NC3Rs

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

Collaboration and Innovation

Annual Report 2007

Contents

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Foreword

The last 12 months have seen the NC3Rs launch a number of new and exciting activities and continue to build on those already established. Clear outcomes are emerging from the work the Centre has been doing to raise the profile of the 3Rs and, importantly, also from the research that it funds in universities and companies. None of this would be possible without the impressive range of partnerships that the NC3Rs has forged with individuals and organisations across the biosciences sector. A number of new collaborations were established in 2007, including the launch of an annual symposium on the 3Rs with the Biosciences Federation Animal Science Group, which represents over 40 of the UK's learned societies and other professional bodies.

The Centre is often scrutinised in terms of the funding it attracts and invests. For example, this year has seen an increasing number of parliamentary questions on the NC3Rs. Having funding to invest in 3Rs activities and research is critical if we are to continue to progress our objective of using the 3Rs to support science and innovation. This year our research budget was not sufficient to support all of the grant applications we wished to, and with the additional generous support of the MRC, the BBSRC and the Wellcome Trust, we were able to increase our investment in high quality 3Rs research.

It is clear that our income must increase if we are to continue to position the 3Rs within the mainstream of the life sciences, and we are delighted with the settlement from the recent comprehensive spending review, which is a strong endorsement by the Government of the work we have been doing. However, it is not just about money. We should not forget the time, effort and resources that many individuals and organisations freely give to NC3Rs working groups, workshops and symposia. There are over 220 individuals, not only from the UK, but also from elsewhere in Europe, and the USA, involved in providing expertise to our working groups. This support is absolutely invaluable if we are to achieve progress in the 3Rs.

During 2007, the NC3Rs staff has expanded to meet the increased workload and new priority areas, including an exciting programme in partnership with the chemical industry. There are now seven scientific staff and a business team of six. It is impossible to include in the annual report the vast amount the staff does, particularly in terms of their ambassadorial work for the NC3Rs in the UK and elsewhere. Without their dedication, enthusiasm and expertise, the NC3Rs would not have the credibility and status that it has achieved within a relatively short period of time. The team are supported by a Board which provides excellent input and oversees the development of a comprehensive range of activities. This year, saw Leslie Turnberg step down as the NC3Rs Board Chairman. Leslie was an outstanding chairman and we would like to take this opportunity to thank him for his stewardship of the NC3Rs.

It is now three years since the NC3Rs was established. We believe the Centre has begun to change the perception of the 3Rs, but it is clear that there is much more to be done if they are to be positioned at the heart of the life sciences. The NC3Rs has generated considerable interest and support for the 3Rs, and as we move forward continued goodwill from our partners will be essential.

Paul Flecknell
Acting Chairman

Vicky Robinson
Chief Executive

Key successes in 2007

- Increased funding for 3Rs research, with £2.4 million invested in 11 grants, £1 million more than in 2006
- Doubling of the NC3Rs income from Government to £5 million per annum by 2010/11
- Developing a programme of initiatives with the chemical industry
- New collaboration with the BBSRC on tissue engineering
- First NC3Rs event at Westminster for parliamentarians
- Launch of annual symposium with the Biosciences Federation Animal Science Group

An evolving strategy

The NC3Rs was established by the Government in 2004 to translate, strategically and operationally, its commitment to the 3Rs in facilitating high quality, humane science. The Centre is primarily funded by Government and in addition has funding from industry and the charitable sector. Reporting to the Department for Innovation, Universities and Skills (DIUS), the NC3Rs is an independent scientific organisation which has a non-executive Board, an expert staff, and a wide range of stakeholders. These include scientists, vets and animal care staff in academia and industry, Government and parliamentarians, regulators, research funders, animal welfare organisations, the media, and the general public. Since its launch, the Centre's key objective has been to stimulate awareness and activity in the 3Rs by providing increased investment, resources and opportunity. A broad programme of initiatives has been developed encompassing all three Rs.

Since the 1970s the number of animals used in scientific procedures in the UK has steadily declined to approximately three million animals per annum. Recently, this trend has started to reverse and the number of animals used is likely to rise substantially over the next decade as the use of genetically modified mice continues to increase. Although the 3Rs are a legal requirement there has traditionally been inertia in some sectors. Many organisations, including research funders, learned societies and journals, have policy statements supporting the 3Rs. In practice, however, there have been limited resources for, or recognition of, 3Rs research, such that it has largely been considered to be a satellite activity attracting relatively little direct investment or attention from researchers. In addition, much of the discussion around the use of animals has been focused on the activities of animal rights extremists, diverting attention away from the real progress that can be made through the 3Rs.

