Impact case study (REF3b)

Institution: Newcastle University
Unit of Assessment: UoA 6: Agriculture, Veterinary and Food Science
Title of case study: Improving animal welfare through effective pain assessment and alleviation in laboratory rodents and rabbits

1. Summary of the impact (indicative maximum 100 words) Newcastle University research has changed policy and practice relating to the provision of pain relief to rodents and rabbits. This has impacted on up to 35 million animals worldwide during the REF period. Having established the under-use of analgesics in laboratory rodents, Newcastle researchers developed objective pain scoring systems. These established that analgesics should be administered to rodents and rabbits, and that the efficacy of this treatment should be assessed objectively. The research resulted in changes to policy statements, institutional policies (both academic and industrial) and individual research worker practices in the USA, Canada, Australia, Europe and the UK. This has produced clear benefits to the welfare of animals used in biomedical research, helps to satisfy public concerns that animals used in research should experience the minimum pain and distress, and improves scientific outcomes of research, since pain is an uncontrolled experimental variable, that can adversely affect study results.

2. Underpinning research (indicative maximum 500 words) Background Each year over 7 million research and veterinary procedures are carried out worldwide on small rodents and rabbits, with around 472,000 procedures carried out in the UK alone. These can result in post-procedural pain and suffering. Aside from the important animal welfare issues, pain can influence research outcomes. Therefore, the elimination or control of pain within animal research represents both good science and good welfare. In the 1990s, the use of analgesia in animal research was incorporated into UK and EU legislation. However, it was recognised that the guidelines were having little impact on the use of analgesics in laboratory animals (Flecknell, 1994, Lab Anim, 28[3]:222–31). Indeed, neither the UK nor EU legislation included practical recommendations for the assessment and alleviation of post-procedural pain in animals. Research The relative under-use of analgesics following surgical procedures in animal research was confirmed by the Newcastle group via informal contact with research workers and regulators, by an email survey and a literature review [**P1**]. The use of analgesics to prevent or alleviate pain in animals used in research was reported to be minimal in rodents, if given at all. Use in larger species was more widespread, but not routine. It was determined that a poor ability to recognise pain and the subsequent uncertainties surrounding the use of pain relief were the main reasons for this [**P1**]. Crucially, any analgesics used were administered at arbitrary doses, with no evidence of efficacy. This was established by the Newcastle-run surveys [**P1**] and a survey of research establishments conducted by the RSPCA. In 1997, Prof Flecknell and his team at Newcastle began their unique research into identifying means of objectively assessing post-procedural pain in animals and the intensity of that pain, in order to enable efficient pain relief to be given. They analysed the behaviours of rabbits and rodents following surgical and non-surgical procedures, and distinguished behaviours specific to pain sensation [**P2**, **P3**]. A pain scoring system was developed and used in subsequent studies to establish appropriate and effective doses of analgesics. This behaviour-based pain scoring system was evaluated against a simple subjective approach commonly used in clinical practice and research settings and was shown to be significantly more effective in assessing pain. The group also showed that an obstacle to recognition of pain using this behaviour-based approach was a tendency to attend to the face of the animal, rather than other areas where pain-related behaviours were expressed [**P4**]. This obstacle was overcome by developing "cage-side" pain scoring based on facial expression assessment, in collaboration with colleagues in Canada who had initially developed the approach in mice for use in the development of novel analgesics [**P5**, **P6**]. The work

of the group has led to the only, validated, cage-side pain scoring methods available for these species.

Researchers

Professor Paul Flecknell, 1985-95, Academic-related staff, 1995- Professor of Laboratory Animal Science; Project Leader; developed the behaviour-based assessment and pain scoring systems.

Dr Matt Leach – Postdoctoral Research worker, 2005-2012., Lecturer in Animal Science, 2012-; developed the pain-face scoring systems and behaviour-based pain assessments in rabbits.

Amy Miller –Post-doctoral researcher, 2010- validated the mouse behaviour based systems.

Dr Claire Richardson, 2003, Academic-related staff, 2012- Postdoctoral research fellow –carried out the literature reviews.

