NC3Rs

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

Annual Report 2006

A year of progress

Contents

Picture credits

Cover	Left: Wellcome Trust
Page 1	Agricultural Research Service
Page 3	Agricultural Research Service
Page 4	By cmiper (CC)
Page 5	Science Photo Library
Page 7	Medical Research Council
Page 8	Wellcome Trust
Page 9	Wellcome Trust
Page 10	Bottom: Wellcome Trust

Foreword

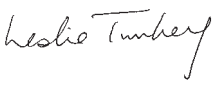
2006 has been an exciting year for the NC3Rs as our influence, range of activities, staff, and income have increased. There have been many highlights and we continue to be encouraged by the support and interest we have received from all of our stakeholders. Our success continues to depend on the wholehearted efforts of the many individuals and organisations who have worked with us over the last year, providing expertise, data and resources.

The value of the novel approach we take in dealing with contentious or sensitive issues has been demonstrated by our partnership with the Association of the British Pharmaceutical Industry (ABPI) on the use of primates in drug discovery and development. This is well illustrated by the workshop we hosted in the spring to challenge experts to design a pathway for the development of monoclonal antibodies in an environment where the use of primates was no longer possible. A difficult task but one where we hope real progress can be made by working together.

Like that example, a lot of the work we have done this year will not show benefits until 2007 and beyond. We have had a joint call for proposals, with the Biotechnology and Biological Sciences Research Council (BBSRC), for grant applications for tissue engineering solutions to replace the use of animals and we have been very pleased by the response. Next year, we will be hosting a symposium on '*Science and the 3Rs*' with the Animal Science Group of the Biosciences Federation which represents 40 learned societies and other professional bodies. Sponsorship from the Wellcome Trust and ABPI to cover all costs of the meeting will allow us to attract the widest possible participation.

Some of our projects are reaching their conclusion and this is a particularly exciting time for a young organisation. The initiative to challenge the requirement for single dose acute toxicity studies for the development of pharmaceuticals has shown the importance of sharing data and practice to enhance application of the 3Rs, and this is a model we intend to build on for future activities. Importantly, we are now at the stage with this project where data sharing gives us an opportunity to work with the regulators. We hope that this will lead to an end to the use of this test as a preliminary to the first studies done in man.

The annual report contains other examples of the work and impact of the NC3Rs over the last 12 months. We hope you will share our enthusiasm for the achievements we have made and will continue to support us with our efforts in the future.



Leslie Turnberg Chairman

Vicky Robinson Chief Executive

Summary of key successes

- Increased profile for NC3Rs e.g. more grant applications, more meeting attendees, more visitors to website
- Launch of e-newsletter to improve contact with stakeholders
- Awarded nine grants for 3Rs research, totalling £1.4m
- Publication of guidelines on primate accommodation, care and use
- Engagement of regulators and learned societies in NC3Rs activities
- Increased funding from chemicals industry for new projects in the sector

Bringing 3Rs research into the mainstream

A primary role of the NC3Rs is to encourage and support new research to advance the 3Rs. The main route for achieving this is an annual, response mode funding scheme which funds high quality research across all areas of science, with the aim of challenging the preconception that 3Rs research is peripheral to mainstream science.

This year, the NC3Rs awarded nine grants totalling £1.4 million *(see Research grants awarded in 2006)* compared to eight grants and £1 million in 2005. The grant applications were peer-reviewed by national and international referees and an expert panel, chaired by Professor Nancy Rothwell, ensured that only high quality work in first rate groups was recommended to the Board for funding.

Following the trend of 2005, the majority of grants (six of nine) were for projects focused on replacement. Although all three Rs are given equal consideration, the bias towards replacement reflects the high quality of the science in the applications for this area.

The number of applications also increased substantially from 40 in the first year to 60, illustrating the success of the Centre's efforts to raise the profile of the 3Rs and it is anticipated that this demand will continue to rise.

Supporting smaller projects

The NC3Rs, in partnership with the Laboratory Animal Science Association (LASA), runs an annual Small Awards Scheme specifically to support research (e.g. pilot studies) and training (e.g. new techniques, exchange visits) in the 3Rs and animal welfare. The scheme is open to any person employed in a UK research establishment and awards are available up to a maximum of £2k.

