Introduction to the
Principles of Morals &
Legislation*

Range of views

Absolute
Dominion

UAR

UFAW

RSPCA

ALF
BUAV
NAVS



Speciesist

“Troubled middle”

Abolitionist


- UAR – Understanding Animal Research (2008)
- UFAW – Universities Federation for Animal Welfare (1926)
- RSPCA – Royal Society for the Prevention of Cruelty to Animals (1824)
- ALF – Animal Liberation Front (1976)
- BUAV - British Union for the Abolition of Vivisection now called Cruelty Free International(1898)
- NAVS - National Anti-Vivisection Society (1875)

The 3R's

- Reduce the number of animals used to a minimum
- Refine the way experiments are carried out, to make sure animals suffer as little as possible
- Replace animal experiments with non-animal techniques wherever possible.

Russell and R.L. Burch (1959) The Principles of Humane Experimental Technique.

<http://www.nc3rs.org.uk/>



Worldwide requirements to do animal studies before licensing human medicines

- Safety pharmacology
- Toxicology (2 species)
 - Acute
 - Chronic
- Teratogenicity
- Carcinogenicity

Animal (Scientific Procedure) Act 1986

- Certificate of Designation
- Project Licence.
- Personal Licence.
- Requirement for training.



The Act relies on sound ethical judgement

- Are there opportunities for reducing harm?

Apply 3Rs

- How significant are the likely benefits?
Critically evaluate necessity and experimental design...

Animal trials are not always predictive

BBC NEWS

Six taken ill after drug trials **Six men remain in intensive care after** **being taken ill during a clinical drugs** **trial in north-west London.**

The healthy volunteers were testing an anti-inflammatory drug at a research unit based at Northwick Park Hospital when they suffered a reaction.

Relatives are with the patients, who suffered multiple organ failure. Two men are said to be critically ill.

An investigation has begun at the unit, run by Parexel, which said it followed recommended guidelines in its trial.

The men were being paid to take part in the early stages of a trial for the drug to treat conditions such as rheumatoid arthritis and leukaemia until they were taken ill on Monday within hours of taking it.

Eight volunteers were involved, but two were given a placebo at the unit which is on Northwick Park Hospital's grounds but is run independently.

- Cats and aspirin
- Guinea pigs and penicillin
- Failure to spot effects of thalidomide



Thalidomide developed in the 1950's

Anticonvulsive drug,

Practically impossible to achieve an LD50 level, or deadly overdose.

Animal tests did not include tests looking at the effects of the drug during pregnancy.

Reduced morning sickness, so it became popular with pregnant women.

Increase in births of thalidomide-impaired children. However, no was made until 1961.