JV Roughan (1998 onwards), research associate/senior research associate, staff scientist 2006-

3. References to the research (indicative maximum of six references)

[**P1**] Richardson, CA and Flecknell, P.A. (2005) Anaesthesia and post-operative analgesia following experimental surgery in laparotomy rodents – are we making progress? ATLA, 33, 119-127. **Cited by 55.**

[**P2**] Leach, M.C, Allweiler, S., Richardson, C., Roughan, J.V., Narbe, R., Flecknell, P.A. (2009) Behavioral effects of ovariohysterectomy and oral administration of meloxicam in laboratory housed rabbits. Research in Veterinary Science 87, 336-347 **Cited by 24.** doi: 10.1016/j.rvsc.2009.02.001

[**P3**] Wright-Williams S. L., Courade J.-P., Richardson C.A., Roughan J.V., Flecknell P.A. (2007). Effects of vasectomy surgery and meloxicam treatment on faecal corticosterone and behaviour in two strains of laboratory mouse. Pain, 130, 108-118. **Cited by 43.** doi:10.1016/j.pain.2006.11.003

[**P4**] Leach, M.C, Coulter, C.A., Richardson, C.A. and Flecknell, P.A. (2011) Are We Looking in the Wrong Place? Implications for Behavioural-Based Pain Assessment in Rabbits (Oryctolagus cuniculi) and Beyond? PLoS ONE, 6, e13347. **Cited by 8, 3,894 views.** doi:10.1371/journal.pone.0013347

[**P5**] Leach MC, Klaus K, Miller A, Scotto di Perrotolo M, Sotocinal SG, Flecknell PA. (2012) The Assessment of Post-Vasectomy Pain in Mice using Behaviour and the Mouse Grimace Scale. PloS One, 7(4), e35656. **Cited by 4, 3,437 views.** doi: 10.1371/journal.pone.0035656

[**P6**] Keating, C.J., Thomas, A.A., Flecknell,P.A. and Leach, M.C. (2012) Evaluation of EMLA Cream for Preventing Pain during Tattooing of Rabbits: Changes in Physiological, Behavioural and Facial Expression Responses. PLoS One, 7 (9), e44437 **Cited by 5, 7,845 views.** doi:10.1371/journal.pone.0044437

Grants

The research was funded by a series of peer-reviewed project grants from the BBSRC, MRC, the UK National Centre for the 3Rs, UFAW, Swiss 3Rs, VETO, and the Swedish Agriculture Board (total value of awards >£0.75 million, 2001-2011). It has also been recognised by 10 awards from a range of organisations including the Prince Laurent Foundation, FELASA, LASA, CAAT and the Academy of Surgical Research.

4. Details of the impact (indicative maximum 750 words)

Prior to Newcastle's research, it was commonplace to see statements such as '[the] rodents did not experience pain' or 'rodents and rabbits show no signs of pain and so require no analgesics' in scientific publications. However, our research has had a major impact in changing such attitudes. The findings of the research at Newcastle were summarised and disseminated to a wider audience

via a website, workshops, conferences, text books, book chapters, review articles and a Dutch television documentary. The website was set up with the aim of '…providing practical guidance in recognising signs of health and good welfare and to help users of the site to become better able to identify signs of pain, distress and poor welfare in laboratory animals' (www.ahwla.org.uk). The successful outcomes of research, coupled with the extensive and sustained efforts to disseminate our results has led to worldwide changes in a range of policy statements, practice guides, institutional policies (academic and industrial) and individual research worker practices. As a result, analgesic use in research animals has increased. This was confirmed by repeating the literature review (1, above), for the time periods 2005-6 and 2012-13. Reported analgesic use for laboratory rodents increased by 50%, from 14% to 21%, between these two time periods (in preparation).

UK policy and practice

In the UK animal research which may cause pain, suffering, distress or lasting harm is regulated under the Animals (Scientific Procedures) Act 1986. In England, Scotland and Wales, this Act is implemented by the Home Office. It is clearly stated in the licence conditions that 'The licence holder must use analgesia or another appropriate method to ensure that the pain, suffering and distress caused by regulated procedures are kept to a minimum'. The Home Office also carry out regular inspections to ensure that all animal research is in accordance with licence conditions, and have confirmed that their inspectors '…frequently make use of [the Newcastle findings] when evaluating research procedures in rodents that require assessment and alleviation of post-surgical pain' [**E9**] In addition, the Inspectors '*…frequently recommend research workers to refer to [the Newcastle findings] when formulating their post-operative care regimens*' and '*…regularly facilitate direct contact between research workers and* [the] *group at Newcastle whenever specialist advice on analgesia is required*' [**E9**]. In the UK, this impacts directly on up to 472,000 animals per year that undergo procedures under general anaesthetic and so may require analgesics [**E9**, Home Office Statistics of Scientific Procedures on Living Animals Great Britain 2012, **E8**].