The NC3Rs, with its extensive links with the research community, including funders, industry and academia, learned societies, and regulators, has rapidly established itself as an authoritative scientific organisation and is driving the 3Rs within the UK. Positioning the 3Rs within the mainstream of the biosciences is critical to the Centre's mission and strategy, and work has been directed towards changing the perception of the 3Rs with targeted resources, funding, and collaboration.

There are ongoing challenges to the 3Rs from scientific and regulatory pressures. These include the increased use of genetically modified animals and the introduction of new chemicals legislation (REACH) in the EU, which will have a significant impact on the use of animals. Conversely, the Cosmetics Directive (2003/15/EC) will come into force banning the testing of cosmetics using animals in the EU. The revised Directive 86/609/EEC is also likely to place greater emphasis on animal welfare and the use of alternatives. In all scenarios, the 3Rs provide a framework for innovation and the development of new technologies and paradigms for science, risk assessment, and regulatory change. The NC3Rs, with its strong science focus and links, is well positioned to lead the UK's 3Rs efforts.

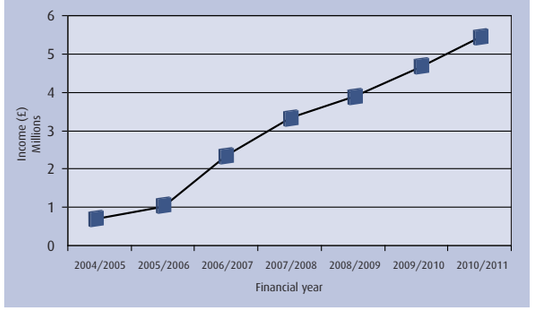
Doubling of Government funding for the NC3Rs

Most of the funding for the NC3Rs comes from the DIUS via the Medical Research Council (MRC) and the Biotechnology and Biological Sciences Research Council (BBSRC). This year the NC3Rs submitted a business plan for increased funding as part of the Government's comprehensive spending review. In December 2007, Ian Pearson MP, Minister of State for Science and Innovation, announced that Government funding of the NC3Rs will more than double by 2011. The Centre currently receives just over £2 million per year which will increase to £5 million in 2010/11.

This additional funding gives a significant boost to the NC3Rs. The extra funding will allow the Centre to broaden its outreach in the scientific community and to fund more high quality research, investigate other types of research funding opportunities such as studentships, and to continue to expand its extensive programme of work to stimulate and promote the 3Rs.

	2007/08	2008/09	2009/10	2010/11
MRC	£1,815,000	£2,640,000	£3,240,000	£3,840,000
BBSRC	£553,000	£828,000	£1,028,000	£1,228,000

Total income: Past, present and future



Investing in 3Rs research

Developing and investing in the 3Rs requires sustained investment in research. The NC3Rs has two routes for supporting research – its main funding scheme and the Small Awards Scheme.

3Rs research funding scheme

Supporting and encouraging the scientific community to conduct high quality 3Rs research is the foundation of the Centre's drive to develop scientific and technological solutions to replace, reduce and refine the use of animals. Importantly, it is also key to the Centre's strategy of demonstrating the advantages of the 3Rs in improving science and animal welfare by funding work that will provide clear examples to inspire others and stimulate new approaches.

Research portfolio

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

In 2007, the NC3Rs awarded 11 grants *(see Grants for 2007)* totalling £2.4 million, which was an increase of £1 million on the previous year. Awards to groups considered to be leaders in their field illustrate that the Centre's strategy to bring the 3Rs into the mainstream is working. This year, the number of applications that the Centre identified for funding exceeded its research budget and increased contributions from the MRC, the BBSRC and the Wellcome Trust made up the shortfall.

The number of grants and amount invested has increased every year. This year, 21% of applications received were funded which is consistent with the success rate of the major research funding bodies. In addition to 'response mode' funding, for the first time in 2007 the NC3Rs also identified two priority areas for investment – tissue engineering for replacing animal use, run jointly with the BBSRC, and refining procedures which cause substantial suffering. Four awards were made in the tissue engineering priority area and three in the refining procedures of substantial suffering priority area.

Some of the research projects the NC3Rs has funded in previous years are now producing results and publications[1,2] with important implications for the 3Rs. In October 2007, the Centre held its first meeting of grant holders to discuss how the NC3Rs can help ensure the output of the research it funds is disseminated, and implemented, as widely as possible.

[1] Brito-Martins M, Harding SE, Ali NN. b^1- and b^2AR responses in cardiomyocytes derived from human embryonic stem cells: comparison with failing and non-failing adult human heart. British Journal of Pharmacology 2007, In press

[2] Tymvios C, Jones S, Moore C, Pitchford SC, Page CP, Emerson M. Real-time measurement of non-lethal platelet thromboembolic responses in the anaesthetized mouse. Thrombosis and Haemostasis 2008, In press

Grants for 2007

The following eleven research projects were funded by the NC3Rs in 2007.

