Annual Report 2010

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

Contents

_1 Foreword

_2 Chemicals and consumer products industries
2.1 Changing practice under existing test regulations
2.1.1 Acute toxicity testing of chemicals
2.1.2 Reducing fish use in ecotoxicology
2.2 Promoting research on alternatives for risk assessment
2.2.1 *In vitro* approaches to carcinogenicity testing
2.2.2 Mathematical modelling of toxicity

_3 Pharmaceutical industry
3.1 Minimising the use of non-human primates in drug discovery and development
3.1.1 Non-clinical development of monoclonal antibodies
3.1.2 Assessing abuse potential
3.1.3 Predicting human pharmacokinetics
3.2 Acute toxicity studies for pharmaceuticals
3.2.1 Acute toxicity data for clinical management of overdose
3.2.2 Refining maximum tolerated dose studies

_4 Academic sector
4.1 Funding excellence in 3Rs research
4.1.1 3Rs research funding scheme
4.1.2 New strategic research awards
4.1.3 Pilot project scheme
4.1.4 Studentships
4.2 3Rs prize
4.3 Improving standards in animal research
4.3.1 Advising the major bioscience research funding bodies
4.3.2 New guidelines on reporting of animal experiments
4.3.3 New web resources
4.4 Raising the profile of the 3Rs

_5 Financial summary
5.1 Income
5.2 Expenditure

_6 Appendices

1

Foreword

During 2010, we have continued to show the value of taking a science led and collaborative approach to the replacement, reduction and refinement of animals in research (the 3Rs). The success of this strategy was recognised in the first quinquennial review of the NC3Rs which was undertaken on behalf of the Department for Business, Innovation and Skills. The review led by Sir Ken Calman reported in March, scoring our work very highly. Following the recent Government Spending Review, this endorsement has been translated into decisions by the funding bodies to maintain our funding at the current level in real terms[1].

Through our role as a research funder we have continued to support the best ideas and scientists with over £6 million in new grants and studentships awarded in 2010. We have also strengthened our research funding capability with the introduction of a strategic awards scheme. This allows us to define and invest in specific research areas where we believe there is significant potential for advancing the 3Rs. Our priorities for 2010 were two-fold: first, to sponsor research to refine the use of carbon dioxide euthanasia of rodents, a controversial subject where policy is being developed without an adequate evidence base; and second, to fund the development of new models of asthma, a disease with a substantial health burden because of the lack of effective treatments for many patients and where the utility of existing animal models is questionable. In 2010 we committed £1.3 million in strategic awards and we plan to add to this in 2011.

Our scientific staff have continued to lead a diverse range of exciting programmes during the last year, working in partnership with scientists from universities, industry and regulatory authorities. We collaborate with over 30 companies from the pharmaceutical, chemical, agrochemical and consumer product industries. Our expertise as an 'honest broker' for data sharing across industry has identified opportunities to reduce the use of non-human primates (NHPs) in drug discovery and development, improve rodent welfare in toxicity testing and to influence regulations and practice both in the UK and internationally. We have also added new activities to our portfolio, including reducing the use of fish in environmental safety testing of pesticides, an area which has historically received relatively little attention.

[1] *www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC007642 'MRC remains committed to reduction, refinement and replacement of animal use in scientific research. To help deliver on our commitment, as well as the government pledge to reduce animal usage, MRC will continue supporting NC3Rs, working with BBSRC to maintain our joint contribution at the current level in real terms (rising to £5.6m pa by 2014/5).'*

To disseminate the findings of our scientific programmes, our staff have published over 20 papers in 2010. This includes recommendations on refining the use of food and fluid control in NHPs used in neuroscience research and guidelines called ARRIVE (Animal Research: Reporting *In Vivo* Experiments) which will improve the reporting of animal experiments. The ARRIVE guidelines have already been adopted by the major bioscience research funders and a range of journals and we will be working to further promote their uptake in 2011.

We have also organised 11 events including symposia and workshops, both in the UK and USA, on diverse topics from cardiovascular models to *in vitro* tests for assessing carcinogenicity. These aim to stimulate new ideas and approaches and raise the profile of the 3Rs. This year our programme of events included new partnerships with the British Pharmacological Society, the Physiological Society and the Society of Biology. Working closely with scientists who use animals is core to our mission; we also foster interdisciplinary collaborations with scientists in other fields to exploit the potential importance of these areas in reducing animal use. In 2010 we began working with the UK mathematical modelling community on the enormous challenge of identifying toxicity without animals. This will develop further in 2011 with a workshop and support through our strategic awards scheme.

Our work makes an important contribution to the Coalition Government's policy to work to reduce the use of animals in scientific research. Many of the programmes we lead and the research we sponsor across a range of sectors, disciplines and therapeutic areas are delivering 3Rs benefits. Much of what we do is to change attitudes to the 3Rs so they are seen as a valuable scientific endeavour and to stimulate novel ideas and approaches. It will take time to see the full benefits arising from this. Nevertheless, it is important that we are able to measure the impact of our work and we will be inviting organisations such as the RSPCA to work with us over the next 12 months to define better metrics of success. As a start in Spring 2011 we will be publishing a review of the impact of the research we have funded in universities.

We have used the 3Rs as a framework for addressing major challenges faced by the industrial and academic sectors, providing new models and tools with reduced reliance on *in vivo* research and improved animal welfare. The environment, knowledge base and momentum we have provided has over the last year continued to enable individuals, research groups, institutions and companies to exploit new opportunities to apply the 3Rs. Our aim now is to widen this engagement. In 2011 we will be launching an initiative to promote greater academic/industry collaboration, unlocking opportunities for scientific progress on the 3Rs which also have commercial benefits such as providing better ways to screen drugs and chemicals and ensuring protection of man and the environment. By capitalising on the networks, reputation and expertise we have developed over the last five years we will use this initiative to increase our impact across the whole of the bioscience sector, benefiting the health and wealth of the nation.

Vicky Robinson, Chief Executive
Ian Kimber, Chairman

2

Chemicals and consumer products industries

The chemicals, agrochemicals and consumer products industries are faced with a complex and changing regulatory environment with animal testing requirements varying between regions and sectors. In Europe the Cosmetics Directive bans animal testing whereas regulations for pesticides have high testing requirements, and the chemicals legislation REACH will drive increased animal use. Methods for chemical testing using animals are resource intensive and their utility in protecting human health and the environment is controversial. There is a business need for more efficient, alternative methods.

We work with the chemicals, agrochemicals and consumer products industries and regulatory authorities to improve chemical risk assessments, while also minimising animal use. Unilever, Shell, Syngenta, The Dow Chemical Company and SC Johnson collectively sponsor a scientific post in the NC3Rs to facilitate this. Our activities are broadly divided into two main areas: increasing application of the 3Rs within the current test regulations and aligning the latest developments in science and technology with chemical risk assessment.