In 2006 there were a total of 19 applications and, after assessment by an expert panel, the following 14 were awarded funds:

1. A reliable method for the cryopreservation of zebrafish spermatozoa and embryos to reduce the number of animals needed to maintain strains
2. Generation of stable cell lines from mouse embryo limb buds to replace whole animal use
3. Measuring cortisol in the water as an indicator of stress in the African clawed frog
4. Assessing the welfare of aquarium fish

5. Addressing concerns preventing widespread uptake of ear notch genotyping in the mouse
6. Training in a laser assisted method of Intra-Cytoplasmic Sperm Injection to reduce the number of animals used to maintain GM lines
7. An assay to quantify stress in Xenopus
8. An *in vitro* dental pulp human stem cell assay system to replace animal use
9. Training in amphibian and zebrafish medicine
10. An assay to detect fungal disease in Xenopus
11. A chronic wound bioassay to replace animal use
12. A non-animal alternative to eye irritancy tests
13. Can orthopaedic biomaterials be adequately wear tested without a lubricant based on animal products?
14. Further development of an *in vitro* model of airway epithelial wound repair to replace animal use

The continuing enthusiasm for these awards, particularly from animal care staff, shows that it caters for different needs to the main grants scheme.

Research grants awarded in 2006

Dr Fullwood, Lancaster University - £145k
Development of an *in vitro* model for the anterior region of the eye

Dr Emerson, Imperial College London - £149k
Refinement of a mouse model of pulmonary embolism

Professor Perry,
University of Southampton - £181k
In vitro multi-chamber systems for studying neural degeneration processes

Dr Baker, University of
Newcastle upon Tyne - £149k
Transcutaneous signal transmission without breaching the skin's natural barrier to infection

Dr Walmsley, University of Manchester
Gentronix Ltd - £133k
Development of a new human cell genotoxicity assay to reduce the use of live animals in drug development

Dr Xing, National Institute for Biological Standards and Control - £262k
Development of alternatives to histamine sensitisation test for pertussis vaccines by *in vitro* biochemical and biological assays

Professor Harding,
Imperial College London - £201k
Embryonic stem cell-derived cardiomyocytes as a model system for cardiac investigations

Dr Thompson,
Central Science Laboratory - £27k
The use of honeybees to screen for toxins

Dr Sloan, Cardiff University - £194k
An *ex vivo* mouse mandible culture model to study inflammatory bone disease

Toxicology and the 3Rs

Applying the 3Rs to the use of animals in toxicology is an important part of the Centre's portfolio. During 2006, the NC3Rs has made real progress in a number of initiatives which it had previously started, in addition to identifying new opportunities for collaboration.

A collaborative industry challenge

Working with the European pharmaceutical industry and contract research organisations, the NC3Rs has continued to coordinate an initiative to challenge the requirement for conventional single dose acute toxicity studies, which are currently required to support the registration of any pharmaceutical intended for human use. The main objective of the studies is to identify a dose that causes major adverse effects, usually in rodents.

There are two unique aspects to conventional acute toxicity studies. They are the only regulatory study type in pharmaceutical development where, firstly, lethality is a defined endpoint and, secondly, testing via an administration route other than the intended clinical route is routinely required.

By conducting an evidence-based review of the value of conventional acute toxicity data, the initiative has shown that significant reductions in the numbers of animals used per study can be achieved and that, ultimately, these studies could be phased out completely without compromising patient safety. In order to facilitate this, the NC3Rs hosted an international workshop in November with European, American and Japanese regulatory authorities to discuss the case for regulatory change to obviate the need for acute toxicity tests.

Attended by over 50 representatives from industry and regulatory authorities, there was consensus on the working group's recommendations and as a result the regulators have agreed to review the International Conference on Harmonisation guidelines on conventional acute toxicity testing. This represents significant progress and illustrates the value of the NC3Rs in providing a neutral environment to bring together, and stimulate action from, a complex range of stakeholder groups.

The 3Rs

The principles of the 3Rs – Replacement, Refinement and Reduction – were originally developed by UFAW Scholars, Professor William Russell and Rex Burch, and are now widely accepted internationally as criteria for humane animal use in research and testing.