Dr N G Coldham, Veterinary Laboratories Agency (£181,072)
Replacement of hamsters with physicochemical analytical methods for *Leptospira* vaccine batch potency testing

Professor D E Davies, University of Southampton (£299,875)
Modelling the human asthmatic airway by tissue engineering

Professor J A Davies, University of Edinburgh (£364,044)
A tissue engineering approach to reduce animal use in renal development and renal organ replacement technology

Dr T Friedberg, University of Dundee (£323,624)
Metabolically competent stem cell systems: novel means to implement 3Rs in better drug safety assessment

Dr A J Grierson, University of Sheffield (£164,760)
Refinement of therapeutic intervention in a mouse model of amyotrophic lateral sclerosis

Dr M Guille, University of Portsmouth (£59,208)
Non-invasive identification of individual *Xenopus* by photography and image processing

Dr W Hope, University of Manchester (£210,664)
An *in vitro* model of the human alveolus to predict the efficacy of systemic antifungal therapy

Dr P Jones, Hutchison/MRC Research Centre (£235,096)
Reduction, refinement and replacement of animal use by clonal sampling

Professor P M Jones, King's College London (£387,732)
Pseudoislets as a model system to study beta cell dysfunction in diabetes

Dr A MacNicoll, Central Science Laboratory (£63,780)
Humane endpoints for rodenticide testing

Dr G Woodhall, Aston University (£152,048)
Development of a reduced severity rat epilepsy model

Small Awards 2007

The NC3Rs runs an awards scheme in partnership with the Laboratory Animal Science Association (LASA) to support small-scale research projects, exchange visits, training and continuing professional development for researchers and animal technicians. In 2007, there were a total of 28 applications and, after assessment by an expert panel, 15 applications were each awarded up to £2k.

Amongst the applications funded were a workshop on implementing the 3Rs in wildlife research, and a project to support the development of a human colonic tissue culture model to investigate bowel diseases. The full list of awards can be found at www.nc3rs.org.uk/fundedsmallawards

Identification of individual frogs by photography and image processing

Dr Matt Guille, University of Portsmouth

Over 10,000 *Xenopus* frogs are used in the UK each year, often to produce eggs and embryos to study how cells divide and differentiate. The aim of this project is to find a more humane way of identifying individual frogs. Currently, techniques such as toe clipping, threading tags through the skin and implanting microchips are used, but these are all invasive and harmful to the animals.

Preliminary data suggest that individual frogs can be identified using a computerised digital imaging system. The patterns on the backs of the animals and the vein patterns on their feet are distinctive and can be measured. The researchers will develop a system to image these patterns and will determine whether a single measurement or a combination of measurements is necessary to identify individual frogs and whether the markings change over time.

Implications for the 3Rs
An automated imaging system for identifying the frogs will be a refinement over the current identification techniques and reduce the level of suffering experienced by the animals.

Tissue engineering to minimise animal use in kidney disease research

Professor Jamie Davies, University of Edinburgh

Kidney disease is a major cause of human suffering, with approximately 40,000 people in the UK seriously affected each year. An estimated 15,000 mice are used annually in the UK for research into kidney regeneration and transplantation.

This research will focus on developing different types of cell lines which can generate the component parts of a kidney and these will then be used in combination to try to create a whole kidney. The cultured organ will then be used to gain a better understanding of normal kidney development to aid the search for treatments for kidney disease.

Implications for the 3Rs
Developing these cell lines has the potential to not only largely replace the use of animals in this type of research, but also to provide a system in which doing experiments is much quicker, easier and cheaper.

Humane endpoints for rodenticide testing

Dr Alan MacNicoll, Central Science Laboratory

Rodenticides are a category of pest control chemical intended to kill rodents and they are tested on rodents to see if they are effective. This project aims to identify biological markers from blood, faeces, and urine, which can be used in testing to predict whether a rodent will die before the onset of suffering rather than waiting for death to occur.

With all anticoagulant rodenticides there is a lag-time of 4-6 days from ingestion of the rodenticide-impregnated bait, to death. The behaviour of the rats will be observed before and after the poison is given to them. Corticosteroid levels will be monitored as an indicator of stress and a range of vitamin K-dependent blood clotting proteins will be measured. Other techniques will be used to identify changes in the biochemistry of blood, faeces and urine. The results will then be used to identify which factors can be monitored, preferably using non-invasive procedures, to predict death and survival of rats after exposure to anticoagulant rodenticides.