2.1 Changing practice under existing test regulations

Our work has focused on acute toxicity and environmental safety testing.

2.1.1 Acute toxicity testing of chemicals

Tackling redundancy in acute toxicity testing

We have highlighted redundancy in testing requirements for acute oral, dermal and inhalation toxicity, skin and eye irritation and skin sensitisation. These tests are often associated with significant animal suffering and lethality. Working with scientists from industry, the Health and Safety Executive and Chemicals Regulation Directorate, we have analysed oral and dermal acute toxicity data for 240 pesticides and 438 industrial chemicals. This has shown that testing by the dermal route in addition to the oral has little added value for hazard identification or classification and labelling purposes and should only be carried out in exceptional circumstances. This work and a wider review of redundancy in acute toxicity testing requirements was published in *Critical Reviews in Toxicology* in 2010[2].

We are also a member of the European Partnership for Alternative Approaches to Animal Testing Acute Toxicity Task Force, which has built on our study with a review of the scientific and regulatory drivers for acute toxicity testing[3]. This combined work was presented at a workshop in Brussels in September. The focus for next year is to work across industry sectors to remove regulatory requirements for dermal testing where oral data are available.

[2] *Creton S, Dewhurst IC, Earl LK, Gehen SC, Guest RL, Hotchkiss JA, Indans I, Woolhiser MR, Billington R (2010). Acute toxicity testing of chemicals – opportunities to avoid redundant testing and use alternative approaches. Critical Reviews in Toxicology 40: 50-83*

[3] *Seidle T, Robinson S, Holmes T, Creton S, Prieto P, Scheel J, Chlebus M (2010). Cross–sector review of drivers and available 3Rs approaches for acute systemic toxicity testing. Toxicological Sciences 116: 382-96*

"We have worked...to provide evidence to support the regulatory acceptance of a test for acute inhalation toxicity which uses fewer rodents and minimises suffering."

Refinement of acute inhalation toxicity tests

We have worked with the UK's national coordinator for the OECD Test Guidelines programme and the EU Test Methods coordinator and industry to provide evidence to support the regulatory acceptance of a test for acute inhalation toxicity which uses fewer rodents (typically 2-11 instead of 10-40) and minimises suffering.

Previous attempts to get international acceptance of the Fixed Concentration Procedure (FCP) have failed due to concerns from some countries about the test's performance and its reliance on signs of toxicity rather than death. We have commissioned a statistical analysis comparing the FCP with the currently accepted methods. This analysis was published in 2010 and shows that the FCP's performance is comparable to the other methods[4,5].

A major obstacle to FCP acceptance is the use of 'evident toxicity' which relies on signs of toxicity rather than death. This is seen as less objective than counting the number of dead animals because of the need for interpretation of clinical signs. We are working with four contract research organisations to develop and test a new scoring system for evident toxicity. The data from this study will be used for the re-introduction of the FCP into the OECD Test Guidelines Work Programme in 2011.

[4]*Price C, Stallard N, Creton S, Indans I, Guest RL, Griffiths D, Edwards P. A statistical evaluation of the effects of gender differences in assessment of acute inhalation toxicity. Human and Experimental Toxicology Epub ahead of print doi: 10.1177/0960327110370982*

[5]*Stallard N, Price C, Creton S, Indans I, Guest RL, Griffiths D, Edwards P. A new sighting study for the fixed concentration procedure to allow for gender differences. Human and Experimental Toxicology Epub ahead of print doi: 10.1177/0960327110370983*

2.1.2 Reducing fish use in ecotoxicology

We have started a new programme on the 3Rs in environmental safety testing which has so far focused on the use of fish in the agrochemical industry. We are also a member of the ILSI-HESI committee on Emergence of Animal Alternative Needs in Environmental Risk Assessment.

Fish acute toxicity testing for pesticide products

We are working with agrochemical companies and regulators to foster the adoption of a new method – the threshold approach for fish acute toxicity testing – which could substantially reduce animal numbers and suffering. The threshold approach is already used for pharmaceuticals and chemicals, but is not yet accepted by regulators for pesticides.

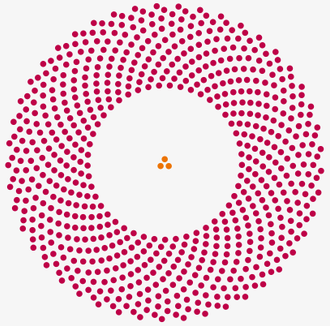
The threshold approach is based on the observation that fish are not always the most sensitive species used for aquatic toxicity testing. It involves testing a small number of fish at a single concentration selected from the results of tests in algae and invertebrates such as *Daphnia*. If toxicity does not occur then this indicates that fish are not the most sensitive species and further acute testing in fish (typically using 42 animals) can be avoided.

Fish acute toxicity testing is a basic requirement for pesticide ingredients and products. Product testing accounts for a large proportion of acute tests as ingredients are frequently reformulated to improve and develop new products. An historical data analysis by Syngenta on the application of the threshold approach to pesticide products has shown that it could reduce fish use by 40% and also minimise suffering, with lethality avoided in over 70% of studies.

In December, we hosted a workshop to share this analysis with other companies and regulators. A testing strategy was proposed and in 2011 we will be working on its further development, including validating with historical data and seeking to achieve regulatory acceptance.

40%

Data analysis suggests the threshold approach could reduce fish use for acute toxicity testing of pesticides by up to 40%



Acute dermal toxicity testing was redundant for 675 of 678 chemicals and pesticides where oral data were available

TOP FIVE

Our review of redundancy in acute toxicity testing of chemicals is among the top five most read articles in *Critical Reviews in Toxicology*

Fish chronic toxicity testing for pesticide products

We have published a survey of seven major European agrochemical companies which shows that chronic toxicity testing of pesticide products in fish is rarely if ever scientifically justified.

Harmful effects seen in fish in the laboratory following chronic testing of pesticide products cannot be compared to real life environmental exposures. This is because when the product is applied in the environment the individual ingredients dissipate so that fish in the wild will not be exposed to the actual product. The survey, which was published in 2010 in *Toxicology Letters*[6], will be used to inform the revision of the European guidance on aquatic toxicity testing of pesticide products which is expected to commence in 2011.

[6] *Creton S, Douglas M, Wheeler JR, Hutchinson TH (2010). Challenging the requirement for chronic fish toxicity studies on formulated plant protection products. Toxicology Letters 199: 111-114*

2.2 Promoting research on alternatives for risk assessment

We are fostering new research aimed at improving chemical risk assessment without using animals. Our work in this area aims to shift practice from traditional *in vivo* methods and to adopt the latest science and technology. This is a long-term strategy which involves engaging new scientific communities, building on progress in basic research and ultimately incorporating these advances into toxicity testing and risk assessment. Our initial focus has been on *in vitro* approaches for carcinogenicity testing and the exploitation of mathematical modelling to predict systemic toxicity.

