

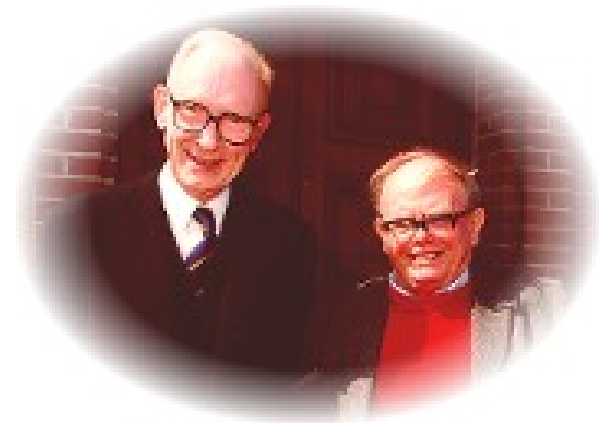
# Advice on running a centre for the 3Rs

Dr Mark Prescott

NORECOPA AGM, Oslo, 12 June 2008

# Evolution of the 3Rs

- 1959 Russell & Burch's book
- 1969 FRAME
- 1981 CAAT
- 1986 A(SP)A
- 1986 Directive 86/609/EEC
- 1991 ECVAM
- 1993 1st World Congress on Alternatives

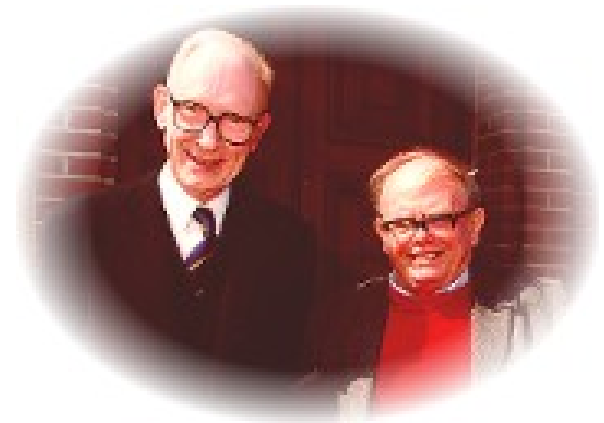


# The challenges

- Lack of understanding of the 3Rs
- Widespread support for the 3Rs – but can be lip service
- Traditionally little 3Rs investment or activity from researchers, major funding bodies etc.
- A(SP)A seen as tough regulation controlling animal use – but not necessarily proactive on 3Rs
- Scientific and regulatory process – intrinsically supports continued animal use, even where animal models are poor
- Regulatory conservatism on risk assessment
- Extremist activities divert attention from the 3Rs

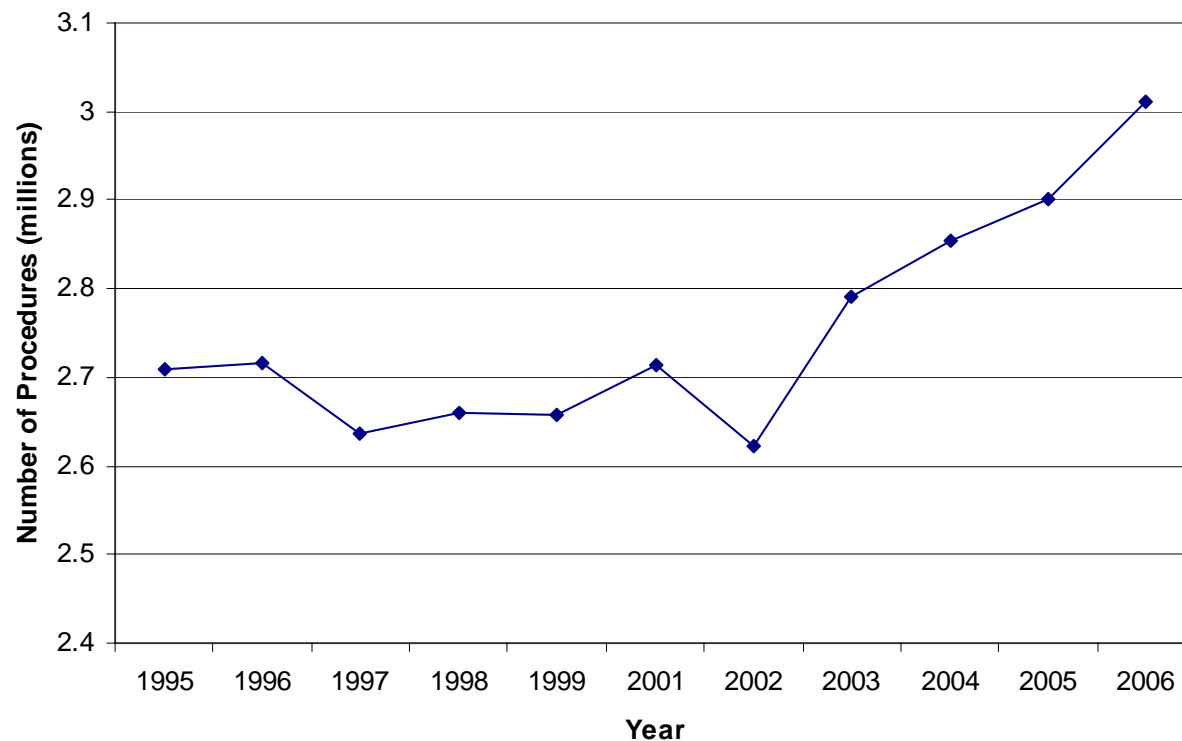
# Evolution of the 3Rs

- 1959 Russell & Burch's book
- 1969 FRAME
- 1981 CAAT
- 1986 A(SP)A
- 1986 Directive 86/609/EEC
- 1991 ECVAM
- 1993 1st World Congress on Alternatives
- 2004 NC3Rs



# House of Lords report 2002

*“There is scope for the scientific community to give a greater priority to the development of non-animal methods, and more consideration could be given to the pursuit of the 3Rs”*



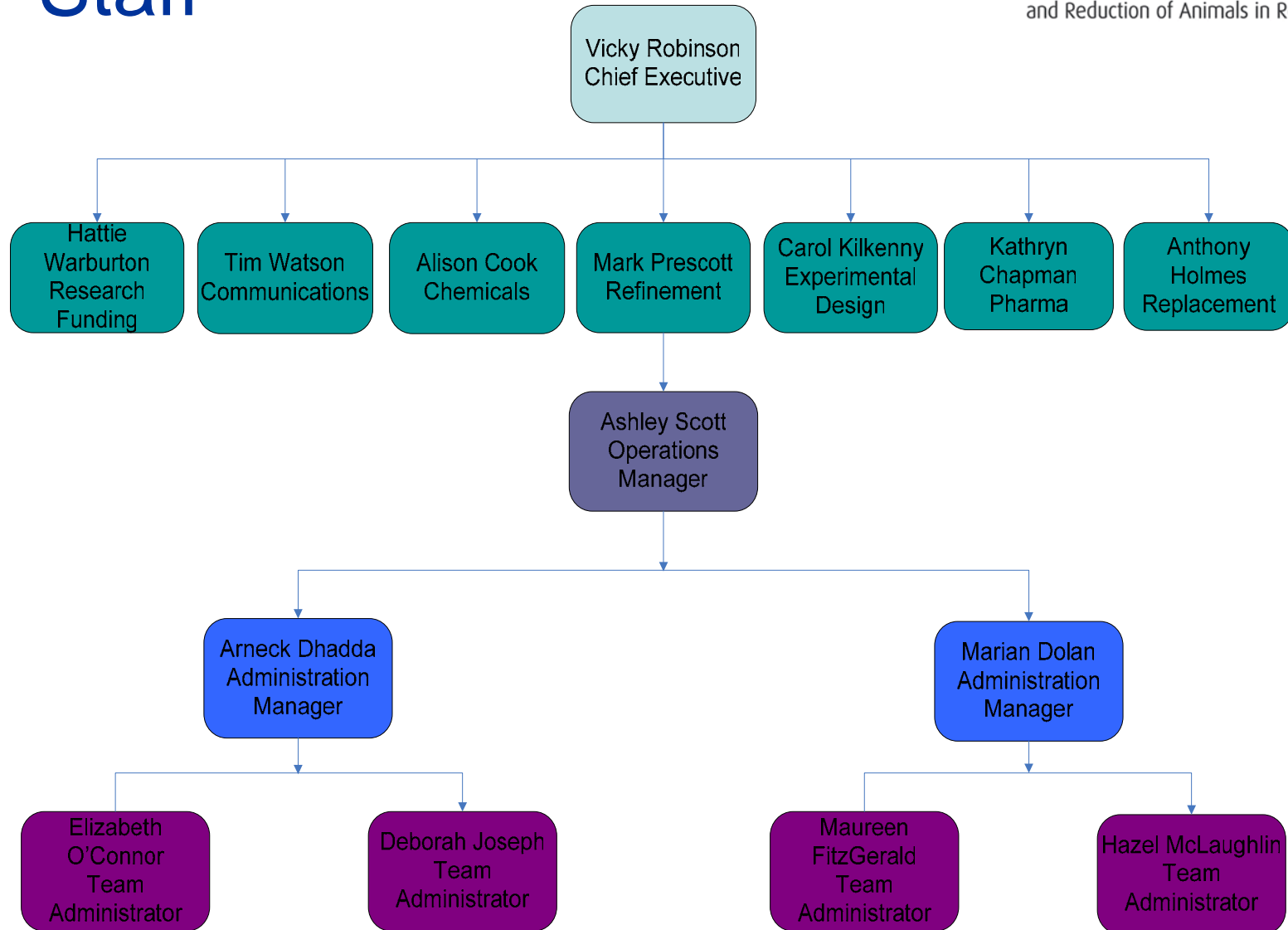
Home Office data

# About the NC3Rs

- Independent, scientific organisation
- Catalyst and focus for all 3Rs
- 15 staff with non-executive Board
- Based at MRC Head Office, London
- Funding from Government, industry, charity
- Budget £3.85M per annum