Implications for the 3Rs
Being able to humanely kill the animals instead of waiting for death to occur will significantly refine a procedure of substantial severity so that the animals used experience less suffering.

Modelling the human asthmatic airway by tissue engineering

Professor Donna Davies, University of Southampton

Asthma affects 1 in 5 children and 1 in 10 adults in the UK and even though animal models of asthma are routinely used, very few new treatments have been developed since the 1960s. In this project, a model of human airway cells grown in culture will be used to mimic the asthmatic pathway, potentially replacing current animal models.

One disadvantage of animal models is that they fail to reproduce the interplay between the environmental and genetic factors that cause human asthma. This project will use cells taken from the airways of human volunteers with asthma. The cells will be used to develop a human tissue-based model that will retain important genetic aspects of asthma and can be used to develop new treatments. The models will enable several different types of cells to be studied, including epithelial cells that are known to respond abnormally to the common cold virus in people with asthma.

Implication for the 3Rs
This model of the asthmatic airway has the potential to replace the use of animals in developing and testing new treatments for asthma.

Communicating and promoting the 3Rs

Part of the Centre's mission is to raise awareness and promote the implementation of the 3Rs by providing contemporary and comprehensive information. In September 2005, the NC3Rs launched its website (www.nc3rs.org.uk) which provides access to a wide range of information including online databases and other useful resources. The audience for the website has grown steadily over the last two years, and this reflects not only the growing content on the site but also the increasing profile of the NC3Rs. New website content, as well as information about events and funding schemes, is promoted via the Centre's electronic newsletter. This has 800 direct subscribers but it is widely distributed internally at many establishments and via other specialist email lists to further increase the readership.

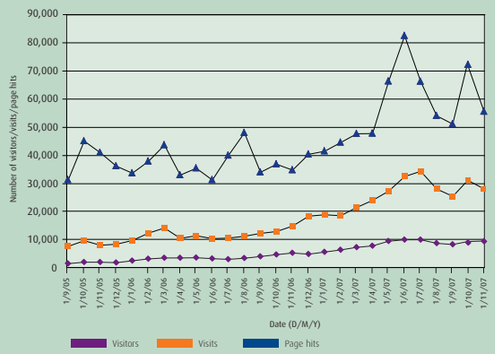
Access to existing 3Rs information alone is not sufficient as the information needs to be reviewed and collated into useful and authoritative resources which provide the details necessary to ensure the 3Rs are put into practice. To facilitate this, the NC3Rs also develops guidelines, organises workshops and working groups, and hosts symposia.

The Centre's workshops and symposia provide a unique formula in that they bring together a wide range of expertise. The annual primate welfare meeting is an excellent example of this, providing a forum for scientists, vets and animal technicians from different establishments to meet to discuss issues of common interest or concern.

In 2007, the primate welfare meeting focused on housing and husbandry and attracted 120 delegates from 34 establishments. The annual animal technicians' symposium, which this year was sponsored by AstraZeneca, also continued to be popular – attracting 118 delegates from 37 establishments.

In addition to the Centre's established events, 2007 also saw the first joint meeting on *Science and the 3Rs* with the Biosciences Federation Animal Science Group, which represents over 40 learned societies and professional bodies. This proved to be a popular event with 138 delegates, many new to the NC3Rs.

Website Statistics Sept 05 – Nov 07



Winning posters

Possible alternative in inhalation toxicology

Tracy Hughes and Kelly BéruBé, University of Cardiff

A model of the human lung has been developed using respiratory cells from the surface lining of a normal human lung. The cells, grown in layers to form a 3D structure, have the same characteristics and function as the airway lining found naturally in the human body. This model can be used to identify early signs of damage to the lung caused by inhaled particles, and can potentially replace animals in inhalation toxicology testing.

A novel refined oral dosing method

Claire Rourke and Darrel Pemberton, GlaxoSmithKline

Testing new drugs often involves administering the drug orally to rodents by manually restraining the animal and inserting a narrow tube into the oesophagus to deliver the drug directly into the stomach (gavage method). This method can cause the animals stress and, occasionally, injury. In this study, rats were trained to drink from a syringe instead. The syringe contained either a sugar solution or a sugar solution containing the drug donepezil, used to treat Alzheimer's disease. After six days training, the rats drank both solutions faster by syringe compared with the gavage method. This new approach refines the oral dosing procedure by reducing restraint-induced stress and possible oesophageal injury.