"Our work in this area aims to shift practice from traditional in vivo methods and to adopt the latest science and technology."

Engaging regulators with research on new methods is critical if they are to be successfully used to replace animals. In October we launched a roadshow for regulators to promote greater understanding and dialogue between industry and the regulatory community on novel approaches for chemical risk assessment. The first event was held at the Health and Safety Executive and included regulators from the Chemicals Regulation Directorate, Food Standards Agency and Defra.

2.2.1 *In vitro* approaches to carcinogenicity testing

We have championed the latest scientific developments in cell transformation assays to stimulate new research on alternative methods for carcinogenicity testing. In November we held an international workshop which was co-sponsored by the UK Environmental Mutagen Society.

The standard approach for assessing the cancer causing potential of a chemical is a two year rodent study. This uses large numbers of animals (approximately 400 per test) and is time consuming and expensive, limiting its practicality for use in large scale chemical testing programmes like REACH. Under the Cosmetics Directive this test will be banned from 2013. Cell transformation assays, which measure carcinogenic potential *in vitro,* have been proposed for use as part of an alternative testing strategy.

A lack of understanding of the mechanistic basis of the test (e.g. the changes in genetic and molecular pathways that lead to cell transformation in the assay) has limited its acceptance for regulatory purposes.

We have funded research at Brunel University to improve the mechanistic understanding of cell transformation assays. This, and other relevant research, was showcased at the workshop. A report on the knowledge gaps identified at the workshop is being prepared for publication and will be used as a basis for our future investment in research in this area.

"We have started to engage the UK mathematical modelling community with the challenges of replacing animals for systemic toxicity testing."

2.2.2 Mathematical modelling of toxicity

We have started to engage the UK mathematical modelling community with the challenges of replacing animals for systemic toxicity testing. The potential of applying mathematical modelling to toxicology was a major theme that emerged from a workshop we held late in 2009 on novel approaches to safety assessment (www.nc3rs.org.uk/newapproachessafetyreport).

As a first step we have developed links with the Mathematics in Medicine Study Group initiative, which promotes interaction between mathematicians and biologists. We are now organising a joint workshop in May 2011, which will bring together toxicologists and mathematicians to consider research priorities as a foundation for future funding.

3

Pharmaceutical industry

Despite increased investment there are fewer new drugs reaching the clinic. Lack of efficacy or safety issues are major reasons for failure and animal models are widely cited by industry and regulatory authorities as bottlenecks in drug discovery and development. The increased focus on biotherapeutics such as monoclonal antibodies brings new challenges for non-clinical studies, with non-human primates (NHPs) often the only relevant species for testing.

We work with the pharmaceutical and biotechnology sectors and regulatory authorities to apply the 3Rs to improve the development of safe and efficacious medicines whilst minimising animal use. The Association of the British Pharmaceutical Industry sponsors a scientific post in the NC3Rs to facilitate this. Renewal of the post was agreed in 2010.

We have focused on two areas: minimising the use of NHPs (typically cynomolgus or rhesus macaques) and ending the requirement for single dose acute toxicity studies. Our experience of providing a unique forum for industry to share data has been key to the success of these activities.

3.1 Minimising the use of non-human primates in drug discovery and development

We have provided an evidence base for minimising NHP use in three areas: the development of monoclonal antibodies, abuse potential studies and predicting human pharmacokinetics in the selection of candidates for clinical development.

3.1.1 Non-clinical development of monoclonal antibodies

We have identified opportunities to at least halve the number of NHPs used in monoclonal antibody development to around 52 animals per antibody. In 2010 we have promoted this work internationally, collaborating with experts leading the addendum to the international guidelines on non-clinical safety testing of biotherapeutics (ICH S6) and presenting our findings at a number of international meetings. This included a presentation at the Charles River symposium in San Diego, where we also led the ‘Great Debate’ on whether rodents can substitute for the use of NHPs in chronic toxicology studies and at the American College of Toxicology annual meeting in Baltimore, where we also organised a continuing education course on reducing NHP use in non-clinical safety assessments.

Acting as an 'honest broker' we have coordinated further data sharing across the industry to bolster the evidence base for reducing group sizes, number of recovery animals and dose groups. This has included an analysis of non-clinical data on 59 antibodies currently in development provided by 12 companies from the UK, elsewhere in Europe and the USA. We have also published a paper in *Drug Discovery Today* on the future use of NHPs in monoclonal antibody development[7].

"Acting as an 'honest broker' we have coordinated further data sharing across the industry to bolster the evidence base for reducing group sizes, number of recovery animals and dose groups."

3.1.2 Assessing abuse potential

We have published a review with scientists from Pfizer showing that the rat is highly predictive for determining human abuse potential for a wide range of drug classes[8]. This has provided evidence to recommend use of the rat instead of the NHP. The publication includes an analysis of data from 350 papers on 71 compounds to determine the utility of different species for the prediction of human abuse potential – assessment of which is required for registration of most medicines acting on the central nervous system (CNS).

The opportunity to use the rodent rather than the NHP has been communicated during 2010 at the College on Problems of Drug Dependence annual meeting in Arizona, the Safety Pharmacology Society meeting in Boston and through the non-clinical cross-company abuse liability consortium. Our analysis has also been used to inform reviews of European Medicines Agency and US Food and Drug Administration requirements for abuse potential studies. We are now carrying out a meta-analysis on opiates – a major class of CNS acting compounds – to determine the most appropriate study design in the rat to reduce the number of animals used and improve animal welfare.

[7] *Chapman K, Pullen N, Andrews L, Ragan I (2010). The future of non-human primate use in mAb development. Drug Discovery Today 15: 235-242*

[8] *O'Connor EC, Chapman K, Butler P, Mead AN. The predictive validity of the rat self-administration model for abuse liability. Neuroscience Biobehavioural Reviews. Epub ahead of print. doi: 10.1016/j.neubiorev.2010.10.012*

3.1.3 Predicting human pharmacokinetics

We have collaborated with scientists from Pfizer to assess the accuracy of *in vitro* models for predicting human pharmacokinetics early in drug discovery, thus avoiding the use of animals. By analysing data on the clearance of 74 compounds we have shown that human liver microsomes can be used to predict human pharmacokinetics for cytochrome P450 enzyme cleared compounds and that the rat rather than the NHP can be used for renally cleared compounds. A framework has been proposed where compounds are selected using *in vitro* methods alone or *in vitro* methods combined with single species scaling in the rat, avoiding the use of the dog and NHP. This work will be published in 2011[9].