# Staff



# Board

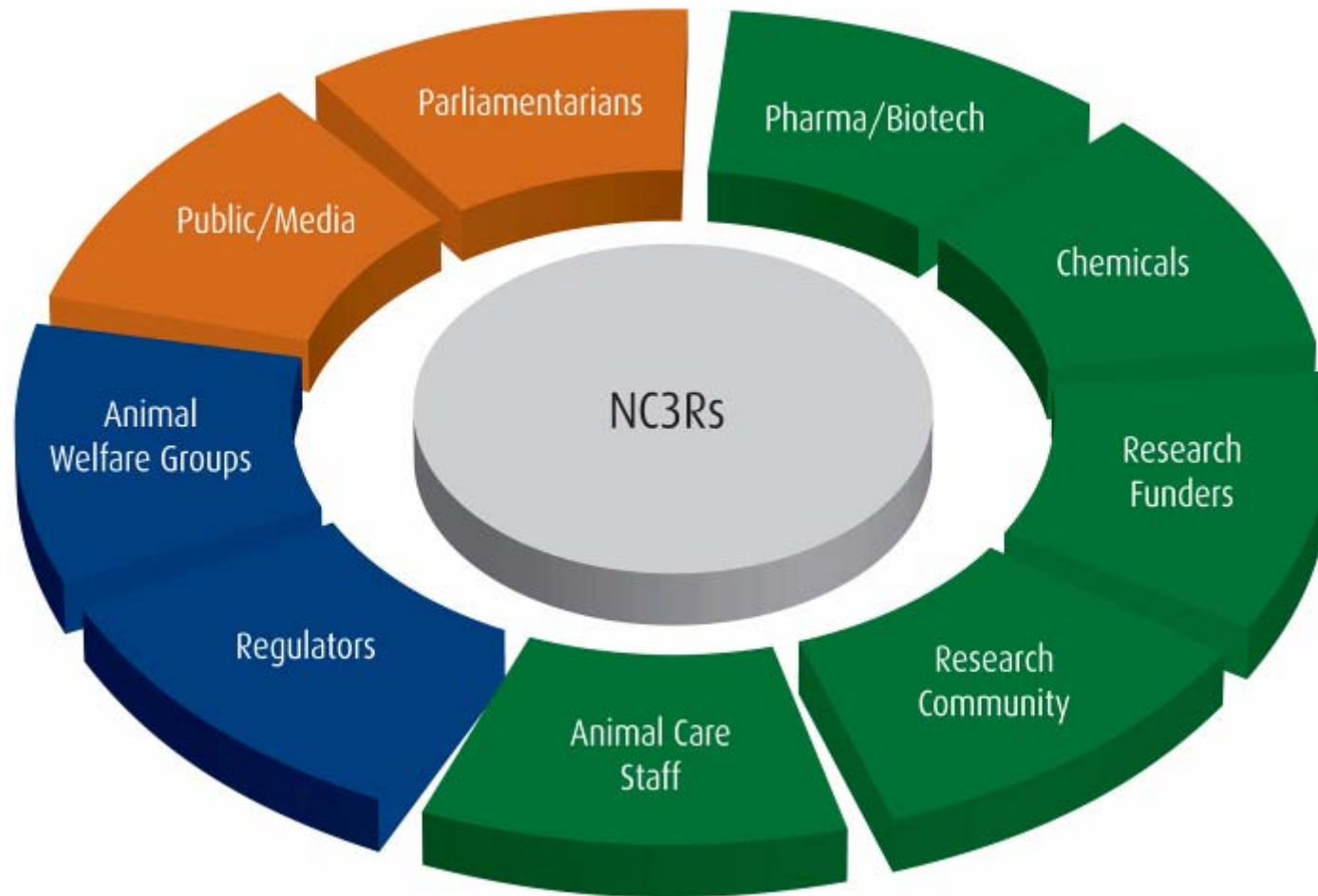


National Centre for the Replacement, Refinement  
and Reduction of Animals in Research

Professor P. Flecknell	Chair
Dr V. Robinson	NC3Rs
Dr J. Fentem	Unilever
Dr L. Heppell	BBSRC
Dr B. Howard	LASA
Professor J. Hurst	University of Liverpool
Dr M. Jennings	RSPCA
Dr J. Kirkwood	UFAW
Dr T. Peatfield	MRC
Dr J. Richmond	Home Office
Professor N. Rothwell	University of Manchester
Professor M. Rowland	University of Manchester
Dr D. Smith	AstraZeneca



# Range of stakeholders

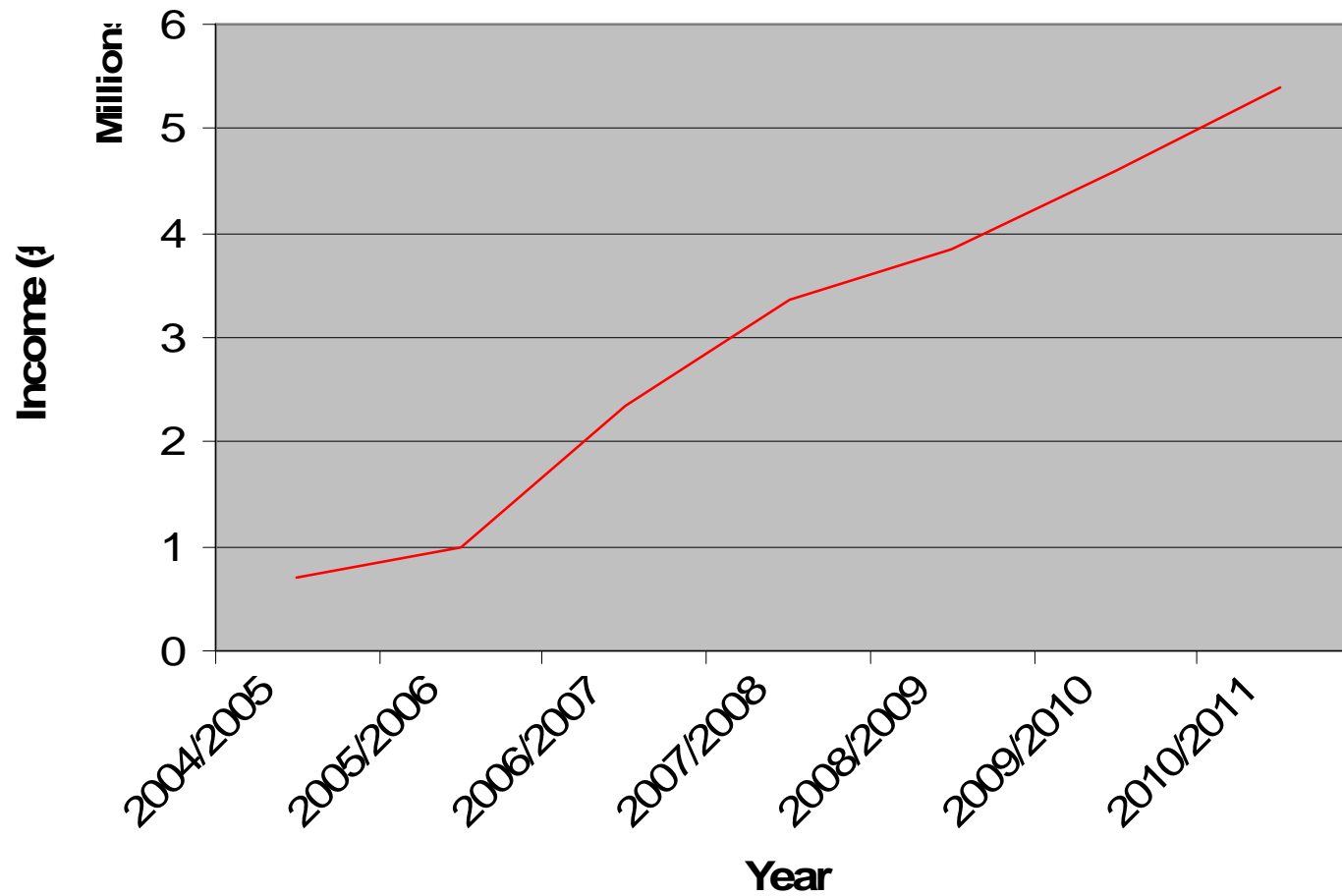


# NC3Rs goal

To use the 3Rs to support science, innovation and  
animal welfare in the biosciences