Identifying cancer-causing chemicals

Richard Walmsley and Nick Billinton, Gentronix
Paul Hastwell, GlaxoSmithKline

Cancer can arise due to chromosome damage caused by some chemicals (genotoxins). All chemicals are therefore tested for genotoxicity. Current tests are often inaccurate and can result in the incorrect classification of safe chemicals as potentially cancer-causing. A new test using a human cell line that fluoresces when exposed to genotoxic chemicals has been used to test over 150 compounds and is 95% accurate in identifying those chemicals which are truly toxic. Currently, chemicals that have incorrectly been classified using the old tests require further animal testing to confirm the result; this new, more accurate, test could therefore reduce animal use.

Showcasing the 3Rs

MPs are frequently asked by their constituents about the use of animals in research, so it is important that they are aware of the work of the NC3Rs. With this in mind, the NC3Rs held an event at Portcullis House in Westminster in February 2007 called *Showcasing the 3Rs*, which was hosted by Phil Willis MP, chair of the House of Commons Science and Technology Committee.

Over 40 posters of 3Rs research carried out in UK establishments were on display and MPs and other parliamentarians were invited to talk to the researchers. There was also a judging panel which selected three winning posters – one for each 'R'. The event was sponsored by the Association of the British Pharmaceutical Industry (ABPI) and the Wellcome Trust and the winners *(see Winning posters)* received prizes of £2k each.

Identifying and driving 3Rs priorities

The NC3Rs has continued to focus on engaging and collaborating with the scientific community, in universities and industry, on a wide range of issues relating to the 3Rs. The Centre has 30 different initiatives, including 20 working groups with over 220 members.

Working with the chemical industry

This year the NC3Rs has been working with the chemical industry to develop a programme of 3Rs initiatives. The majority of the animals used by the chemical industry, in the UK and globally, are required to satisfy the regulations that ensure the safety of substances and products. This regulatory use of animals is anticipated to increase over coming years, particularly in response to REACH *(see REACH and the 3Rs)*.

To strategically advance the 3Rs in the industry, the NC3Rs has established a Regulatory Toxicology Forum. The forum brings together established and respected toxicologists from industry, academia and the UK chemical regulatory authorities to identify needs and priorities for implementing the 3Rs in this area. A key goal of the forum is to identify opportunities to promote basic research, but also to bridge the gap between scientific advance and regulatory change in order to achieve regulatory acceptance. In the regulatory arena, worldwide acceptance of new methods or strategies is essential and so the forum also aims to provide a strong, co-ordinated UK voice on the international stage. A number of priority areas have been identified by the forum and are currently being progressed.

REACH and the 3Rs

Increased animal use in chemicals testing

The EU-wide REACH (**R**egistration, **E**valuation, **A**uthorisation and restriction of **Ch**emicals) regulation entered into force in June 2007. Under REACH the safety of an estimated 30,000 chemical substances will be evaluated over a span of ten years. The new regulation is the most comprehensive legislation of its kind globally and provides a common platform for assessing the safety of chemicals in the EU.

The comprehensive nature of the legislation provides significant benefit in terms of protecting human health and the environment. However, it is estimated that 6-12 million animals will be required to satisfy the requirements of REACH, so the legislation also presents significant challenges for the 3Rs. Alternative methods and approaches including adapting data requirements are encouraged under REACH and, in addition, data sharing is mandatory for vertebrate studies. Implementation and acceptance of such alternative approaches in practice is as yet unknown and this is an area that the NC3Rs is actively seeking to address through some of the projects initiated under the Regulatory Toxicology Forum.

A success story

Reducing animal use in the single dose acute toxicity test

Approximately 15,000 rodents per year are no longer used for testing new medicines following a collaboration involving 18 European pharmaceutical companies and contract research organisations and the NC3Rs.

The initiative, which involved inter-company data sharing on animal numbers and study design, looked at the use of the single dose acute toxicity test in rodents. The test, currently required for safety testing new pharmaceuticals, has traditionally been conducted prior to the first clinical trial in humans and has been used to identify the dose of a pharmaceutical drug that causes major toxic effects. It is the only test used in pharmaceutical development where lethality is a defined endpoint.

By sharing data it was shown that the single dose acute toxicity test was redundant in assessing the risk to humans. The information required could be provided by the results of other, less harmful, animal tests already being carried out as part of the drug development process.

There has already been a reduction of more than 70% in animal use in acute toxicity tests by the companies involved and there is even greater potential for reducing animal use for the test worldwide. The next step will be to revise the regulatory requirement for the test, and the data provided by this industry-NC3Rs collaboration is being considered as part of a wider review of the international guidelines on toxicity testing which is currently underway.