3.2 Acute toxicity studies for pharmaceuticals

We have continued to lead, with AstraZeneca, activities on the utility of single dose acute toxicity testing. We have built on our previous work showing that acute studies involving lethality and substantial animal suffering have no value in assessing safety for humans, and that studies such as the maximum tolerated dose (MTD) already carried out during drug development can be used instead.

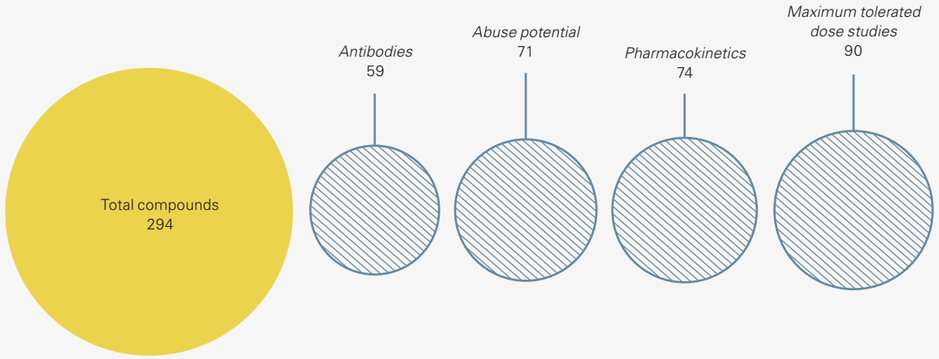
We have focused on two areas: the requirement for acute toxicity data to support human overdose and refining MTD studies to improve animal welfare.

[9] *Beaumont K, Gardner I, Chapman K, Rowland M. Towards an integrated human clearance prediction strategy that minimises animal use. (Accepted subject to revisions)*

64%

Up to a 64% reduction in non-human primates used per monoclonal antibody in drug development

WE HAVE SHOWN ACUTE TOXICITY STUDIES ARE OF NO VALUE IN ASSESSING HUMAN OVERDOSE, REMOVING THE LAST REMAINING DRIVER FOR THEIR USE IN PHARMACEUTICAL DEVELOPMENT



23 pharmaceutical companies and contract research organisations have provided data on compounds for our analysis this year

3.2.1 Acute toxicity data for clinical management of overdose

We have worked with regulators and representatives from international poison centres to question the scientific rationale for generating acute toxicity data to support clinical management of pharmaceutical overdose and chemical poisoning. This included a workshop in January where there was consensus that acute toxicity data are not necessary for pharmaceuticals and are of little value in treating human poisoning from chemicals. The output of the workshop was published in *Regulatory Toxicology and Pharmacology*[10] and will be discussed by regulators in 2011.

"We have collected data from 90 pharmaceuticals on whether body weight loss alone can be used as an objective measure of MTD without having to use other more substantial clinical signs such as convulsions."

3.2.2 Refining maximum tolerated dose studies

We have collaborated with 18 European companies to improve the welfare of rodents used in MTD studies. We have collected data from 90 pharmaceuticals on whether body weight loss alone can be used as an objective measure of MTD without having to use other more substantial clinical signs such as convulsions. This also included an analysis of whether the level of weight loss can be minimised to avoid unnecessary suffering. Preliminary analysis suggests that an upper limit of 15% weight loss may be appropriate compared with current limits of 20 to 25%. This work will be published in 2011.

[10] *Chapman K, Creton S, Kupferschmidt H, Bond GR, Wilks MF, Robinson S (2010). The value of acute toxicity studies to support the clinical management of overdose and poisoning: A cross-discipline consensus. Regulatory Toxicology and Pharmacology 58: 354-359*

4

Academic sector

The use of animals is increasing in universities and other publicly funded establishments. This reflects a number of drivers such as the research priorities of the major bioscience funding bodies as well as technological advances which have led to widespread availability and use of genetically altered rodents. A number of recent studies have questioned the quality of the design, analysis and reporting of animal experiments. Efficient translation of basic research findings into improvements in healthcare and commercial benefits is an important priority and the utility of animal models has come under increasing scrutiny as a result.

"Over the last five years we have awarded 59 grants in open competition taking our research investment to £16.5 million."

We work with the academic sector through our collaborations with the bioscience funding bodies and learned societies and by sponsoring research in universities. Our aim is to ensure the highest standards in animal research and to increase the profile of the 3Rs as a valuable research objective – exploiting developments in science and technology to provide better models and tools with reduced reliance on animals and improved animal welfare.

4.1 Funding excellence in 3Rs research

We are the UK's largest funder of 3Rs research in UK universities. Over the last five years we have awarded 59 grants in open competition taking our research investment to £16.5 million. During 2010 we have developed a new research portfolio website to allow us to better capture and disseminate the output and impact of the research we support. This will be launched early in 2011.

4.1.1 3Rs research funding scheme

We have awarded 13 new grants in 2010 totalling over £4 million across a range of disciplines and therapeutic areas from neurodegenerative disease to oncology to vaccine efficacy testing (see Appendices). This included a grant to scientists at the MRC Human Genetics Unit and University of Edinburgh to reduce the number of mice used in complex genetic experiments with initial pilot data suggesting that this may reduce mouse use by 90% compared with current methods. 54% of the grants awarded in 2010 are for replacement, 38% for reduction and 8% for refinement.

This year our grant assessment panel chaired by Professor Sir Andrew McMichael, University of Oxford, placed greater emphasis on dissemination plans to ensure that the output of the research we fund is widely communicated. We have also provided additional funds to help our existing grant holders to publicise their findings. This included sponsoring a workshop in April led by NC3Rs grant holder Professor Peter Jones, King's College London, to promote to the UK's diabetes research community the use of pseudoislets as a replacement for primary islet cells[11] – an approach which has reduced rodent use in Professor Jones' laboratory by more than 1000 animals per annum.

4.1.2 New strategic research awards

We have introduced a strategic grants award scheme which will allow us to use our expertise to stimulate and shape specific areas of research. We have had two calls for strategic awards in 2010 – 'refining the use of carbon dioxide euthanasia in rodents' and 'the 3Rs in asthma research'.

Refining the use of carbon dioxide euthanasia in rodents

Millions of laboratory rodents are euthanased worldwide each year by exposure to a rising concentration of carbon dioxide. Carbon dioxide is known to be aversive to rodents but the significance of this is controversial. Some organisations have called for a ban and the use of anaesthetic gases as an alternative. Whether such alternatives are demonstrably more humane is questionable and our strategic award to Dr Huw Golledge, Newcastle University, will provide the scientific evidence to address this.