# Income



# Trying to create...

A scientific community where:

- The 3Rs are an integral part of mainstream life sciences
- There is greater willingness to challenge animal models in all sectors and to implement the 3Rs
- There is increased investment in all 3Rs
- There is a new generation of researchers committed to 3Rs from the start of their career
- There is sustained and real progress





# Motivate

# .....money talks!



# Funding high-quality 3Rs research

1. 3Rs Research Funding Scheme – 31 awards
2. Small Award Scheme, with LASA (<£2k) – 43 awards

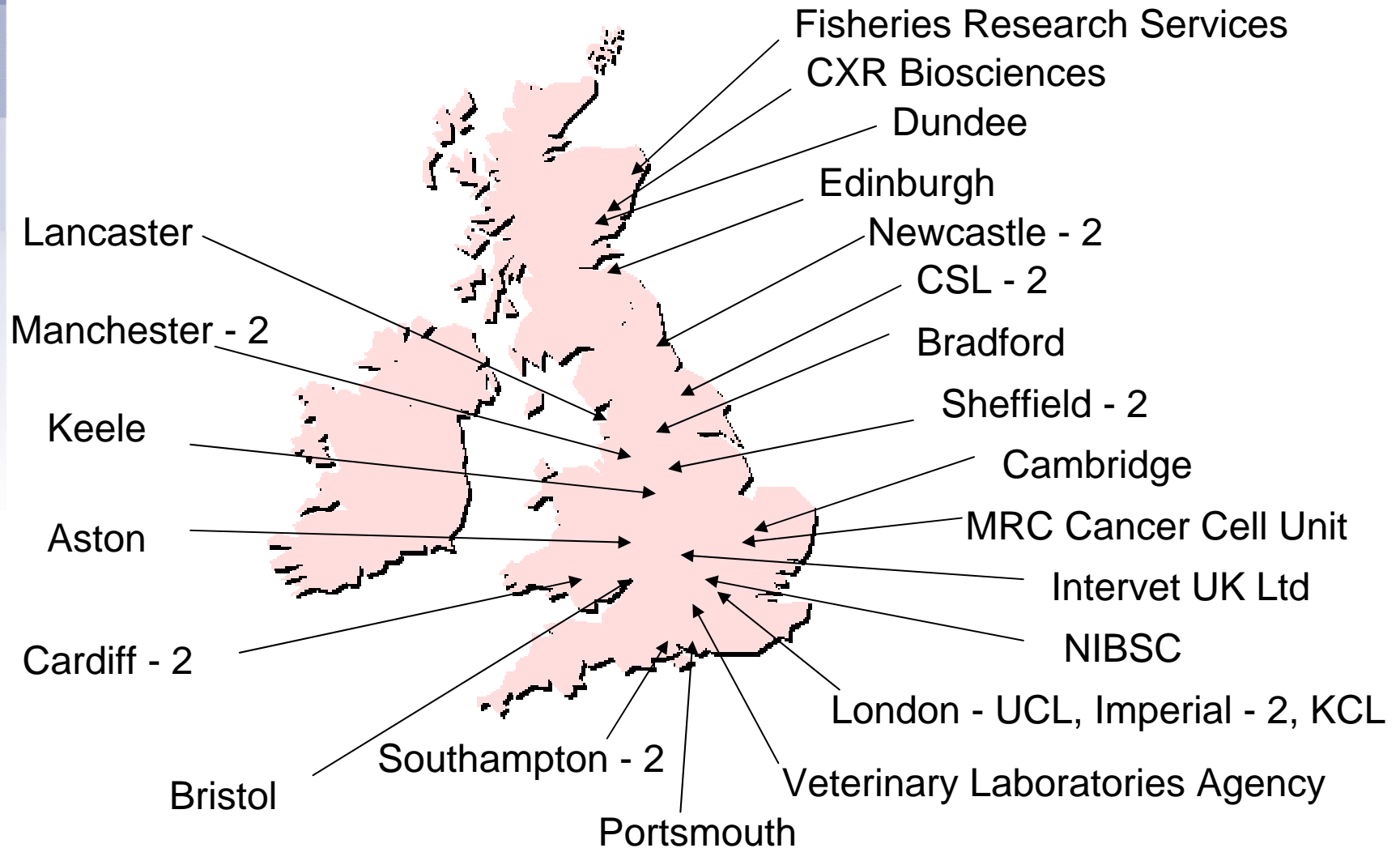
- 3Rs Prize (£10k)



# Research portfolio

	Replacement	Refinement	Reduction	Total (£)
<b>2004</b>	<b>0</b>	<b>2</b>	<b>1</b>	<b>0.5 million</b>
<b>2005</b>	<b>6</b>	<b>1</b>	<b>1</b>	<b>1.0 million</b>
<b>2006</b>	<b>6</b>	<b>2</b>	<b>1</b>	<b>1.4 million</b>
<b>2007</b>	<b>6</b>	<b>4</b>	<b>1</b>	<b>2.4 million</b>
<b>Total (£)</b>	<b>3.4 million</b>	<b>1.1 million</b>	<b>0.8 million</b>	<b>5.3 million</b>

# Research awards





# Strategic priorities

## 2007

- Tissue engineering with BBSRC (4/11)
- Refining procedures of substantial severity (3/11)

## 2008 (£2.5M)

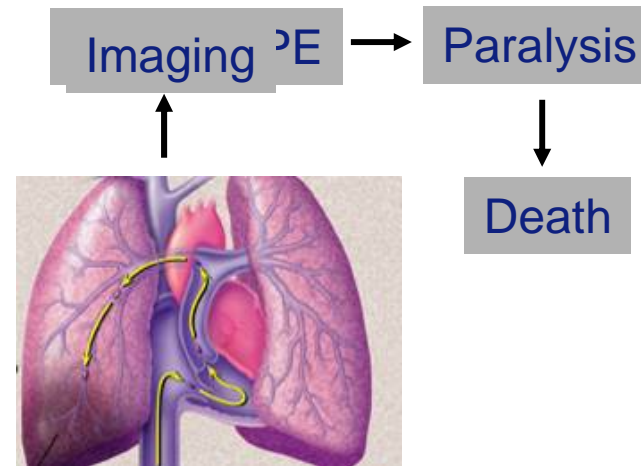
- Refining rodent husbandry, care and procedures
- Fish and 3Rs

Next deadline February 2009 (£3M)



# Pulmonary embolism: animal welfare and science

- Novel method: drugs and gene function in PE
- Inflicts severe pain and suffering
- General anaesthesia
- Limited scientific use
- Refinement (reduced severity limit)
- Reduces animal use
- Models severe, fatal pulmonary embolism
- Better scientifically:
  - Clinical PE has a broad spectrum
    - More information
- Non-specific, what is measured?
  - Models all levels of PE

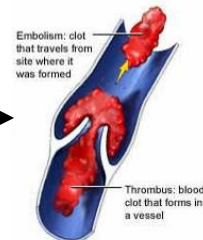


Lower concentrations

Clotting agent

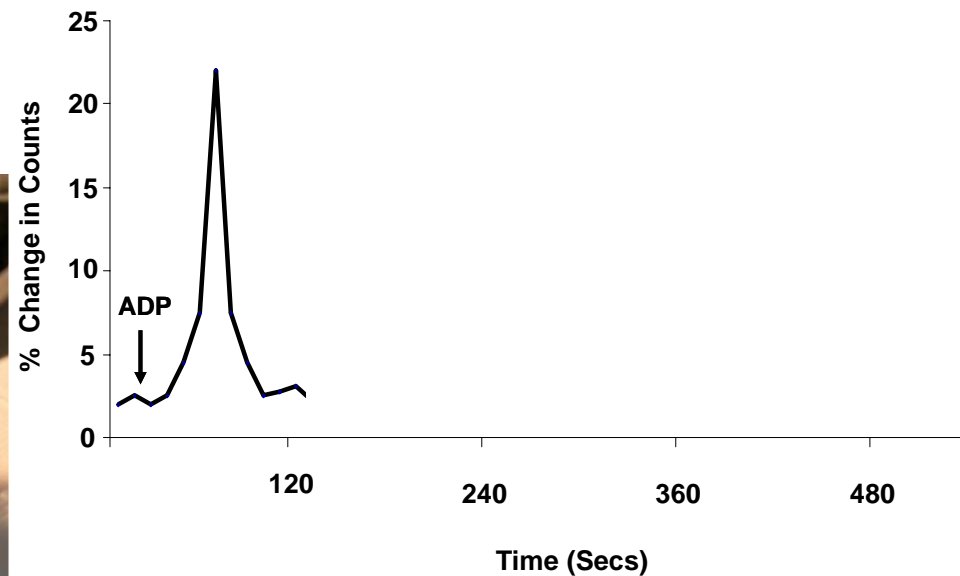


Anaesthetise



PPL Severity Limit: **Substituted**

# Pulmonary embolism: animal welfare and science



**Refinement and reduction:  
30 mice undergoing an unclassified procedure  
Vs.  
200 mice undergoing a severe procedure**



National Centre for the Replacement, Refinement  
and Reduction of Animals in Research