The outcome of the initiative was recently accepted for publication in the journal *Regulatory Toxicology and Pharmacology*.[3]

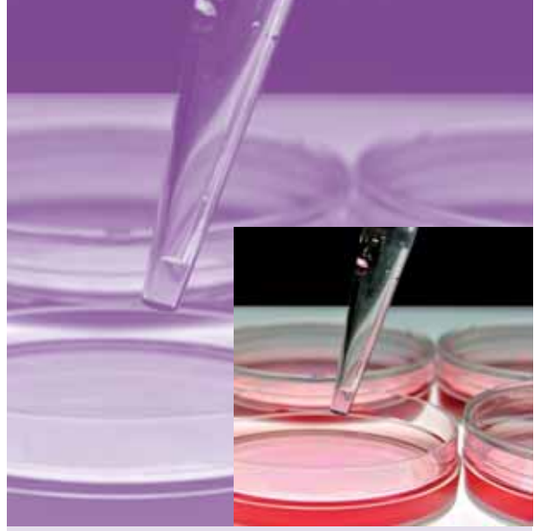
[3] Robinson S et al. A European pharmaceutical company initiative challenging the regulatory requirement for acute toxicity studies in pharmaceutical drug development. Regulatory Toxicology and Pharmacology 2008, In press

Nausea and emesis – an intellectual challenge

In 2007, the NC3Rs embarked on an ambitious and exciting project to review the use of animals in nausea and emesis research. This field provides an excellent test case to approach the problem of replacing the use of animals because it involves a multi-system reflex with no single target tissue or organ. Animal models of multi-system reflexes have always been considered difficult to replace and as such they are often overlooked when identifying 3Rs priorities.

Nausea and emesis can occur as a result of many stimuli ranging from toxic substances in the gut or blood stream, and nervous responses such as fear, to disturbances in the part of the ear related to balance. Multiple interacting systems, from the gut to the brain, are therefore involved.

A wide variety of mammalian species have been used to study nausea and emesis, including cats, dogs, primates and ferrets. Rats are the species most commonly used in nausea



and emesis research, but they are of limited use because they do not have an emetic reflex.

Working with leaders from the field, the NC3Rs hosted a workshop in July 2007 to discuss opportunities for replacement in nausea and emesis research. The aim of the workshop was to stimulate discussion on obstacles to replacement and potential solutions. The workshop attracted 30 delegates from academia, industry, regulatory authorities and funding bodies. A review of the meeting, including recommendations for research priorities, will be submitted for publication in a peer-reviewed journal.

Importantly, because some of the components of the reflex for emesis occur in other reflexes, such as coughing and gastro-eosophageal reflux disease, this initiative may also have implications for the 3Rs in other areas.

Replacement potential for tissue engineering

Tissue engineering and stem cell technologies have the potential to reduce and replace the use of animals in many areas of research and testing. Tissue engineered products are designed to replicate specific types of living tissue in order to replace dead, diseased or non-functional tissue in patients. These products also have increasing scope to replace animals in basic research and toxicity testing, where the use of living tissue behaving as it would *in vivo*, is essential.

To exploit the potential for tissue engineering in the 3Rs, the NC3Rs, in collaboration with the BBSRC, identified tissue engineering as a priority area for funding this year (see page 5). Together with the BBSRC, the NC3Rs has organised a multi-disciplinary meeting to be held in April 2008 to highlight how tissue engineering can be used to provide scientifically robust and relevant alternatives to animal models. This will be a catalyst for future projects within this area that will stimulate collaboration and drive forward the use of tissue engineering in basic research and safety testing.

Working with the major research funders

During 2007 the NC3Rs continued to work closely with the MRC, the BBSRC and the Wellcome Trust on issues relating to the review of grant applications involving the use of animals. The NC3Rs currently reviews all grant applications involving primates, dogs, cats or horses, and advises on 3Rs issues. To date the Centre has reviewed 100 grant applications for these funding bodies.

The Centre has also taken the lead in producing a policy document with the MRC, the BBSRC and the Wellcome Trust, which sets out expectations for animal use and care, and the implementation of the 3Rs. This document will be published in 2008 following consultation with the scientific community, regulators and animal welfare groups.

The use of non-human primates in drug discovery and development

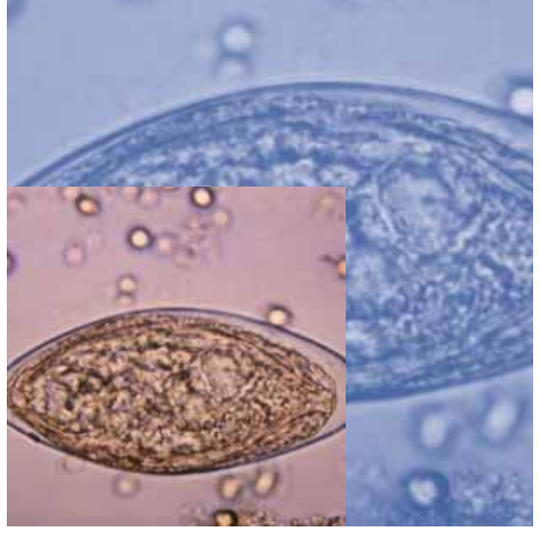
The NC3Rs and the ABPI have continued to work in partnership on an ambitious programme to review the opportunities to replace and reduce non-human primate (herein referred to as primates) use in drug discovery and development with particular emphasis on pharmacokinetics, abuse potential and monoclonal antibodies. A major key to the success of this initiative has been the ability of the NC3Rs to provide an objective environment for data sharing and open discussion about animal research, and a novel approach to engaging the pharmaceutical and biotechnology industries.