3Rs in asthma research

Two strategic awards of almost £500k each have also been made to Professor Donna Davies, University of Southampton and Dr Felicity Rose, University of Nottingham, to develop tissue engineered models of asthma using cells from patients. A range of animals from mice to macaques have been used to study asthma and to test the efficacy of new treatments. The failure to translate promising drug candidates from animals to man has led to questions about the utility of the *in vivo* studies and demand for more predictive models and tools based on the latest technologies. These two awards build on key themes emerging from our workshop on asthma held jointly with the MRC late in 2009 and are part of our programme of work to provide better tools for scientists in universities and industry which avoid the use of animals.

4.1.3 Pilot project scheme

We have launched a pilot project scheme for our 2011 grants round. Many research proposals we receive are high risk because they aim to move away from historical, conventional or 'gold-standard' models and to shift to novel technologies and approaches. The pilot project scheme will provide a mechanism for funding small scale projects which aim to generate data to demonstrate proof of principle and to support subsequent larger applications. This will allow us to minimise risks and continue to ensure value for money in the research we fund. Awards of up to £75k and 12 months duration will be available.

"We have introduced a strategic awards scheme which will allow us to use our expertise to stimulate and shape specific areas of research."

[11] *Persaud SJ, Arden C, Bergsten P, Bone AJ, Brown J, Dunmore S, Harrison M, Hauge-Evans A, Kelly C, King A, Maffucci T, Marriott CE, McClenaghan N, Morgan NG, Reers C, Russell MA, Turner MD, Willoughby E, Younis MY, Zhi ZL, Jones PM (2010). Pseudoislets as primary islet replacements for research: report on a symposium at King's College London, UK. Islets 2: 236-9*

4.1.4 Studentships

We have awarded five PhD studentships as part of our strategy to embed the 3Rs in the training and early career development of the research leaders of the future (see Appendices). This year we received over 70 applications from 41 institutions, a 58% increase in applications over 2009. We plan to double the number of places available from 2011.

4.2 3Rs prize

We have awarded our 2010 3Rs prize, which is sponsored by GlaxoSmithKline, to Professor Jane Hurst, University of Liverpool, for her research published in *Nature Methods* which shows the effects of handling on mouse welfare[12]. Most laboratory mice are handled on a regular basis and are usually picked up and restrained by their tail. Professor Hurst's research demonstrates that this method of handling causes high levels of anxiety and stress which can influence the outcome of experiments and that this can be substantially reduced by catching the mice using a plastic tunnel or cupped hands.

"Professor Hurst's research demonstrates that this method of handling causes high levels of anxiety and stress which can influence the outcome of experiments and that this can be substantially reduced by catching the mice using a plastic tunnel or cupped hands."

Mice are the most commonly used laboratory animals and this paper was selected for the award because of its potential widespread impact on animal research. It also illustrates the important link between good animal welfare and good science. The prize grant of £10k will be used to provide training for scientists and animal care staff on handling methods and also to assess the effects of different handling methods on stress physiology.

4.3 Improving standards in animal research

We have focused on delivering high standards in animal research by publishing new guidelines and online resources and by working with the funding bodies to embed the 3Rs in their decision making processes.

[12] *Hurst JL and West RS (2010). Taming anxiety in laboratory mice. Nature Methods 7:825-26*

4.3.1 Advising the major bioscience research funding bodies

We have continued to provide advice and guidance to the major bioscience funding bodies, including peer review of all grant applications involving the use of NHPs, cats, dogs and equidae. The Wellcome Trust funds a scientific post in the NC3Rs to facilitate this and other work, which in 2010 included the development of a new policy for the Research Councils on standards of animal welfare expected at antibody suppliers (www.nc3rs.org.uk/antibodiespolicy).

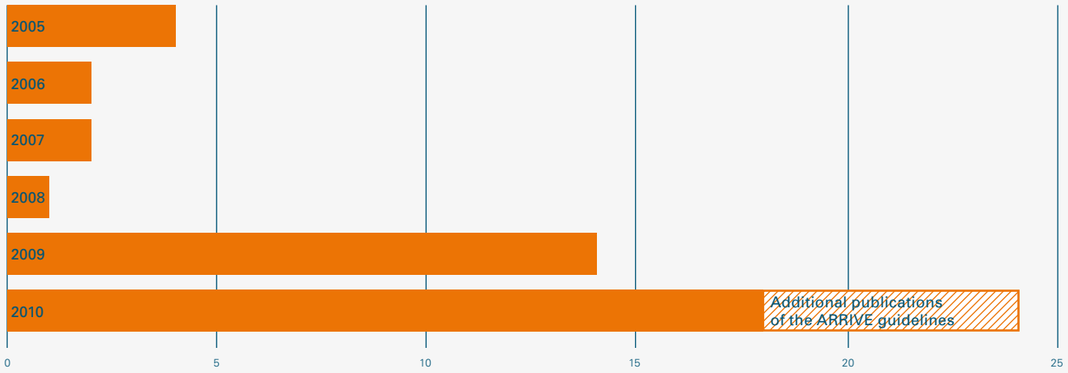
This year we have reviewed 44 grant applications for the MRC, BBSRC and Wellcome Trust, identifying new opportunities to apply the 3Rs and improve animal welfare. Over half of these applications involve the use of macaques, primarily in neuroscience research, and we have therefore focused our refinement activities in this area.

Refining scientific procedures using non-human primates

We have produced recommendations on refining the use of food and fluid control in macaques. These are commonly used procedures in NHP neuroscience studies where hunger or thirst are used to motivate animals to perform repeated specific tasks for food or fluid rewards. This work was published in the *Journal of Neuroscience Methods* in November[13] and has been promoted at neuroscience institutes in the UK, France and Israel. In 2011 we will be launching a new international data sharing initiative to strengthen the evidence base for best practice in the use of food and fluid control.

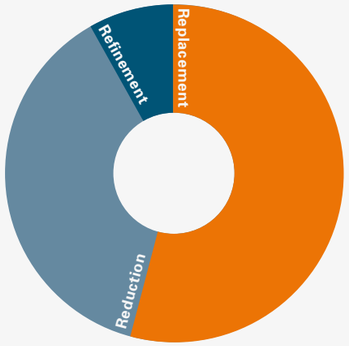
We have also continued to organise an annual meeting on primate welfare, sponsored by the Wellcome Trust, for scientists, veterinarians and animal care staff. In 2010 we brought together 115 delegates from 51 organisations in Europe, the Americas and Asia. The meeting included a survey of delegates on training requirements and this will provide the basis for a new training course covering topics such as NHP behaviour, surgery, anaesthesia and analgesia, which we will begin developing in 2011 with the aim of roll out in 2013.