Relevant and timely  
.....to achieve buy in

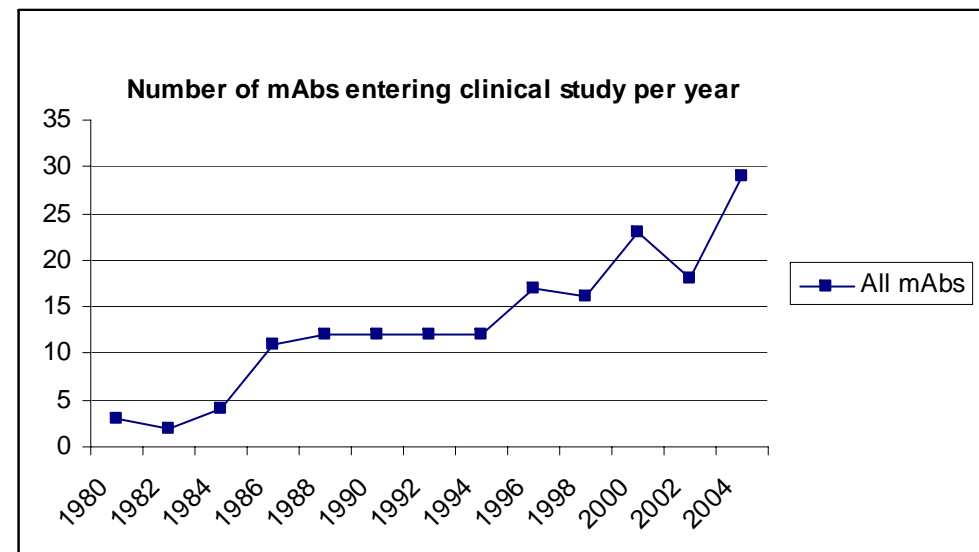
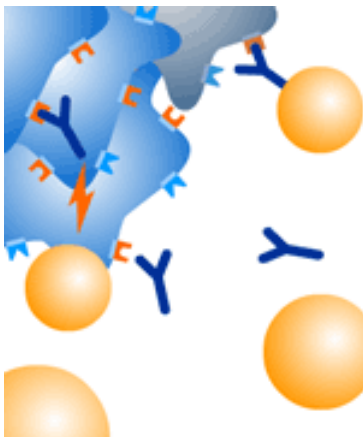


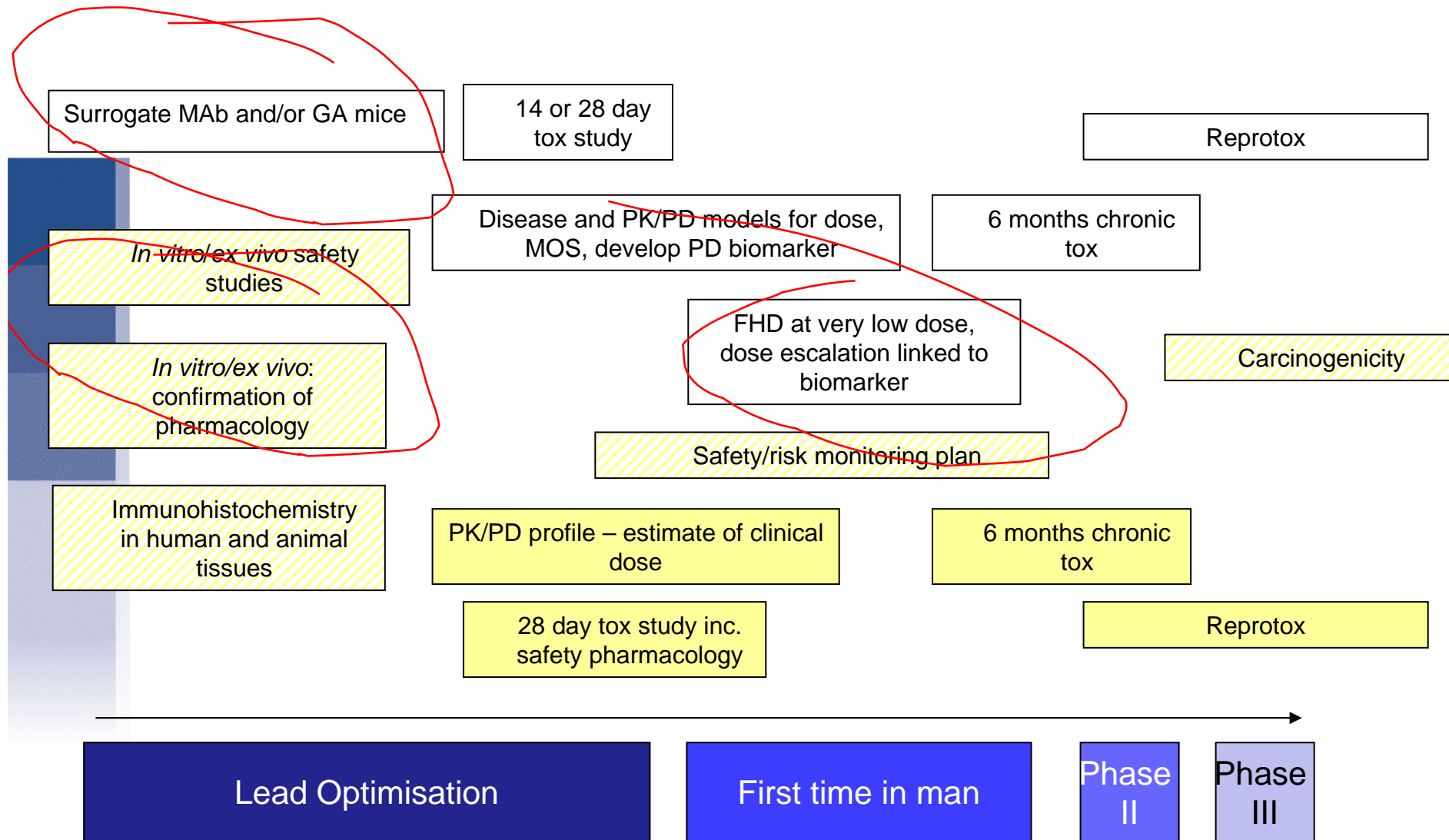
# Monoclonal antibodies (mAbs)



National Centre for the Replacement, Refinement  
and Reduction of Animals in Research

- Increase in primate use due to the development of mAbs as therapeutics
- Workshop with 50 delegates from UK, Europe and US
- Explored hypothetical drug development pathway for monoclonals without primates





■ Conventional MAb development pathway using primates

□ Hypothetical MAb development pathway: emphasis on surrogate MAb and/or GM mice

▨ Shared studies

## PERSPECTIVES



National Centre for the Replacement, Refinement  
and Reduction of Animals in Research



## Opportunities for reducing the use of non-human primates in the development of biologicals – a workshop report

May 2006



### OPINION

## Preclinical safety testing of monoclonal antibodies: the significance of species relevance

*Kathryn Chapman, Nick Pullen, Mark Graham and Ian Ragan*

**Abstract** | Selecting a pharmacologically relevant animal species for testing the safety and toxicity of novel monoclonal antibody (mAb) therapies to support clinical testing can be challenging. Frequently, the species of choice is the primate. With the increased number of mAbs in the pharmaceutical pipeline, this has significant implications for primate use, and so raises several important scientific, ethical and economic issues. Here, following a recent international workshop held to debate this topic, we discuss issues in the preclinical testing of mAbs, with a particular focus on species relevance and primate use, and provide suggestions for how these issues might be addressed.

tem to that of humans, the strong likelihood of cross-reactivity and relevant pharmacology, the similar antibody kinetics, and the lower risk of significant immunogenicity and neutralizing antibody formation for human antibodies. However, concerns about the scientific, economic and ethical implications of a steep rise in primate use have provided a catalyst to evaluate whether primates are the most appropriate species in all cases, and to analyse the extent of added scientific value of risk assessment in primates over and above other approaches.

In collaboration with the Association of the British Pharmaceutical Industry, the UK National Centre for the Replacement, Refinement and Reduction of Animals in Research held an international workshop in March 2006 to discuss issues relating to primate use in the development of mAbs (BOX 1); a follow-up study is now also underway. In order to explore alternatives a hypothetical situation was presented to

#### Written by

Kathryn Chapman, PhD, Programme Manager, NC3RS

#### Using/reproducing information

All requests to use or reproduce any part of this report should be directed to:  
NC3RS, 20 Park Crescent, London, W1B 1AL. Tel: 020 7670 5331



National Centre for the Replacement, Refinement  
and Reduction of Animals in Research

# mAbs working group

- Expert international working group (includes regulators)
- Data sharing
  - 120 unique mAbs (8 European and 4 US companies)
  - Use of rodents and surrogate mAbs
  - Added value of using NHPs
  - Numbers and study designs
- Focus on reproductive toxicity and use of surrogate mAbs

NC3Rs/ABPI Biologicals Expert Working Group Questionnaire 1

NC3Rs  
National Centre for the Replacement, Refinement  
and Reduction of Animals in Research

**CONFIDENTIAL**

**NC3Rs/ABPI Biologicals Expert Working Group Questionnaire**

The NC3Rs and the ABPI are collaborating on an ambitious and comprehensive programme to review the opportunities to replace and reduce to a minimum primate use in drug discovery and development with particular emphasis on pharmacology, drug development, monoclonal antibodies, the reporter and toxicology. An expert working group has been set up as part of this larger project to consider the scientific rationale for the use of primates in the development of mAbs and potential alternatives.