Replacement refers to methods which avoid or replace the use of animals defined as 'protected' under the Animals (Scientific Procedures) Act 1986 in an area where animals would otherwise have been used.

Refinement refers to improvements to husbandry and procedures which minimise actual or potential pain, suffering, distress or lasting harm and/or improve animal welfare in situations where the use of animals is unavoidable.

Reduction refers to methods which minimise animal use and enable researchers to obtain comparable levels of information from fewer animals or to obtain more information from the same number of animals, thereby reducing future use of animals.

Increasing awareness

The NC3Rs co-sponsored the British Toxicology Society's (BTS) Autumn Meeting which looked at recent developments in the 3Rs. The programme was developed jointly by the BTS Regulatory Toxicology Specialty Section, the In Vitro Toxicology Society (IVTS) and the NC3Rs and covered new initiatives in the 3Rs, testing strategies to reduce animal use, and the 3Rs in regulatory testing. Attendance was unexpectedly high with over 150 delegates, and feedback was overwhelmingly positive.

Harmonisation and good practice

Although regulatory toxicology operates according to sets of standard procedures or testing requirements there is variation in practice, and by sharing information on study design there is the potential for harmonisation and better application of the 3Rs.

The NC3Rs, in partnership with LASA, has established a Safety Evaluation Working Group, with an enthusiastic membership drawn from pharmaceutical and chemical companies, and contract research organisations. The objective of the group is to review standard regulatory toxicology procedures (e.g. urine analysis, dose volume limits) in order to explore opportunities for minimising suffering and the number of animals used. In addition, the group is developing a good practice guide to toxicology for study directors which will be published in 2007.

Identifying priorities

With the challenges to the 3Rs imposed by the introduction of the new chemicals legislation in the European Union (REACH), the Cosmetics Directive (2003/15/EC), and the revision of the Pesticides Directive (91/414/EC), the NC3Rs has secured funding from Unilever, Syngenta, SC Johnson and The Dow Chemical Company to support a programme manager post to focus on these important industry sectors. The programme manager will oversee a Regulatory Toxicology Forum which will be launched by the NC3Rs in 2007 as a platform to bring together regulators and toxicologists from industry and academia. The aim will be to identify and prioritise 3Rs issues, such as the development of alternative tests and strategies, and research to support regulatory change. The Forum will also act to drive selected initiatives from a UK perspective within the regulatory community to achieve agreement at an international level.

Primate use and the 3Rs

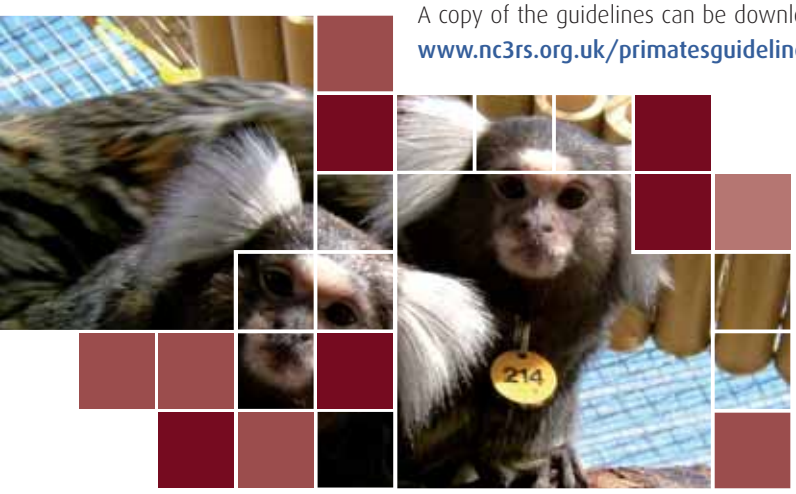
The use of non-human primates (also referred to as 'primates') in research and testing has been identified by many of the Centre's stakeholders as an area of concern. This year, the NC3Rs has made substantial progress in its broad programme of activities on applying the 3Rs to primate use and care.