[13] *Prescott MJ, Brown VJ, Flecknell PA, Gaffan D, Garrod K, Lemon RN, Parker AJ, Ryder K, Schultz W, Scott L, Watson J, Whitfield L (2010). Refinement of the use of food and fluid control as motivational tools for macaques used in behavioural neuroscience research: Report of a working group of the NC3Rs. Journal of Neuroscience Methods 193:167-188*

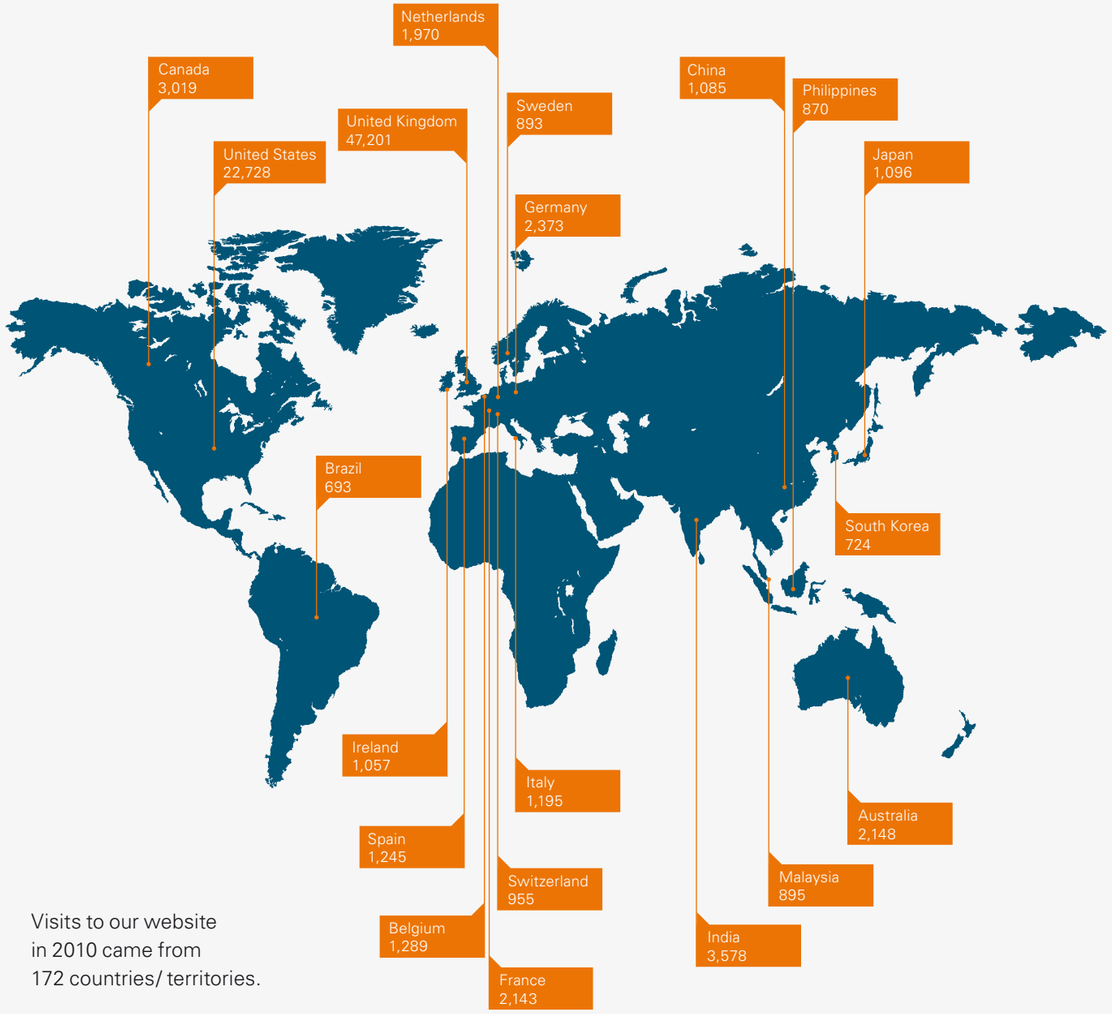


Publications from our staff

58% increase in the number of studentship applications in 2010



Grants awarded in 2010



Visits to our website in 2010 came from 172 countries/ territories.

Top 20 shown

"We have published over 20 papers, presented our work at 36 national and international events and organised 11 symposia and workshops."

4.3.2 New guidelines on reporting of animal experiments

We have published new guidelines called ARRIVE (Animal Research: Reporting *In Vivo* Experiments) which will improve the reporting of animal research[14]. Developed in consultation with the scientific community, including journal editors and statisticians, the ARRIVE guidelines were published in June in *PLoS Biology* and simultaneously in five other scientific journals. They were also covered in a *New Scientist* editorial[15].

The guidelines build on a survey we previously conducted which showed that many publications reporting publicly funded animal research from the UK and USA lack key information on how the study was designed, conducted and analysed . Poor reporting can limit the value of publications in informing future scientific studies and policy and result in unnecessary animal use. The ARRIVE guidelines are intended to address this, consisting of a 20-point checklist of essential information that should be included in publications reporting animal research.

The ARRIVE guidelines have been adopted by the UK's bioscience funding bodies including the MRC, BBSRC and the Wellcome Trust and by a range of journals and publishers. We will focus on further uptake in 2011 to complement a new programme of work on experimental design.

4.3.3 New web resources

We have developed a new website 'Procedures With Care' (www.procedureswithcare.org.uk) in partnership with the Institute of Animal Technology and Newcastle University. Launched in October, the website includes tutorials with high definition video clips on the administration of substances to rodents, highlighting best practice in terms of animal welfare. The site received over 2,500 visitors in its first month, predominantly from the USA (42%), UK (17%) and Japan (14%). We have also increased traffic to our own website by 20%, with over 113,000 visits from more than 77,000 visitors in 2010. This includes a 5% increase in the number of visits from overseas.

[14]*Kilkenny C, Browne WJ, Cuthill IC, Emerson M, Altman DG (2010). Improving bioscience research reporting: The ARRIVE guidelines for reporting animal research. PLoS Biology 8:e1000412 doi:10.1371/journal.pbio.1000412*

[15]*Robinson V (2010). Make every animal experiment count. New Scientist 2767: 3*

4.4 Raising the profile of the 3Rs

We have continued to focus on raising the profile of the 3Rs across the scientific community. In 2010 we have published over 20 papers, presented our work at 36 national and international events and organised 11 symposia and workshops (see Appendices). Our scientific staff are members of various ethical and scientific review panels, committees and editorial boards, including the *In Vivo* Science Strategic Skills Awards panel, the *In Vitro* Toxicology Society Committee, and the *Laboratory Animals* editorial board.