The working group agreed that a questionnaire could be distributed as a first step to help provide essential background information for the project. All responses will be treated in strict confidence.

Name (optional):





National Centre for the Replacement, Refinement  
and Reduction of Animals in Research

Challenge intellectually  
.....generates interest

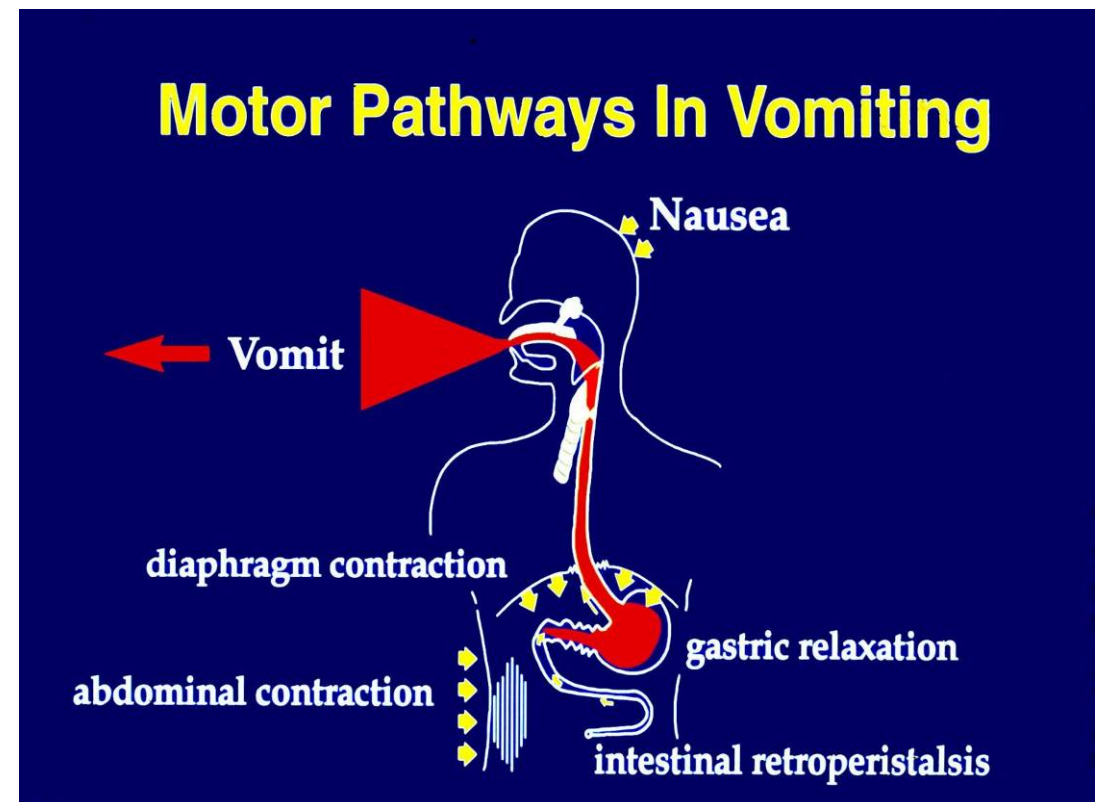


# Replacing animal use in a multi-system reflex

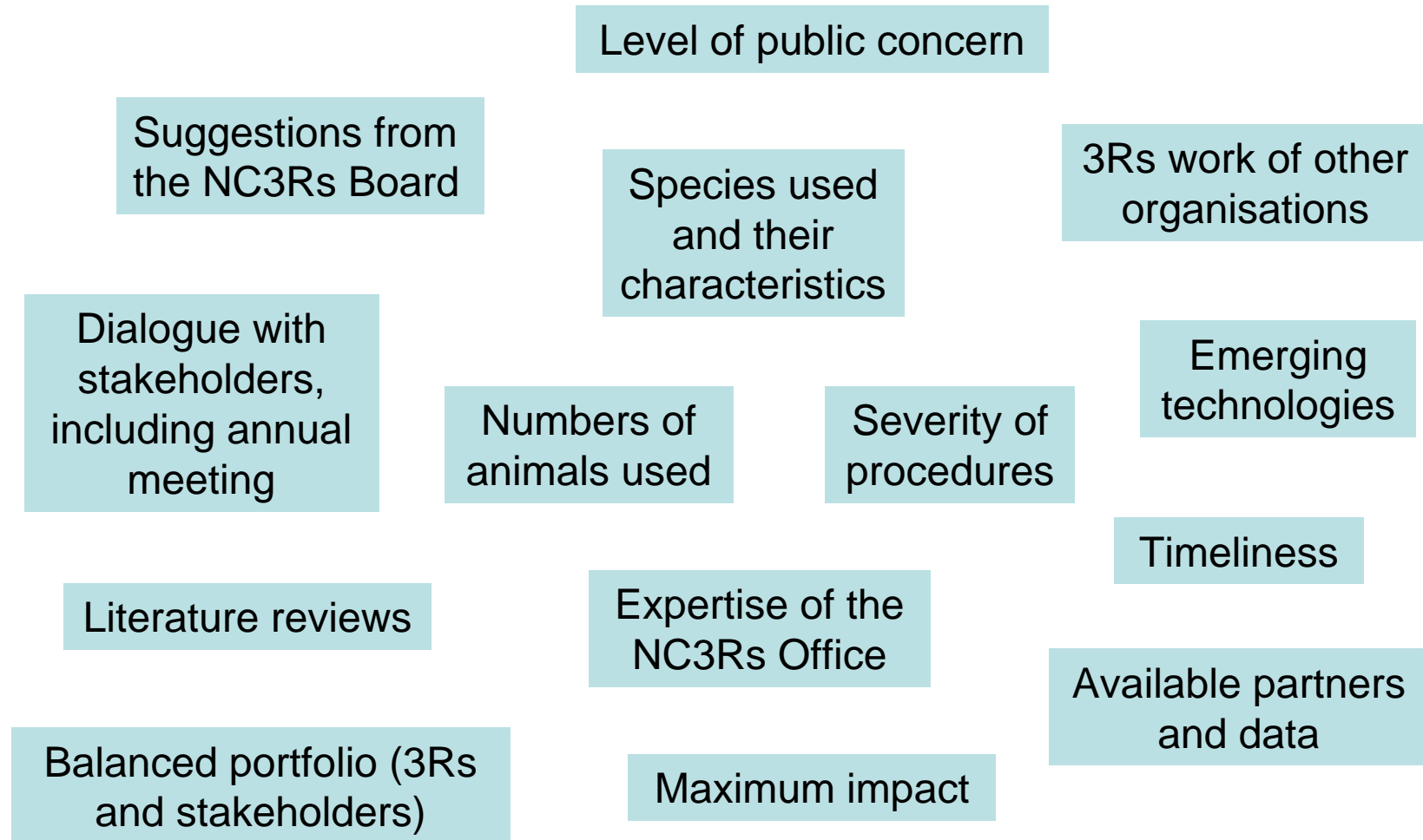


National Centre for the Replacement, Refinement and Reduction of Animals in Research

- Nausea and emesis: complex multi-system reflex; no single target organ or tissue
- Questions about value of animal models, especially for nausea
- Unpleasant studies for animals
- Workshop with 80% of the world's experts to explore alternatives in a scenario where animals can no longer be used



# Priority setting





# Inform and engage

## .....need to maintain interest





National Centre for the Replacement, Refinement and Reduction of Animals in Research

- About NC3Rs
- NC3Rs Publications
- NC3Rs Programmes
- NC3Rs Funding Schemes
- Information Portal

Welcome :: [Home](#)

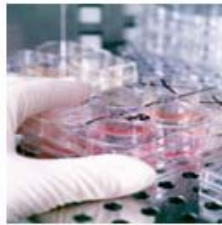
**Events**  
Use the NC3Rs Events Calendar

**Refinement workshop**  
Register for meeting, joint with Wellcome Trust, on refining chronic implants

**Annual Report**  
Key achievements for 2007

**Blood sampling**  
New refinement resource on blood sampling

**Articles**  
Read original articles on the 3Rs



### Engineering tissue alternatives >>

Following on from the successful funding priority in tissue engineering, the NC3Rs and BBSRC are hosting a one day meeting on 30 April 2008 to highlight the potential of tissue engineering as a scientifically robust means to replace animals. The closing date for registration is **4 March 2008**.



### What's new

- NC3Rs seeking new Board Chair**
- Refinement of the use of chronic implants in animal research - a joint NC3Rs / Wellcome Trust workshop**
- NC3Rs e-newsletter - Issue 14** Includes new Annual Report, joint meeting with Biosciences Federation and 3Rs Prizewinner
- A double win – tackling developing world disease and reducing use of animals in research** The winner of the third annual 3Rs Prize is Dr Charlotte Gower
- Use of thousands of animals avoided as test proved redundant** Important step taken to reduce animals used in specific safety test for new medicines



### Information Portal >>

The Information Portal is an area of the website containing annotated links to online databases, websites, journal articles, legislation and other publications. These resources provide information to help you apply the 3Rs and ensure the best possible standards in animal welfare. There are also links for information on funding schemes for 3Rs research.