Guidelines on accommodation, care and use

The Medical Research Council (MRC), the BBSRC, the Wellcome Trust and other Association of Medical Research Charities (AMRC) members fund research that involves the use of primates. These funding bodies recognise the concerns about the use of primates in research and the difficulties associated with meeting the environmental, behavioural and social needs of these highly intelligent animals in a laboratory environment. To help address these issues, the NC3Rs, in partnership with the funding bodies, has produced guidelines on primate accommodation, care and use which have now become the standard against which research applications are judged. Meeting the principles set out in these guidelines is now a condition of research funding.

The guidelines apply to any research conducted in the UK and abroad which is funded by these bodies and set out contemporary good practice in relation to sourcing, housing, capture, handling, restraint and training of the animals, and the provision of technical and veterinary care and support.

A copy of the guidelines can be downloaded from **www.nc3rs.org.uk/primatesguidelines**



Reviewing grant applications

The NC3Rs also works with the funding bodies to provide expert 3Rs and welfare review of all grant applications involving primates, cats, dogs, and horses. 26 applications were reviewed in 2006. In addition, the Centre has helped the funding bodies improve and harmonise the questions on animal use and the 3Rs in grant application forms and final reports.

Providing expert advice

Expert advice and input on primate issues was provided to the Academy of Medical Sciences/MRC/Royal Society/Wellcome Trust study into the use of primates in biological and medical research, the British Veterinary Association/Fund for the Replacement of Animals in Medical Experiments/Royal Society for the Prevention of Cruelty to Animals/Universities Federation for Animal Welfare joint working group on refinement, the Animal Procedures Committee, primatological societies and individual research establishments and grant holders.

Defining best practice for food and fluid control

The use of food and fluid control as tools in the training and testing of macaques used in behavioural neuroscience research can raise significant animal welfare concerns. With this in mind, the NC3Rs convened an expert working group comprising senior neuroscientists, a zoologist specialising in primate welfare, veterinarians, animal care staff and the Home Office Inspectorate, to develop recommendations on contemporary best practice and suggestions for research to substantiate further refinements. The recommendations are based on consideration of the existing literature, current good practice and the professional experience and views of the members of the working group and other experts. A comprehensive report has been produced and submitted for publication in a peer-reviewed neuroscience journal.

Bringing together the community

The annual NC3Rs primate welfare meeting attracted over 100 delegates, greatly exceeding last year's unexpectedly high attendance. The meeting covered methods of welfare assessment for marmosets and macaques and included speakers from UK universities, industry, and the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) International. The meeting is unique in bringing together a wide audience, from senior researchers to junior animal technicians, to discuss common refinement issues, and this formula is responsible for the growing support for the initiative.

Research grant awarded in 2006

Development of an *in vitro* model for the anterior region of the eye

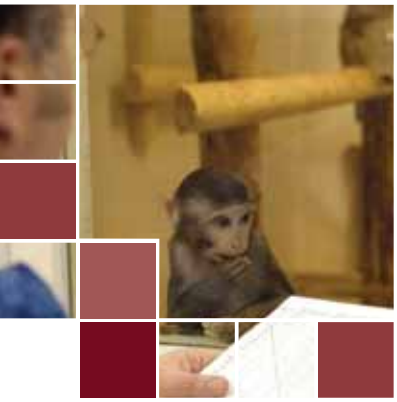
Dr Fullwood,
Lancaster University - £145k

Live animals are currently used for many investigations on the eye, including research into diseases causing blindness, such as keratoconus or Fuch's dystrophy, and the tests carried out by commercial companies to test new substances.

The aim of this project is to develop an *in vitro* model of the front part of the eye (the cornea) to replace significant numbers of these procedures worldwide. The proposal is to use the cornea of cow eyes that are a by-product of the meat industry and maintain them in a special chamber that supplies nutrients to keep them alive for several weeks.

Reviewing use in drug discovery and development

The NC3Rs and the Association of the British Pharmaceutical Industry (ABPI) have developed a stimulating strategy to review the scientific rationale for the use of primates in drug discovery and development, with the aim of highlighting opportunities and challenges to replacing and reducing primate use. Four main areas for investigation have been identified – toxicology, pharmacokinetics, biologicals (e.g. monoclonal antibodies, vaccines) and drug dependency. These have been selected to reflect the differing drivers for primate use from regulatory requirements to emerging technologies and the opportunities for reducing this use.