We have also established new partnerships with the learned societies. In March, we held our first symposium with the Physiological Society and British Pharmacological Society. This meeting challenged some of the UK's top cardiovascular researchers to define a future research agenda with reduced reliance on the use of *in vivo* models. Chaired by Professor Dame Nancy Rothwell, University of Manchester, the symposium was attended by over 100 delegates. Presentations covered the 3Rs in diverse areas from vascular biology to cardiac physiology and diseases such as atherosclerosis. Research sponsored by the NC3Rs at Imperial College London was also presented.

In collaboration with the newly formed Society of Biology we organised a one day symposium in June which built on our previous events with its predecessor the Biosciences Federation. The symposium was attended by over 100 delegates and featured a range of presentations focusing on rodent behaviour and emotions and the implications for assessing animal welfare, and the application of the 3Rs to animal models of disease including gastrointestinal disorders and diabetes. Further events with the learned societies are planned for 2011.

"We held our first symposium with the Physiological Society and British Pharmacological Society."

5

Financial summary

This annual report describes the NC3Rs activities for the calendar year 2010. Our financial accounting period runs from 1 April to 31 March each year. The MRC provides the NC3Rs with accounting and budget management services. The financial information provided covers the period 1 April 2009 to 31 March 2010 and has been provided to us by the MRC.

5.1 Income

Total income for this financial period was £4.78 million, an increase of 5% from the period April 2008 to March 2009. Our income from 'Government' comes from the Department for Business, Innovation and Skills (through the MRC and BBSRC) and the Home Office. In 2009/2010 there was a 23% increase in funding from the MRC and a 24% increase from the BBSRC. Funding from the Home Office remained level at £0.25 million. Income from 'charities' was less in the financial year ending 31 March 2010. This is because in 2008/2009 we received a one-off supplement from the Wellcome Trust for grant awards. Income from 'industry' includes sponsorship from the pharmaceutical, chemical, agrochemical and consumer product industries. This increased in 2009/2010 as a result of new funding to support scientific posts and specific activities.

Income

	2009/2010 £ million	2008/2009 £ million
Government	4.52	3.82
Charity	0.10	0.58
Industry	0.16	0.13
Total	**4.78**	**4.53**

5.2 Expenditure

Our annual budget is agreed by the NC3Rs Board. Total expenditure was reduced from £3.19 million in 2008/09 to £3.15 million in 2009/10.

Board costs include travel for members to meetings and associated honorariums. In the period 2009/2010, Board costs were £11,331, 11% lower than in the previous financial year. In 2008/2009 Board costs included one-off recruitment costs (mainly advertising) for the NC3Rs Board Chairman.

Programme costs include initiatives led by the NC3Rs staff. This covers the costs for events, working groups and the salaries of scientific and business staff who support these initiatives. In the period 2009/2010, expenditure on programme costs was £0.95 million, an increase of 5% over the previous financial year. We increased spending on commissioned research to support our activities on pharmacokinetics and acute inhalation toxicity.

Operating costs include staff salaries for core administrative duties, staff travel and training, recruitment, stationery, rental and service charges and publishing costs. In the period 2009/2010, expenditure on operating costs was £0.33 million, 4% lower than in the previous financial year. This is due to a reduction in staff recruitment costs.

Research funding expenditure covers grants awarded in 2005, 2006, 2007, 2008 and 2009. This was £1.86 million in the period 2009/2010, 3% lower than in the previous financial year. This is due to a £0.35 million rebate from MRC for previous grant payments.

Expenditure on studentships awarded in October 2009 does not commence until October 2010 and there is therefore no spend in 2009/2010.

Grants awarded typically commit expenditure over a three year period. Commitments for future years are covered by agreed funding from the MRC and BBSRC.

Expenditure

	2009/2010 £ million	2008/2009 £ million
Board costs	0.011	0.013
Programme costs	0.95	0.91
Operating costs	0.33	0.34
Research funding	1.86	1.93
Total	**3.15**	**3.19**

Research funding expenditure

	Commitments made each year on new grants £ million	Actual spend on grants in year £ million
2004/05	0.52	0.12
2005/06	0.99	0.27
2006/07	1.47	0.82
2007/08	2.47	1.28
2008/09	2.65	1.93
2009/10	4.86	1.86
Total	**12.96**	**6.28**

6

Appendices

Research grants 2010

Professor David Baker and Dr Mark Baker, Queen Mary, University of London
£368,512
2Rs (refining and reducing) of animal models of multiple sclerosis

Professor Wendy Barclay, Imperial College London
£125,368
Highly differentiated cultures of ferret airway epithelium for the study of respiratory viruses, including influenza

Dr Caroline Brennan, Queen Mary, University of London
£356,952
Zebrafish behavioural assays to identify genetic mechanisms underlying drug seeking and addiction

Dr Louis Chesler, Dr Suzanne Eccles and Professor Andrew Pearson, Institute of Cancer Research
£291,488
Replacement of animals in cancer drug development by using 3D *in vitro* functional assays for increased predictive power

Professor Sian Harding and Dr Nadire Ali, Imperial College London
£323,316
Stem cell-derived cardiomyocytes for detection of cardiotoxicity in cancer therapeutics

Professor Christer Hogstrand and Dr Nic Bury, King's College London and Dr Peter Kille, Cardiff University
£386,300
FIGCS: An *in vitro* model to replace ecotoxicity testing of fish to pharmaceuticals

Dr Peter Hohenstein and Professor Nicholas Hastie, MRC Human Genetics Unit, and Professor Jamie Davies, University of Edinburgh
£428,344
Reducing mouse number in complex genetic experiments

Dr Roland Jones, University of Bath
£362,968
A chronic model of epilepsy in organotypic brain slice cultures of the rat entorhinal cortex

Professor Charles Vyvyan Howard, Dr George McKerr, Dr Kurt Saetzler and Professor Ana Soto, University of Ulster
£361,934
A 3D tissue model of breast morphogenesis for replacing animals in testing for endocrine disrupting substances

Dr Mohammed Nassar, Professor David Grundy and Professor Mathew Holley, University of Sheffield
£387,392
Derivation of conditionally immortalised mouse dorsal root ganglia cell lines

Dr Owen Sansom and Dr Marcos Vidal, University of Glasgow
£350,528
Using the *Drosophila* fly intestine to investigate Wnt targets *in vivo*

Professor Christopher Secombes, Dr Yolanda Corripio-Miyar and Dr Jun Zou, University of Aberdeen
£156,812
Development of *in vitro* assays to determine vaccine efficacy in fish

Dr Dorothea Sesardic, Dr Christine Escargueil and Dr Roland Fleck, National Institute for Biological Standards and Control (NIBSC)
£337,308
Development of cell based assays as replacement assays for botulinum toxins and antitoxins