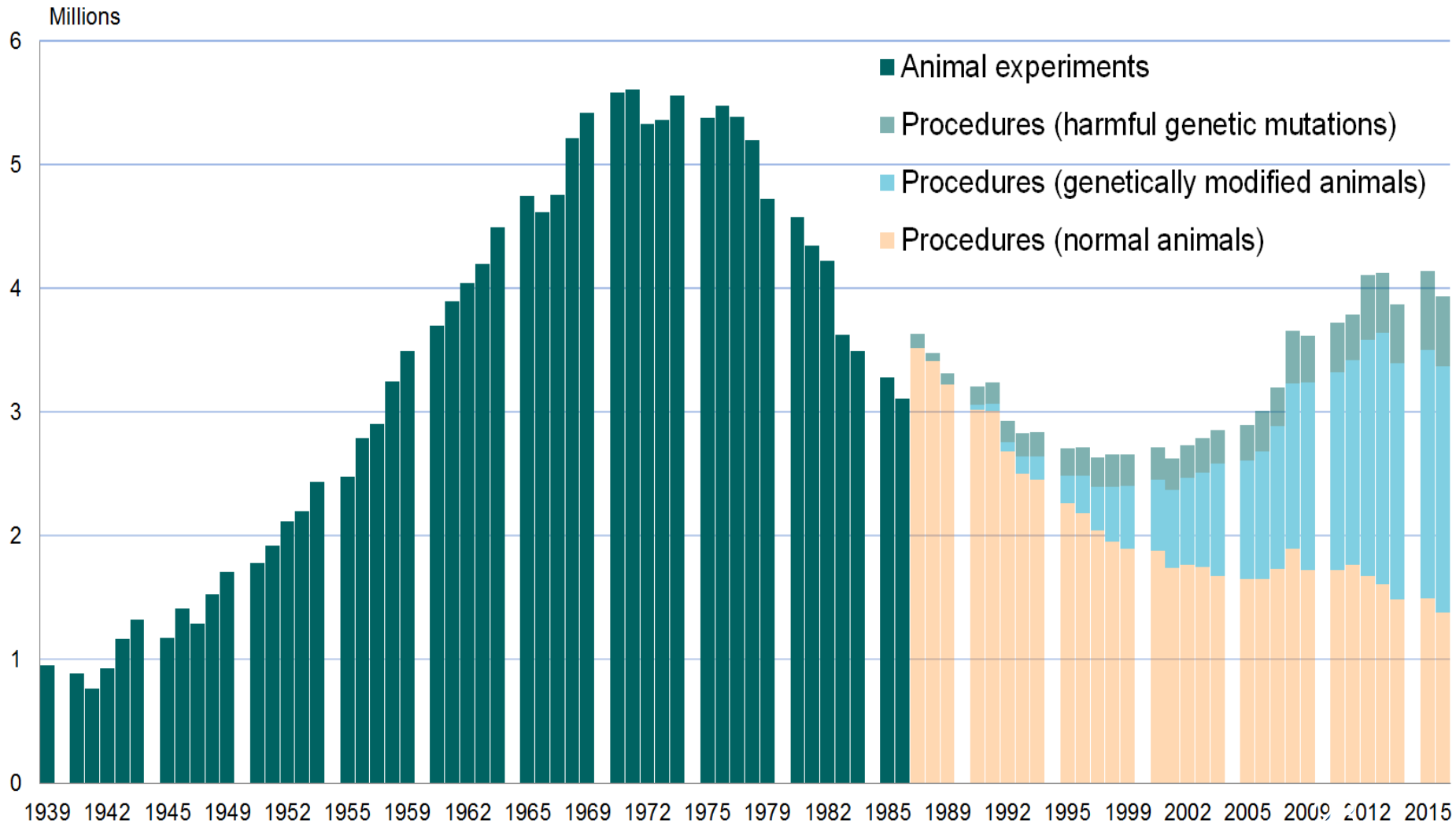
Over 10,000 children were born with thalidomide-related disabilities worldwide.



Comparisons between countries

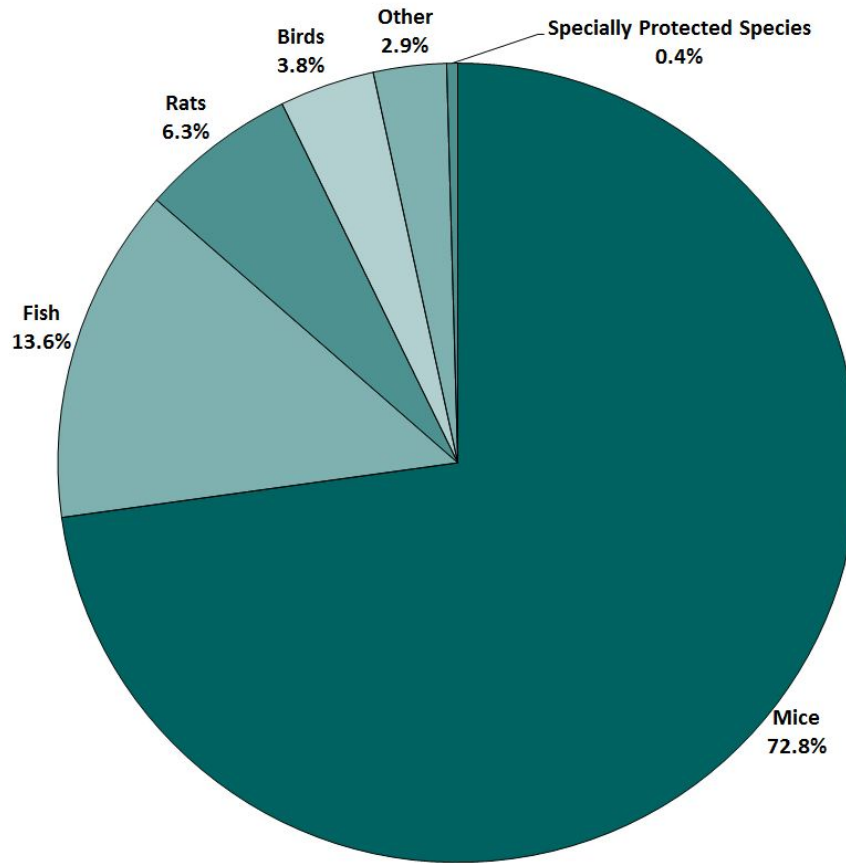
- UK is one of a few countries with a complete national scheme for controlling all animal experiments
- Involves local institutional review as first step in licensing process
- In many other countries most, if not all of the control is at the Institutional level (IACUC)
- EU attempting to harmonise European legislation – Directive 2010/63/EU