To date the focus has been on the use of primates in the development of monoclonal antibodies and drug dependency studies.

Monoclonal antibodies

The use of primates in the development of monoclonal antibodies was a timely area for review given the increasing number of antibodies in the pharmaceutical pipeline, the specific challenges faced in providing preclinical data because of target and species-specificity, and the concomitant implications for primate use.

To initiate the review, the NC3Rs organised an international workshop attended by 50 delegates from the pharmaceutical and biotechnology sectors, to consider how monoclonal antibodies could be developed without the use of primates, for example as a consequence of legislative ban, disease outbreak or difficulties with supply. Discussion focused on Old World primates although reference was made to the chimpanzee where appropriate. This hypothetical exercise was designed to consider where there might be opportunities for replacing and reducing primate use and the obstacles to this in practice.

Delegates designed a drug discovery pathway where the use of primates was avoided through (i) greater emphasis on, and better understanding of, the mechanism of action of the monoclonal antibody through *in vitro* studies, (ii) early development and characterization of surrogate antibodies and genetically altered rodents and (iii) early dosing in man with a robust

Research grant awarded in 2006

Refinement of a mouse model of pulmonary embolism

Dr Emerson, Imperial College London - £149k

Blood clots formed in the legs can cause pulmonary embolism if they detach and lodge in the lungs, causing heart and breathing problems, and often death. Animal tests to determine the causes and test potential treatments involve injecting substances into mice so that clots form, leading to paralysis and death.

An alternative model is proposed where the procedure is conducted on anaesthetised mice and neither paralysis nor death is induced. Blood platelets are radioactively labelled and, by injecting lower doses of the clot-forming substance, platelets trapped in the lung can be measured using detection probes over the chest.

The model will refine this area of research and also reduce animal numbers by obtaining multiple sets of data from the same mouse over time.

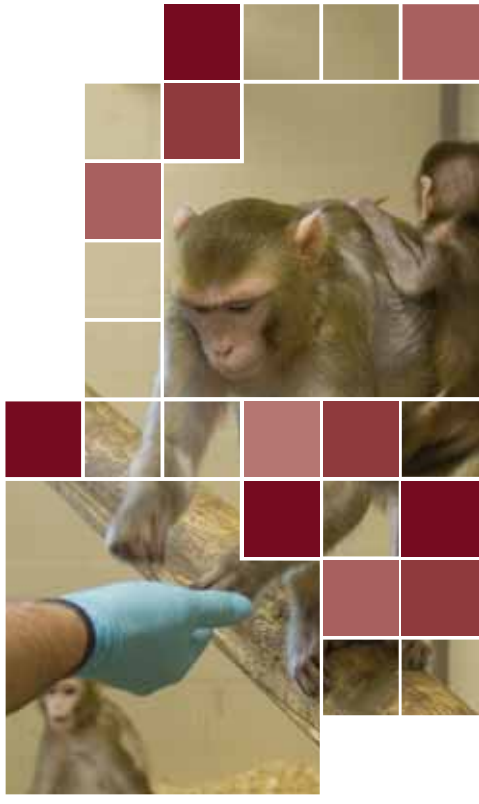
safety monitoring plan. The workshop was characterised by the common desire of the delegates to explore the feasibility of alternative approaches. A paper describing the issues raised at the workshop will be published in *Nature Drug Discovery* and an expert working group has now been established to consider and substantiate the hypothetical pathway.

Abuse potential

Abuse liability is considered an adverse drug reaction and ideally needs to be identified prior to clinical trials to ensure the safety of human volunteers and patients. The recent increase in the development of centrally-acting drugs for pain, neuropsychiatric diseases and non-central nervous system indications such as sexual health has implications for abuse liability testing, particularly as primates are considered to be the 'gold standard'.

An international group of scientists from industry and academia, led by the NC3Rs, is evaluating whether other approaches can substitute for the use of primates. Data strongly support the use of rodent self-administration studies as an alternative strategy for establishing abuse liability in humans due to a 1:1:1 correlation between human, primate and rodent data. While this approach will decrease the use of primates there is the potential for an increase in rodent use. This is not an ideal solution but taking account of the animals' whole life experiences, and the fact that the primates used in these types of studies may be used for many years to test multiple compounds, the working group concluded that, on balance, it is preferable to use rodents in short-term studies.