Strategic awards 2010

Dr Huw Golledge,
Professor Paul Flecknell,
Dr Melissa Bateson,
Dr Johnny Roughan,
Dr Silke Corbach-Soehle
and Dr Matt Leach,
Newcastle University

£295,620

Assessing and refining the humaneness of gas euthanasia techniques for laboratory rodents

Professor Donna Davies,
Professor Hywel Morgan,
Dr Emily Swindle,
Professor Stephen Holgate,
Professor Peter Howarth,
Dr Tim Millar and
Dr Jane Collins,
University of Southampton

£499,728

A tissue engineered construct to monitor mucosal immunity in asthma

Dr Felicity Rose,
Dr Amir Ghaemmaghami,
Professor Alan Knox,
Dr Jonathan Aylott,
Professor Chris Brightling,
Professor Chris O'Callaghan,
and Dr Yassine Amrani,
University of Nottingham

£499,498

Developing a platform of *in vitro* models of asthmatic and healthy lung: An alternative to the use of animals in asthma research

Studentships 2010

Dr Colin Brown,
Newcastle University

£120,000

Development of *in vitro* human and rat proximal tubule cell models as a platform for drug transporter and drug-drug interaction studies

Dr Alexander Easton and
Professor Madeline Eacott,
Durham University

£120,000

Spontaneous recognition tasks and the 3Rs

Dr Fionnuala Lundy,
Dr Timothy Curtis,
Dr Lorcan McGarvey and
Professor S. Louise Cosby,
Queen's University Belfast

£90,000

An *in vitro* model for pain and neurogenic inflammation in the oro-facial region and upper airways

Dr Mark Lythgoe,
Professor Elizabeth Fisher,
Dr Abraham Acevedo and
Dr Sebastien Ourselin,
University College London

£120,000

Using non-invasive *in vivo* imaging to address the 3Rs in high-throughput mouse phenotyping

Professor Melanie Newport,
Dr Sandra Sacre,
Dr Simon Waddell,
and Dr Chris Finan,
Brighton and Sussex
Medical School

£90,000

Neonatal BCG vaccination: screening for genetic factors that influence host-pathogen interactions and reducing and replacing the requirement for animal infection models in immune mechanism discovery

Events organised by the NC3Rs

Acute toxicity workshop

20 January, London

Meeting to determine whether acute toxicity data are used to support pharmaceutical overdose and chemical poisoning and what other information could be used if acute toxicity data are not available.

Science review meeting

27 January, London

Annual event providing a scientific overview of the NC3Rs progress and future plans, including presentation of the 3Rs prize.

Second annual predictive
toxicology workshop

23 February, London

Included a workshop organised by the NC3Rs on 'Predicting Toxicology without Animals: Realistic Prospect or Utopian Fantasy?'

Institute of Animal Technology
annual congress

18 March, Scotland

Included a session organised by the NC3Rs on animal welfare and refinement.

Cardiovascular models
symposium

31 March, London

A joint symposium with the Physiological Society and the British Pharmacological Society to define a future cardiovascular research agenda with reduced reliance on the use of *in vivo* models.

Joint symposium with
the Society of Biology

10 June, London

Showcasing the latest advances in the 3Rs, focusing on rodent behaviour, welfare assessments and the application of the 3Rs to animal models of disease.

Regulators roadshow

1 October, Liverpool

With UK regulators and experts from the chemicals and consumer products industry, to discuss recent developments in alternative methods for safety assessment.

Primate welfare meeting

27 October, London

Annual event, sponsored by the Wellcome Trust, providing a forum for scientists, veterinarians and animal care staff to discuss NHP use and welfare.

American College of Toxicology
annual meeting

7 November, Baltimore, USA

Included a continuing education course co-organised by the NC3Rs on minimising NHP use in monoclonal antibody development.

Cell transformation workshop

9 November, London

To discuss the latest advances in research on cell transformation assays for assessment of the carcinogenic potential of chemicals. This event was co-sponsored by the UK Environmental Mutagen Society (UKEMS).

Workshop on the threshold
approach for acute fish toxicity
testing of pesticides

16 December, London

With representatives of European crop protection companies and regulators to consider how the threshold approach can be applied to reduce the use of fish for acute toxicity testing of pesticide products.

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Board

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NC3Rs

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Thank you to the following Board Members whose term ended in 2010:

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University of Nottingham

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Centre for Environment, Fisheries and Aquaculture Science

Professor Ian Jackson
MRC Human Genetics Unit

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until April 2010
(Experimental design and reporting)

Dr Mark Prescott
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Ms Ashley Scott
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Dr Harriet Warburton
until July 2010
(Research funding)

Mr Tim Watson
until June 2010
(Communications manager)

Dr Emma Willoughby
until June 2010
(Research funding)

Acronyms

ARRIVE:	Animal Research: Reporting *In Vivo* Experiments
BBSRC:	Biotechnology and Biological Sciences Research Council
CNS:	Central nervous system
FCP:	Fixed Concentration Procedure
ICH S6:	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use: Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals S6
ILSI-HESI:	International Life Sciences Institute Health and Environmental Sciences Institute
MTD:	Maximum tolerated dose
MRC:	Medical Research Council
NHP:	Non-human primate
OECD:	Organisation for Economic Co-operation and Development
REACH:	Registration, Evaluation, Authorisation and restriction of Chemicals

Glossary

Abuse potential
Likelihood of a drug being used in non-medicinal situations for the positive pyschoactive effects it produces, such as euphoria.

Acute toxicity
Harmful effects occurring in a short time after administration of a single dose of a substance or after multiple doses given in up to 24 hours. Acute toxicity studies may be conducted by the oral, dermal or inhalation routes.

Chronic toxicity
Harmful effects following repeated exposure to a substance over an extended period of time.

Carcinogenicity
Ability of a substance to induce cancer or increase its incidence.

Ecotoxicology
The study of the toxic effects of chemicals on living organisms within ecosystems.

Maximum tolerated dose
The highest dose at which target organ toxicity is likely to be observed in animals without morbidity or mortality.

Pharmacokinetics
Process of the uptake of drugs by the body, the metabolism they undergo, the distribution of the drugs and their metabolites in the tissues and their elimination from the body.

Pseudoislets
Groups of pancreatic cells grown together *in vitro* to form structures which behave in a similar way to the islets of Langerhans, clusters of cells that secrete insulin in the pancreas.

Recovery animals
Animals that are used in a toxicity study to assess whether any harmful effects observed are reversible once the study has ended.

Skin sensitisation
Potential of a chemical to cause skin allergy.

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Dr SC Smith,
University of Sheffield

Gibbs Building
215 Euston Road
London, NW1 2BE

T : 020 7611 2233
F : 020 7611 2260
E : enquiries@nc3rs.org.uk
W : nc3rs.org.uk

NC3Rs

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