Number of research animals used in UK



Types of animals used

In 2017, there were 3.79 million procedures (3,789,373) on animals, a fall of 3.7% compared with 2016.



Mice - 2.78m procedures
Fish - 0.51m procedures
Rats - 0.24m procedures
Birds - 0.13m procedures

International estimates of animals used in research

- Many countries do not provide comprehensive statistics.
- The major centres for research:
 - USA (about 15 million procedures)
 - EU (about 11 million procedures)
 - Japan (about 5 million procedures)
 - Canada (2 million), Switzerland (less than 1 million) and Australia (less than 1 million).
- Can estimate that other countries might carry out 10 million animal procedures every year.
- The total worldwide maximum is in the order of 50 million animal procedures per year.



Animals not included in annual statistics

- ▶ Taylor et al. 2008 set out several reasons for the differences in national statistics between
- ▶ animals killed solely to supply tissues for ex-vivo or in-vitro research
- ▶ genetically-modified animals used solely to maintain established breeding colonies
- ▶ conventional animals bred for scientific purposes but killed as surplus to requirements
- ▶ foetal and embryonic forms
- ▶ certain invertebrate species, such as cephalopods
- ▶ purely observational studies
- ▶ fish tagging and other environmental studies on wild animals

Numbers killed for food

- ➡ UK meat and fish eaters consume 2.5 billion animals every year.
- ➡ 140 billion animals slaughtered every year worldwide.
- ➡ Of these estimates suggest that 90 billion fish are killed worldwide each year.

Comparison to research use

- UK eats nearly 700 times the numbers used in research.
- Cats estimated to kill between 100-200 million wild animals per year in the UK – up to >50 times that used in research



What to consider before embarking on animal research projects

- Which animal(s) are fit for purpose?
- How many? (Sample size – not too few or too many)
- Husbandry (Again animal dependent)
- Which demographic is suitable (age, sex, etc).
- This will help format and determine your experimental design (Stratified, Randomised, etc).
- Poor Design ➡ Poor/No results ➡ Poor research
➡ Wastes time, money ➡ causes unnecessary harm/death.

(WHICH IS UNFORGIVABLE)

Monitoring Experimental Animals

For example:

Category	Indicators
The cage environment	Evidence of eating and drinking
	Evidence of fresh faeces and urine
	Evidence of nest building and use / a good quality nest (mice)
	Any blood staining of the cage sides or bedding
Animal behaviour	Alert to external stimuli
	Interested in surroundings (e.g. use of enrichment items)
	Normal interactions with handlers (e.g. not overly aggressive or overly passive)
	Normal interactions with other animals (e.g. no increase in aggression or anxiety behaviour, such marked escape responses or hiding)
	Isolated or withdrawn from other animals in the social group
	Abnormal posture (e.g. hunched posture, tilted head)
	Abnormal movements (e.g. abnormal gait, uncoordinated movement, lack of movement in the cage or on the bench)
Physical appearance of the animal	Good body condition (i.e. not overconditioned or underconditioned as defined in Ullman-Culleré & Foltz 1999)
	Appropriate body weight (i.e. within normal range for age-matched controls; no significant weight loss or increase)
	Mucous membranes pink and moist
	Eyes clear and bright; free from discharge or porphyrin staining (rat) indicative of stress or disease; not sunken, dull or closed/semi-closed
	Nose free from discharge
	Mouth (including teeth and tongue) free from injury or abnormalities (e.g. malocclusion/overgrown teeth, salivation)
	Tail and anal genital area free from injury and discharge/soiling
	Normal skin and limbs (e.g. free from physical injury, lack of skin tenting = dehydration)
	Poor coat condition (e.g. unkempt due to lack of grooming, greasy, faecal or urine stained, piloerection, hair loss)
	Abnormal facial expressions, indicative of pain (e.g. grimace score of 1 or 2 using the rat (Sotocinal et al. 2011) and mouse (Langford et al. 2010) grimace scales)