The group is now undertaking a more extensive literature review of scheduled compounds, including new data provided by members of the working group, to further validate this finding with the aim of developing a case to challenge the use of primates wherever possible. A poster setting out the group's initial work was presented at the Committee on Abuse Liability Testing in Washington in October and generated a great deal of interest from regulators and industry representatives.



Developing communications

The ability to communicate the ethos, activities and output of the NC3Rs effectively is central to raising the influence of the Centre and profile of the 3Rs.

During 2006, the NC3Rs has concentrated on:

- Increasing its communications capacity by appointing a communications manager.
- Maintaining and expanding the number of audiences reached, including regulatory bodies and learned societies.
- Improving the impact of the Centre's activities by promoting the website, launching a monthly e-newsletter and increasing media coverage.

Website

The content of the NC3Rs website has expanded considerably since it was launched in September 2005 to keep pace with the ever-increasing level of activities in which the Centre is involved and encourge increased implementation of the 3Rs. The number of visitors to the site has also grown, starting with 1,420 individuals in the month of launch and rising steadily to 5,196 recorded for November 2006.

In order to highlight new website content, such as news items, events and the publication of reports or guidelines, a monthly e-newsletter has been launched which can be subscribed to online. Over 400 individual subscribers are now registered and, through dissemination within establishments and via email lists, the actual size of the readership is many times greater than this.

Another comprehensive addition to the website is a Blood Sampling Microsite which describes and illustrates the various techniques used to obtain blood samples from laboratory animals, organised by species and routes, and lists the advantages and disadvantages of each technique and the opportunities for refinement. The original content for the microsite was provided by GlaxoSmithKline, with subsequent external peer review by a broad range of experts to ensure that the information reflects good practice. This is a valuable refinement resource given that blood sampling is such a common procedure.

Research grant awarded in 2006

Embryonic stem cell-derived cardiomyocytes as a model system for cardiac investigations

Professor Harding
Imperial College London - £201k

Research into heart disease involves large numbers of animal studies, partly because human tissue is difficult to obtain and, although animal cardiac myocytes (a type of cell in the heart) have been used in the laboratory, only lasts for a few days. This project aims to examine the possibility that heart cells derived from embryonic stem cells could be used. They have been known to continue beating for more than five months in the lab and, by measuring the strength of the beats, it may be possible to record the response of the myocytes to chemicals being investigated for their role in heart failure. If successful this could replace 180 animals per year in one laboratory and 1500 studies (10-50 animals each) per year worldwide.

Looking ahead

Horizon scanning for research and technologies which have implications for animal use and the implementation of the 3Rs is important for setting the strategic direction of the NC3Rs, for providing topics for commissioned research and highlighting new science which should be widely disseminated. To assist the NC3Rs in horizon scanning, a network of scientific ambassadors is being appointed within academia and industry to help alert the NC3Rs to work relevant to the 3Rs. This is another example of the Centre's ability to draw on the expertise of the external community to extend its outreach.

An initial six-month pilot study is currently underway which has recruited research groups representing a number of different scientific disciplines from neurodegenerative diseases to nanotechnology. The ambassadors have been asked to supply references relevant to the 3Rs on an ad hoc basis, along with a final report at the end of the pilot scheme which will outline any wider trends in their area which could have either a positive or negative impact on the 3Rs.

Celebrating innovative 3Rs research

In order to further raise the status of 3Rs research, the NC3Rs launched a prize last year, sponsored by GlaxoSmithKline, to recognise a piece of research, published in the previous two years, which makes a significant contribution to the 3Rs in medical, biological or veterinary research.

This year, the £10k prize will be awarded to Professor Alan Fairlamb (University of Dundee) by Joan Ryan MP, Parliamentary Under-Secretary of State for the Home Office, at the NC3Rs annual stakeholder meeting early in 2007 for his work on refinement of a hamster model used to study the propogation of the disease-causing parasite Leishmania. By using a different route of infection, Professor Fairlamb has significantly refined the procedure by reducing the duration and severity of the disease and has also reduced the number of animals needed per experiment.