International policy and practice

In the US National Academy of Sciences Report (Institute of Laboratory Animal Resources), reference to the work by the Newcastle group is given in conjunction with the statement that '…fundamental to the relief of pain in animals is the ability to recognise its clinical signs in specific species'. Their 2011 report [**E4**] informed revisions to Pain and Distress in Laboratory Animals guidelines, produced by The Animal Research Advisory Committee. These mandatory guidelines, which form part of the National Institutes of Health (NIH) policy, now clearly state that 'Pre-emptive measures should be taken to minimise or prevent the development of pain and/or distress', citing the Newcastle work. NIH funds research at over 2,500 institutes and is the largest source of funding for medical research in the world. This guidance is also included by the USA Department of Agriculture, Animal Welfare Information Centre [**E7**]. These policies impact significantly on European research, as USA-European collaborations must adopt this guidance. Hence approximately 4 million animals per year in the USA would benefit.

In Canada, oversight of scientific animal use is the responsibility of the Canadian Council on Animal Care. They cite the Newcastle work on their website (updated 2012, e.g. Keating et al, 2012, and www.ahwla.org.uk), stating that analgesic dosing '*…should be tailored to the individual animal*' [**E1**]. The Australian and New Zealand Council for the Care of Animals in Research and Teaching website also includes references to the Newcastle findings [**E2**]. A further 0.6 million animals per year would benefit. As mentioned earlier, numerous institutions cite the research work in their requirements for analgesic use (eg Univerities of Western Ontario, West Virginia, Michigan, Iowa, Pennsylvania, Alabama, New York School of Medicine)

UFAW (Universities Federation of Animal Welfare) is internationally recognised as having led the way in improving, and promoting high standards of, animal welfare, and their Handbook on the Care and Management of Laboratory and other Research Animals serves to inform and guide practice. Their most recent edition (2010) frequently cites the Newcastle research in relation to the assessment of pain and welfare. The behaviour-based assessment developed at Newcastle and their researcher training system is suggested as an aid for researchers to '*…identify and score*

pain more accurately and reliably' [p.86, **E3**].

Education and training

The work at Newcastle has led to a major change in practice across the world. These changes relate to which analgesics are given, the dosing of these products and the assessment of pain via behaviour observation [e.g. **E4**]. The website AHWLA (Assessing the Health and Welfare of Laboratory Animals, www.ahwla.org.uk) was set up (with support from the Swiss 3R Research Foundation) to '…provide practical guidance in recognising signs of health and good welfare and to help users of the site to become better able to identify signs of pain, distress and poor welfare in laboratory animals' . Since January 2008, the website has had 70,000 unique visitors from 75 countries, This material, together with instructional video-material produced from data collected on the other studies listed above (in mouse and rabbit) has been made available to those delivering training to new research staff, and is used on numerous training course (e.g. [**E5**], [**E10**]). The Newcastle work is also cited in the Australian government's 'Guidelines to promote the wellbeing of animals used for scientific purposes', where the film is recommended as an educational resource for behaviour-based pain scoring [**E6**]. The assessment methods are taught at workshops at Newcastle (established with funding from BBSRC) and elsewhere. The dose recommendations have been incorporated into the training notes provided to the majority of UK research workers undertaking mandatory Home Office training in surgery and anaesthesia (Module 4) and over 3000 copies of the CDs containing this material have been distributed since 2008. In addition to the specific impact on pain relief for rodents and rabbits, the work has been extrapolated to other species, so these activities impact on all animals used in research.

5. Sources to corroborate the impact (indicative maximum of 10 references)

[**E1**]: Website: Canadian Council for Animal Care (CCAC)

[**E2**]: Website: The Australian and New Zealand Council for the Care of Animals in Research and Teaching (ANZCCART), http://www.adelaide.edu.au/ANZCCART/

[**E3**]: Hubrecht & Kirkwood (2010). The UFAW Handbook on the Care and Management of Laboratory and Other Research Animals. Blackwell Publishing Ltd, UK. (letter from editor and deputy director of UFAW commenting on importance of work)

[**E4**]: National Research Council of the National Academies (2009) Recognition and alleviation of Pain in Laboratory Animals, National Academies Press, Washington D.C.

[**E5**]: Letter from Karolinska Institutet, Stockholm, Sweden.

[**E6**]: Australian Government, National Health and Medical research Council: Guidelines to promote the wellbeing of animals used for scientific purposes, 2008.

[**E7**]: United States Department of Agriculture, Animal Welfare Information Centre (http://awic.nal.usda.gov)

[**E8**]: Letter from veterinarian responsible for animal models, GSK, reporting successful adoption of MGS scoring in their facility

[**E9**]: Letter from the head of the Animals in Science and Research Unit, UK Home Office indicating importance of work and use by HO inspectors

[**E10**]: Letter from Swiss Animal Welfare Organisation