**Search**

Search by category

- [Submit Link](#)
- [Submit Reference](#)
- [Submit Event](#)
- [Submit Discussion](#)
- [Email NC3Rs](#)

# www.nc3rs.org.uk

# E-newsletter

- Research funding calls and deadlines
- Publications
- New web pages, reports, DVDs, CD-ROMs etc.
- Meetings and symposia
- >800 online subscribers plus many UK networks

If you cannot view this e-mail properly please go to [www.nc3rs.org.uk/news.asp?id=988](http://www.nc3rs.org.uk/news.asp?id=988)



National Centre for the Replacement, Refinement and Reduction of Animals in Research

## NC3Rs e-newsletter - Issue 8

### Showcasing the 3Rs in Parliament



The NC3Rs will be holding a [poster event in Westminster](#) in late February/early March 2007 to showcase the latest examples of 3Rs research for MPs, Peers and other important stakeholders.

A high-profile judging panel will select the best poster from each of the 3Rs and the winners will be presented with prizes of £2k.

Researchers, veterinarians and animal technicians are invited to submit poster abstracts for work that has had a significant impact on the 3Rs by **24 November 2006**.

### IVTS Winter Meeting



[Pulmonary toxicity: are in vitro models a breath of fresh air?](#)

### Joint symposium with Biosciences Federation

The NC3Rs in partnership with the Bioscience Federation's Animal Sciences Group is hosting a one-day symposium on [Science and the 3Rs](#) to highlight the scientific and technological advances which have implications for the 3Rs and how they have facilitated improved scientific data and better animal welfare.

The symposium which is on **14 March 2007** in London is free to all members of learned societies and professional bodies affiliated to the Biosciences Federation.

The closing date for registration is **5 February 2007**.

### 3Rs Prize deadline



[Final call for entries to the 3Rs Prize and a chance to win £10k](#)

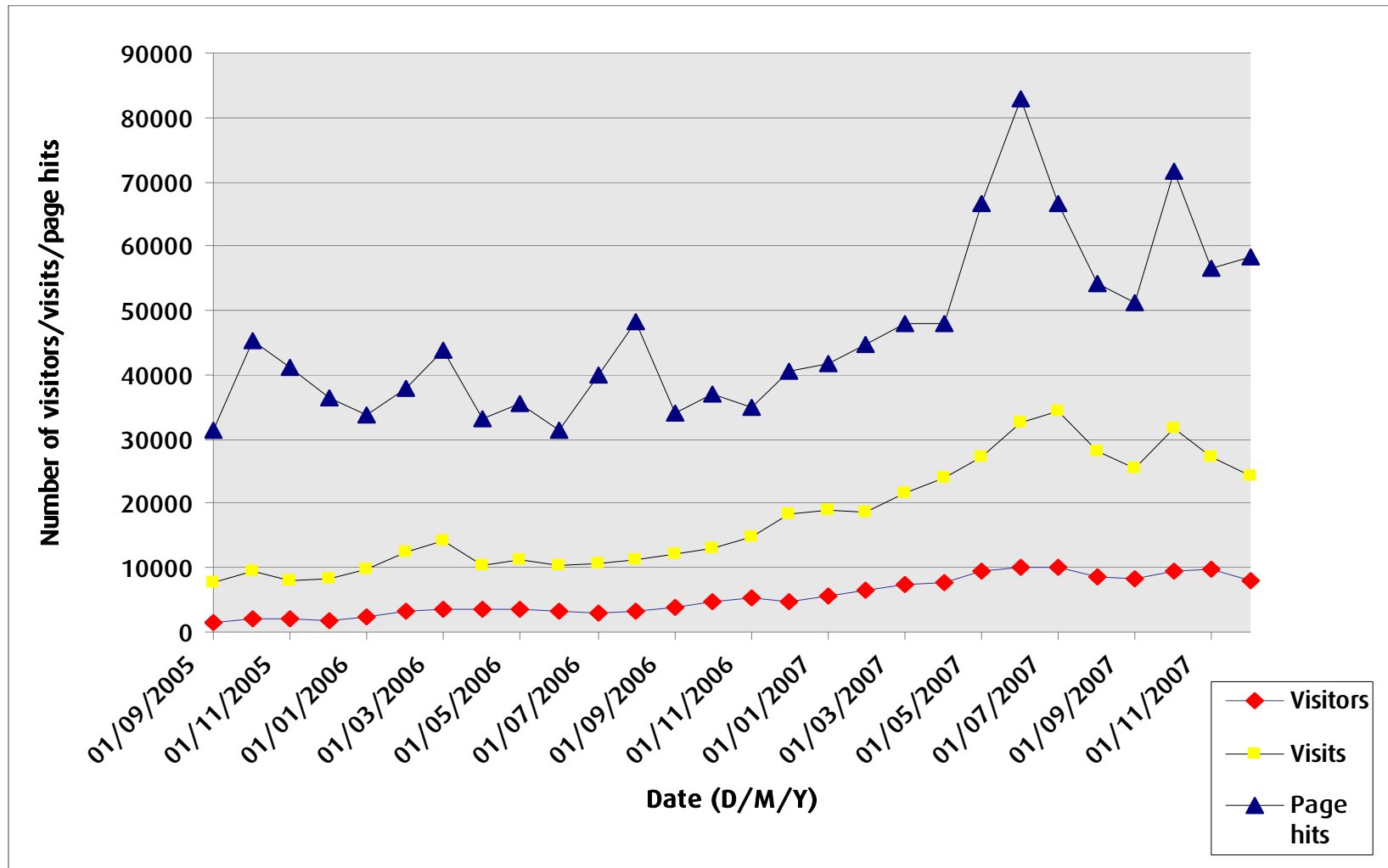
To find out more, go to [www.nc3rs.org.uk](http://www.nc3rs.org.uk)

You have received this newsletter because you may be interested in the contents. You will not receive it again unless you are subscribed. Please pass it on to any colleagues you think may want to subscribe.

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[www.nc3rs.org.uk/subscribe/newsletters](http://www.nc3rs.org.uk/subscribe/newsletters)

# Website statistics





- ☐ 3Rs databases
- ☐ 3Rs research funding
- ☐ Anaesthesia
- ☐ Analgesia
- ☐ Biotelemetry
- ☐ Breeding and supply
- ☐ Dosing and sampling
- ☐ Education and training
- ☐ Ethical review
- ☐ Euthanasia
- ☐ Experimental design/statistics
- ☐ General links
- ☐ Genetic alteration
- ☐ Handling and restraint
- ☐ Housing and husbandry
  - ☐ - Amphibians
  - ☐ - Birds
  - ☐ - Cats
  - ☐ - Dogs
  - ☐ - Farm species
  - ☐ - Ferrets
  - ☐ - Fish
  - ☐ - Non-human primates
  - ☐ - Rabbits
  - ☐ - Reptiles
  - ☐ - Rodents
- ☐ Humane endpoints
- ☐ Imaging
- ☐ Legislation and guidance
- ☐ Mouse databases
- ☐ REACH
- ☐ Safety testing
- ☐ Sourcing of animals
- ☐ Species selection
- ☐ Training animals
- ☐ Transport
- ☐ Welfare assessment



## Information Portal

Information to help you apply the 3Rs and ensure the best possible standards of animal welfare.

The Information Portal is an area of the website containing annotated links to online databases, websites, journal articles, legislation and other publications. These resources provide information to help you apply the 3Rs and ensure the best possible standards in animal welfare. There are also links for further information on funding schemes for 3Rs research.

### How to use the Information Portal

The information in the Portal has been categorised and tiered into thematic pages. These can be accessed using the menu on the left hand side of the screen.

Most pages in the Portal contain descriptive text, setting out key principles for each topic. Clicking on the links below each page heading will take you to further pages which list the resources in our database relevant to that topic.

The resources have been carefully selected by experts for their relevance, quality and utility. They are not intended to represent an exhaustive list of the available information on each topic. You may wish to consult other, more extensive [alternatives databases](#), [websites](#) and search engines for additional information.

### Key resources

The panel on the right hand side of the screen contains links to key websites, online documents, events and discussion groups relevant to each page.

### Submit information to NC3Rs

Dissemination and application of the 3Rs information is a priority for the NC3Rs. If you would like to share knowledge of new advances in the 3Rs, we would be happy to disseminate the information to the scientific community on your behalf via our website. You can submit information resources to the NC3Rs webmaster using the links in the panel on the right hand side of the screen.

### Search

Search by category



Search

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- [General principles](#)
- [Mouse](#)
- [Rat](#)
- [Hamster](#)
- [Guinea pig](#)
- [Rabbit](#)
- [Ferret](#)
- [Dog](#)
- [Pig](#)
- [Marmoset](#)



### Dosing and sampling

[Information Portal page](#)

## Home

This microsite provides information on blood sampling from animals to help laboratory staff choose the most appropriate technique for removal of blood in a humane and efficient manner. The original material was collated by GlaxoSmithKline and donated to the NC3Rs. It has been edited and expanded with assistance from colleagues from the Institute of Animal Technology, academia, industry and animal welfare organisations.