In February 2007, the output of an international NC3Rs workshop on designing a pathway for developing monoclonal antibodies without the use of primates was published in *Nature Reviews Drug Discovery*.[4] A cross-industry working group led by the NC3Rs has now been established to validate the pathway. Involving international regulatory authorities and 15 pharmaceutical and biotechnology companies from the UK, elsewhere in Europe, and the USA, the working group has collected data on 120 monoclonal antibodies and is now focusing on opportunities to reduce primate use in reproductive toxicology studies and the use of surrogate antibodies in rodents.

The NC3Rs continues to progress initiatives to reduce the use of primates in abuse potential and pharmacokinetics studies for drug candidate selection. In collaboration with Pfizer, the Centre has participated in a review of self-administration data for 80 compounds in order to assess whether the rodent is as predictive as the primate for determining abuse potential. This extensive review has been submitted for publication in a peer reviewed journal.

A number of approaches are available to predict human pharmacokinetics when selecting the most promising drug candidates and, together with an expert working group, the NC3Rs is exploring whether or not *in vitro* methodologies can be used to replace the use of primates (and other species). The NC3Rs has commissioned a study to directly compare *in vitro* and *in vivo* data collected from 50 compounds and the results will be published in 2008.

[4] Chapman K, Pullen N, Graham M, Ragan I. Preclinical safety testing of monoclonal antibodies: the significance of species relevance. Nature Reviews Drugs Discovery 2007, 6(2):120-6



3Rs Prize Winners for 2007

Dr Charlotte Gower from Imperial College London was awarded the GlaxoSmithKline-sponsored 3Rs prize for 2007. Dr Gower was awarded the prize for her paper describing a replacement system for studying the parasite which causes the tropical disease schistosomiasis (bilharzia), a serious human and animal disease caused by parasitic flat worms (schistosomes).[5]

The natural lifecycle of the parasite involves both snail and mammalian hosts, with transmission between the two hosts occurring via a larval form in infested freshwater. Little is known about how the genetic and strain variations of the schistosome parasites in different endemic areas might affect disease patterns. Traditionally, obtaining adult worms for study involved collecting worm eggs from human urine or faeces and using them to infect large numbers of snails and laboratory animals, mainly rodents. Dr Gower has developed a method that uses the larval form of the parasite, which can be sampled directly from the infected people in regions where the disease is endemic. The new system uses a DNA fingerprinting technique to study the genetic variation of the larval parasites which not only entirely avoids using animals but has also demonstrably improved the accuracy of the scientific results. Dr Gower received a prize of £10k to carry out further research to investigate the possibility of applying this technique to other types of parasite with similar lifecycles.

This year, due to an exceptionally strong field of entries, the prize selection panel decided to award a highly commended prize to Dr John Doe from Syngenta. Dr Doe's publication describes an improved 'tiered' testing approach to assessing the safety of agricultural chemicals.[6] The approach has the potential to reduce the number of rats, dogs and mice used by 16%, 33% and 100% respectively. Many of the recommendations arising from this project are being considered by major regulatory authorities.

[5] Gower C et al. Development and application of an ethically and epidemiologically advantageous assay for the multi-locus microsatellite analysis of Schistosoma mansoni. Parasitology 134 523–536, 2007

[6] Doe J et al. A tiered approach to systemic toxicity testing for agricultural chemical safety assessment. Critical Reviews in Toxicology 36 37–68, 2006

Looking ahead to 2008

2008 will be another busy year for the NC3Rs. Highlights will include the publication of two major surveys, new funding priorities and a review of research investment.

The first survey aims to assess the attitudes to and understanding of the 3Rs and to explore obstacles to implementation. The survey has been conducted for the NC3Rs by People Science and Policy and was distributed with the help of the Home Office. The survey was sent to all those with a personal or project licence under the Animals (Scientific Procedures) Act 1986. An expert steering group advised the NC3Rs on the content and will be meeting early in 2008 to discuss the top-level findings. The output of this meeting will then form the basis of a final report which will be published in spring 2008.