Variation in Animal Experimentation



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



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 <ul style="list-style-type: none"> Closing of the eyelid (narrowing of orbital area) A wrinkle may be visible around the eye 			
Cheek flattening <ul style="list-style-type: none"> Flattening of the cheeks. When 'obviously present', cheeks have a sunken look. The face becomes more angular and less rounded 			
Nostril shape <ul style="list-style-type: none"> Nostrils (nares) are drawn vertically forming a 'V' rather than 'U' shape Nose tip is moved down towards the chin 			
Whisker shape and position <ul style="list-style-type: none"> 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 <ul style="list-style-type: none"> 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 SC, Thomas AA, Redford PA, Leach MC (2012) Evaluation of facial action units for preventing pain during botulism of rabbits. Changes in physiological, behavioural and field expression responses. PLoS ONE 7(9): e44457. doi:10.1371/journal.pone.0044457
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

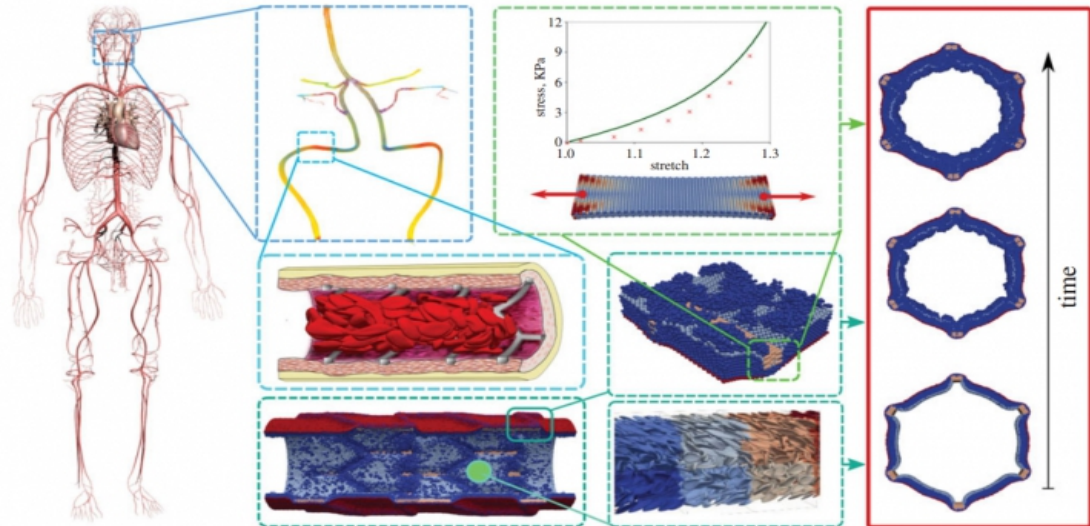
To request copies of this poster, please email: enquiries@nc3rs.org.uk
The NC3Rs provides a range of this resources at www.nc3rs.org.uk/resources
Images kindly provided by Dr Matthew Leach, Newcastle University, and Dr Petrus Heesters, Swedish University of Agricultural Sciences
The Rabbit Grimace Scale would not have been developed without the contributing work of the Pain and Animal Welfare Sciences Group (PAWS) at Newcastle University



Alternatives to Animal Experiments

- Two major alternatives to in vivo animal testing
- Vitro cell culture techniques
- Computer simulation.

ARE THESE TRUE ALTERNATIVES?



References

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