Removal of blood is one of the most common procedures performed on laboratory animals, e.g. -

- for analysis of biochemical, metabolic, toxicological or immunological parameters
- for examination or culture of micro-organisms
- for production of antibodies

Use of a technique appropriate for the purpose and the species, by a trained and competent member of staff, is essential for ensuring that any pain, distress or discomfort is kept to a minimum. Minimisation of such adverse effects is important for scientific as well as ethical and legal reasons, since they can cause biological reactions which may affect the blood sample, and hence the validity of the research results and the number of animals used to achieve the scientific objective.

The microsite contains information on surgical, non-surgical and terminal methods, including removal of blood from veins, arteries, by cannulation, by cardiac puncture and by decapitation, as appropriate for the species. It aims to assist with refinement by -

- Setting out **general principles** for refinement of blood sampling - these should be read first
- Highlighting advantages and disadvantages for most of the available techniques
- Highlighting potential adverse effects and control measures
- Collating references for further reading
- Presenting images and video for training purposes
- Presenting decision trees for **sampling from the mouse** and **sampling from the rat** and information on **safe blood sample volumes**

## Search

Search

## Resources

### Links

DIGIRES (2005), Digital Resources for Veterinary Trainers

[Open Link](#)

### References

A good practice guide to the administration of substances and removal of blood, including routes and volumes.

[Open Link](#)

Biological effects of blood loss: implications for sampling volumes and techniques.

[Open Link](#)

Removal of blood from laboratory animals and birds.

[View PDF \(131KB\)](#)

# Publications

- Guidelines
- Working Group reports
- Journal articles
- Invited articles

December 2005

Animal Technology and Welfare

## Training laboratory-housed non-human primates, part 2: Resources for developing and implementing training programmes

M.J. PRESCOTT,<sup>1</sup> V.A. BOWELL<sup>2</sup> and H.M. BUCHANAN-SMITH<sup>2</sup>

<sup>1</sup>Department of Animals in Research

LA, UK

2:UK

ment; socialisation; training

literature review of primate training developing and implementing a training including resource and personnel

simple training protocol for training used primates to enter a transport box.

duced as part of a set of activities hours and designed to facilitate more systematic, humane and efficient use

professional development course on top, coordinated by the University of advanced skills (strac.uk) and the UK Animal Technology (see Heywood<sup>1</sup> for an v of a previous course on marmoset welfare). The aims of the training

Full report of GA mouse welfare assessment working group for published overview see Wells et al (2006) *Laboratory Animals* 40(2), 111-114

## Assessing the welfare of genetically altered mice

April 2006

Author:  
Jana Hurlst  
Department of Veterinary Clinical Science  
University of Liverpool

Correspondence to:  
Jana Hurlst  
[jane.hurlst@lv.ac.uk](mailto:jane.hurlst@lv.ac.uk)  
[www.liv.ac.uk](http://www.liv.ac.uk)



National Centre for the Replacement, Refinement and Reduction of Animals in Research

### Making sense of scents: reducing aggression and uncontrolled variation in laboratory mice

Available at [www.nc3rs.org.uk](http://www.nc3rs.org.uk)

#### Abstract

Scents are the primary means of communication in mice. They underlie most aspects of their social behaviour and are particularly important in mediating aggressive interactions and status differentiation among males. This competitive aggression can be a major welfare concern and source of uncontrolled variation among laboratory mice. Scents also play an invisible role in priming reproductive physiology and development with additional consequences for immunocompetence, introducing another potential source of uncontrolled variation that could influence many types of experiment. Here, I provide a brief explanation of how wild mice use scents to recognise each other and to control competitive interactions. I then discuss the consequences of this for aggression



The sensory world of mice is quite different from ours. Watch mice for a few minutes and you soon realise that they are largely led by their noses. Their primary



National Centre for the Replacement, Refinement and Reduction of Animals in Research

## NC3Rs Guidelines

Primate accommodation, care and use



# Meetings and symposia

- Annual events –
  - Stakeholder Meeting
  - Primate Welfare Meeting
  - Animal Technicians' Symposium
- Other specialist meetings (2008), e.g -
  - Engineering tissue replacements to animals, 30 April
  - Toxicokinetics and the 3Rs, 29 May
  - Minimising NHP use in mAb development, 26 June
  - Refining the use of chronic implants, 1 October





National Centre for the Replacement, Refinement  
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# Collaboration

.....for sharing data and expertise



# Collaborations

NC3Rs

National Centre for the Replacement, Refinement  
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BIOSCIENCES FEDERATION



syngenta



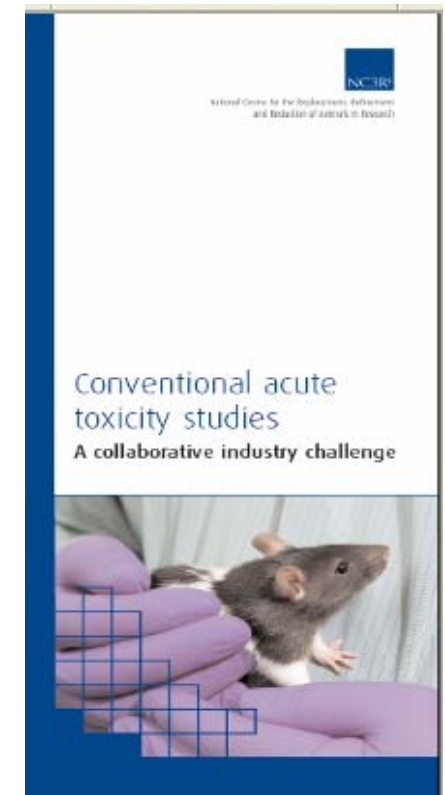
wellcome trust

# Conventional rodent acute toxicity studies

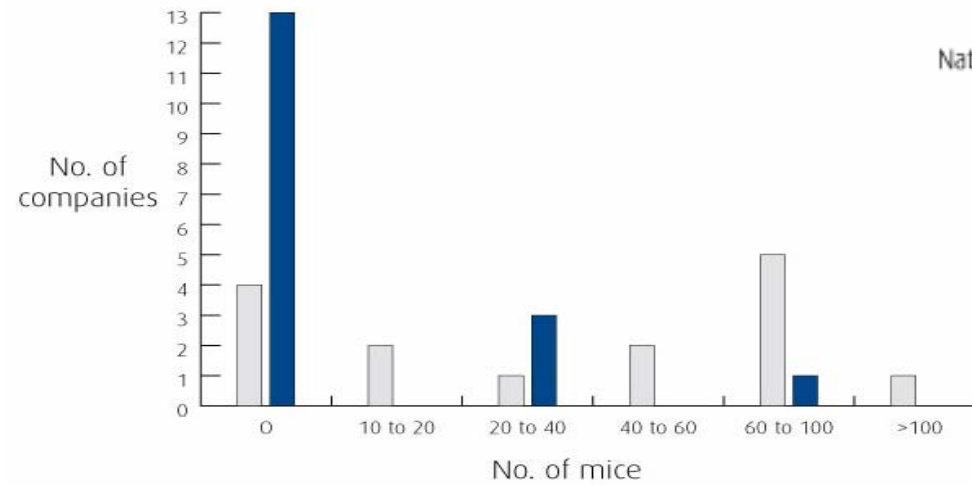


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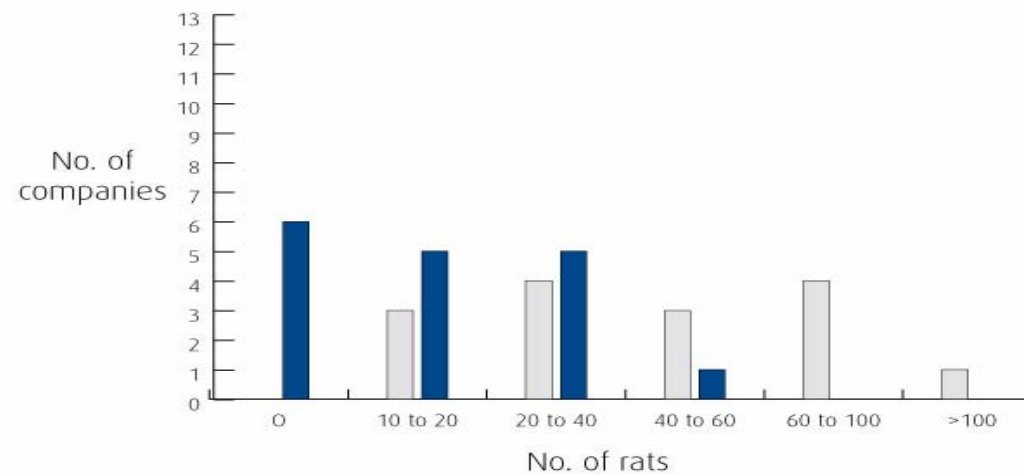
- Joint initiative 15 European Pharma companies and CROs
- Evidence-based approach to question value of these tests
- Data sharing has led to significant reduction in the standard package and number of rodents used
- Recommend no acute toxicity studies prior to FTIM
- International workshop in Nov 2006 with EMEA, MHRA, FDA and JPMA coinciding with review of ICHM3
- Regulatory support for recommendations
- Collaboration with Lyon Poison Centre to assess value of acute toxicity data in supporting overdose in man



**3a** No. of mice used per compound in each company



**3b** No. of rats used per compound in each company



**Figures 3a and 3b** show the downward shift in number of rodents used per project in each company between 2003-2005 and 2007.