The second survey is a detailed assessment of experimental design and statistical analysis in published papers which reported experiments using animals and which was carried out in UK or USA publicly funded research establishments. The NC3Rs is sponsoring the survey jointly with the National Institutes of Health Office of Laboratory Animal Welfare. The survey has been completed and the results have been analysed. A full report of all the results, as well as a short report for publication, is currently being written. The findings will be published in spring 2008.

The results of both surveys are crucial to the Centre's future strategy. The first will inform decisions on what activities to undertake and how to improve communication, while the second will be used to develop guidelines on experimental design and reporting to assist scientists, journal editors and research funding bodies.

Investing in strategically important areas of research will continue in 2008. Two new priority areas have been identified for the latest round of the funding scheme. The first is fish and the 3Rs, and the second is refining rodent husbandry, care and procedures. Both aim to tackle areas of increasing animal use and ensure that the 3Rs are being fully considered.

In light of the increased funding from the comprehensive spending review, the NC3Rs will also be reviewing its research portfolio and funding mechanisms. An important aspect of the review will be to consider how to stimulate new 3Rs research ideas by ensuring that there are appropriate routes for funding for scientists from all disciplines and at all stages in their careers.

Financial summary

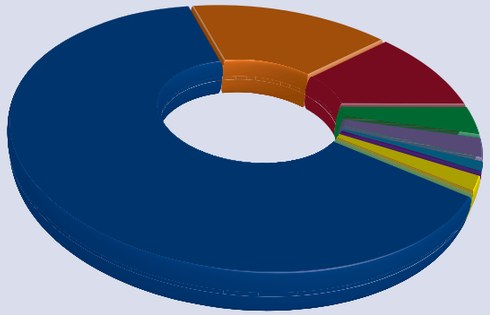
The NC3Rs accounting period runs from the beginning of April to the end of March each year.

Financial year April 2006 to March 2007
The total income for this financial period was £2,325,915, an increase of 144% compared with the period April 2005 to March 2006. This was the result of new funding from the chemical industry and significant increases from the MRC, the BBSRC and the Home Office.

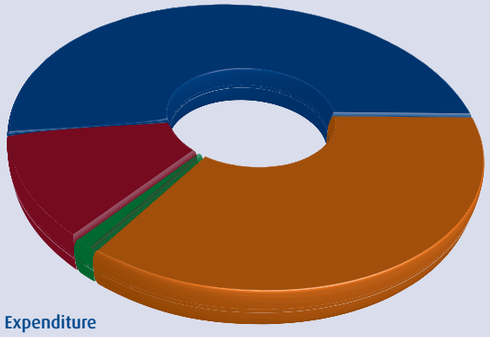
Expenditure increased from £765,951 in the period April 2005 to March 2006, to £1,540,917 in the period April 2006 to March 2007. This can be accounted for by the increased number of staff, initiatives and grants awarded.

Grant expenditure increased by 199% to £805,119 in the period April 2006 to March 2007. This is ongoing expenditure of the grants awarded in 2004, 2005 and 2006.

An independent accountant oversees the management of the NC3Rs finances. For logistical reasons the NC3Rs uses the MRC accounting systems and is therefore subject to its auditing procedures. The NC3Rs is grateful to the MRC for providing office space and infrastructure support including IT, payroll and personnel services.



Income



Expenditure

	April 05 to March 06	April 06 to March 07
Income		
MRC	£600,000	£1,425,000
BBSRC	£66,667	£404,000
Home Office	£125,000	£250,000
Wellcome Trust	£75,000	£85,000
ABPI	£50,000	£70,000
GlaxoSmithKline	£25,000	£26,000
LASA	£12,735	£13,065
Dow Chemicals/Syngenta/ Unilever/SC Johnson		£50,000
Miscellaneous contributions		£2,850
Total Operating Income	**£954,402**	**£2,325,915**
Expenditure		
Administration & Management	£368,697	£546,394
Communications	£82,255	£20,847
Programmes	£46,009	£168,557
NC3Rs Research Grants	£268,990	£805,119
Total Expenditure	**£765,951**	**£1,540,917**

Acknowledgments

The NC3Rs would like to thank the following organisations for their generous financial support:

- MRC
- BBSRC
- Home Office
- Wellcome Trust
- Cancer Research UK
- ABPI
- GlaxoSmithKline
- AstraZeneca
- Unilever
- The Dow Chemical Company
- SC Johnson
- Syngenta
- LASA

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

20 Park Crescent
London
W1B 1AL

Tel: 020 7670 5331
Fax: 020 7670 5178
email: enquiries@nc3rs.org.uk
www.nc3rs.org.uk

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