Building capacity

To meet the demand of the expanding role and influence of the NC3Rs, three new programme managers have been appointed to lead the Centre's activities in the areas of communications, replacement and regulatory toxicology. The administrative team has also grown to support the increased workload of the Centre. The successful recruitment of highly qualified and motivated staff gives the NC3Rs credibility in the scientific community and the ability to network and engage. NC3Rs staff are invited to a broad range of conferences and meetings to describe the Centre's work and are members of a variety of working groups and committees including the Animal Procedures Committee, the Royal Society's Animal Research Group and the National Cancer Research Institute's committee on revising the guidelines on the use and care of animals in cancer research.

NC3Rs collaborations

Workshop and report on the use of CO_2 for euthanasia

CO_2 is one of the most commonly used methods of rodent euthanasia. It can be the most suitable method for euthanasia of large numbers of rodents (easier and less time-consuming than alternatives) and, if used in optimal conditions, CO_2 may also be less stressful than manipulations required for injections or physical methods.

However, at certain concentrations CO_2 can cause rodents pain and/or distress and there has to date been a perceived disagreement between those who believe the use of CO_2 may be acceptable in some circumstances and those who believe it is inhumane.

In February 2006, the NC3Rs sponsored and helped to facilitate a 'consensus meeting' at the University of Newcastle which brought together experts who subsequently produced a report to outline current understanding in this area, highlight where there is agreement among scientists, and identify where questions still remain.

Financial summary

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

Financial year April 2005 to March 2006

The total income for this financial period was £954,402 an increase of 37% compared to April 2004 to March 2005. The increased income reflects new funding from the Wellcome Trust, ABPI, GSK and LASA to support specific projects and posts within the Centre.

Expenditure increased from £303,364 in Sept 2004 to March 2005, to £765,951 in the period April 2005 to March 2006 (a rise of over 252%). This can be accounted for by the increased number of staff, initiatives and grants awarded. Administration and management includes staff salaries, Board costs and consultancy fees.

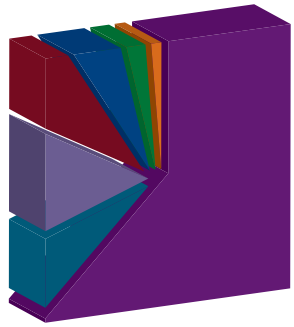
Expenditure on communications and programmes increased by 446% and 340% respectively. This reflects the costs of developing the NC3Rs website which was launched in September 2005 and the initiation of a range of working groups and workshops.

Grant expenditure increased by 227% to £268,990 in the period April 2005 to March 2006. This is the ongoing expenditure of the grants awarded in 2004.

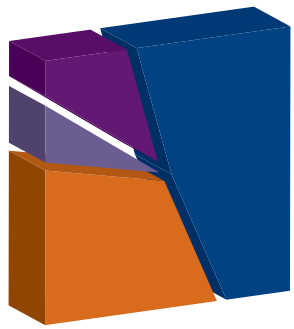
An independent accountant oversees the management of the NC3Rs finances. For logistical reasons the NC3Rs uses the MRC accounting systems and is therefore subject to its auditing procedures. The NC3Rs is grateful to the MRC for providing office space and infrastructure support including IT, payroll and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

Looking ahead

Since April 2006 the NC3Rs has secured additional funding from the UK chemical industry (Unilever, Syngenta, SC Johnson and The Dow Chemical Company) and Cancer Research UK.



Income



Expenditure

April 05 - March 06

INCOME	April 04 to March 05	April 05 to March 06
MRC	£600,000	£600,000
BBSRC	£61,000	£66,667
Home Office	£35,000	£125,000
Wellcome Trust		£75,000
ABPI		£50,000
GSK		£25,000
LASA		£12,735
Total Operating Income	**£696,000**	**£954,402**

EXPENDITURE	Sept 04 to March 05	April 05 to March 06
Administration & Management	£153,021	£368,697
Communications	£18,435	£82,255
Programmes	£13,529	£46,009
NC3Rs Research Grants	£118,379	£268,990
Total Expenditure	**£303,364**	**£765,951**

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