National Centre for the Replacement, Refinement  
and Reduction of Animals in Research

# Influence

.....decision makers





## Working with funders

- Review all grant, fellowship and studentship applications involving primates, dogs, cats and horses
- Joint research priorities e.g. BBSRC
- Joint meetings, e.g. Wellcome Trust
- Guidelines, e.g. primates, vertebrates



Responsibility in the use  
of animals in bioscience research:  
Expectations of the major research council and  
charitable funding bodies





National Centre for the Replacement, Refinement  
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# People

.....pick the right team





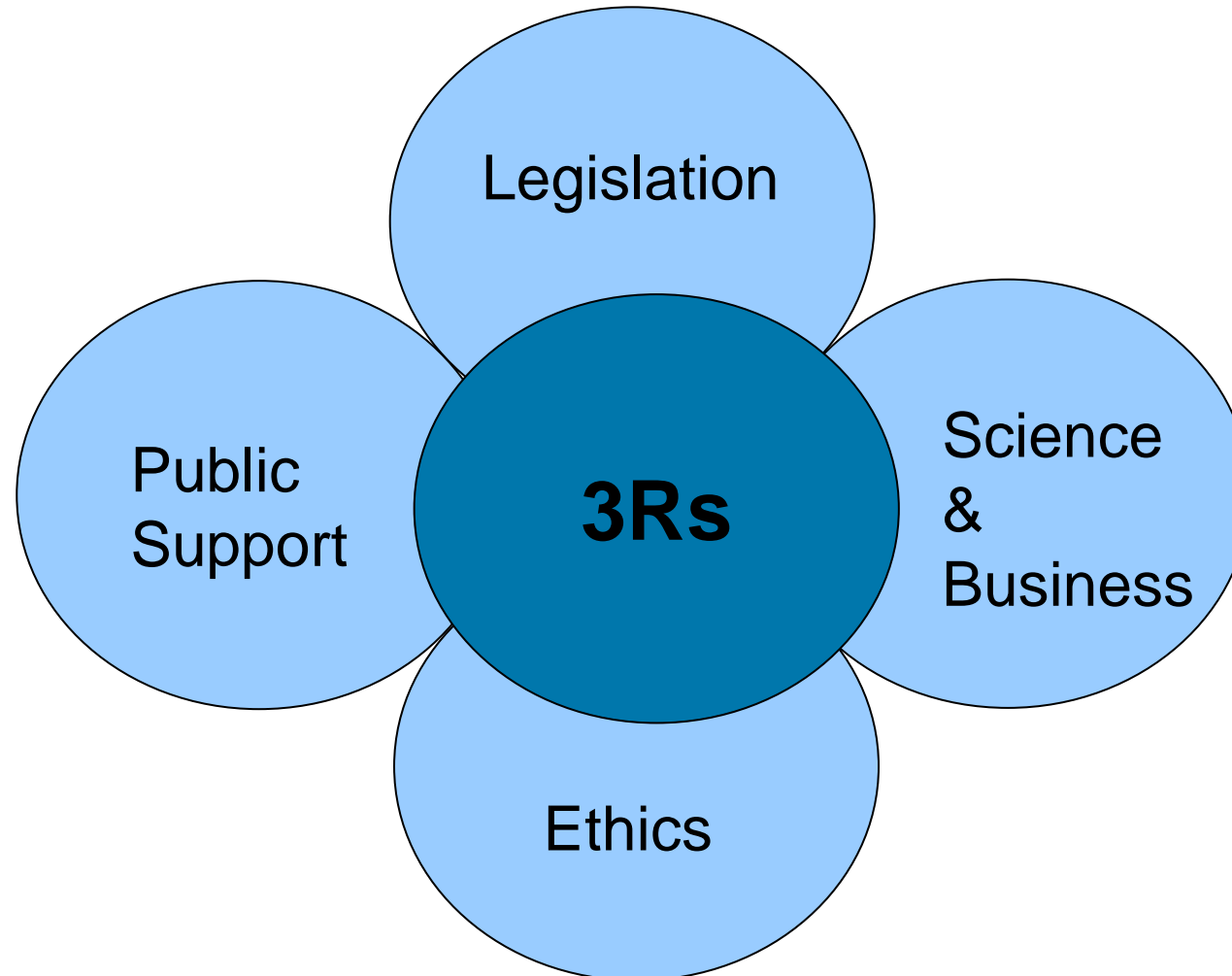
National Centre for the Replacement, Refinement  
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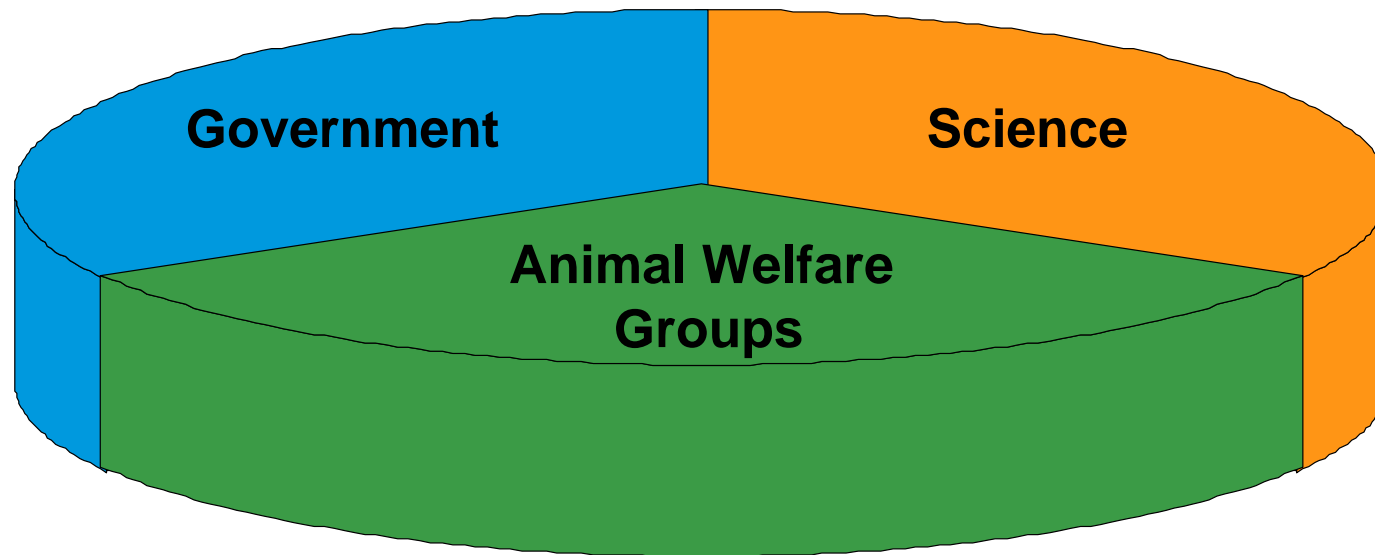
# Successes

- Established NC3Rs as a scientific organisation with a comprehensive portfolio of research projects and activities
- Engaged all stakeholders
- Taken a collaborative approach, acting as an ‘honest broker’
- Raised the profile of the 3Rs as an important scientific output
- Increased investment and effort in the 3Rs across all sectors
- Produced ‘output’
- Begun to deliver real progress on the ground (outcomes)

# Importance of the 3Rs



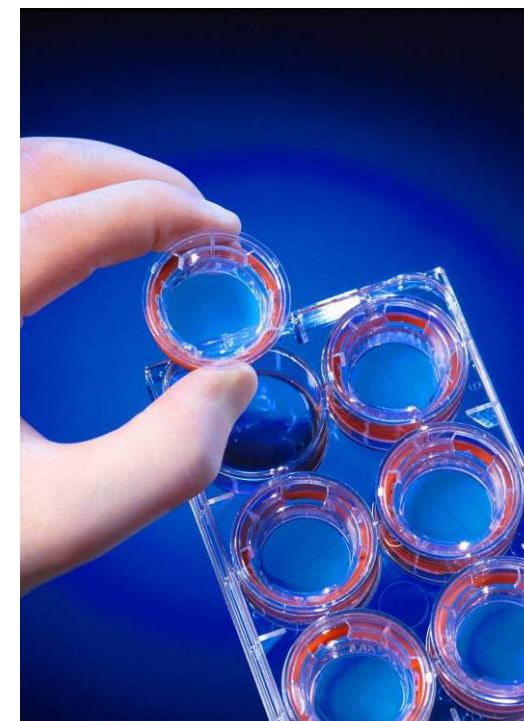
# The complete picture



## NC3Rs press release

“Government is committed to finding alternatives to animal research, as I am personally committed to championing research into replacements for animals.”

Ian Pearson MP,  
Minister for Science & Innovation  
19 September 2007





National Centre for the Replacement, Refinement  
and Reduction of Animals in Research

# Thank you!

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