The **A P C**
Animal Procedures Committee

Review of the assessment of cumulative severity in non-human primates used in neuroscience research

Background and Terms of Reference

Background

The Animal Procedures Committee (APC) is an advisory non-departmental public body. Its role is to advise the Home Secretary on matters concerned with the Animals (Scientific Procedures) Act 1986. This especially relates to any experimental or scientific procedures applied to a protected animal that may have the effect of causing that animal pain, suffering, distress or lasting harm.

The Animal Procedures Committee (APC) has, over recent years, increasingly considered the life-time experience of animals used in animal scientific procedures when it considers project licence applications referred to it by the Home Office (see Annex A for a description of project licences referred to the APC and Annex B for the guidance given to applicants referred to the APC). This has been particularly pertinent in procedures involving non-human primates where the animals may undergo a number of procedures over a period of time.

Therefore, the APC has started this review, in conjunction with the Animals Scientific Procedures Inspectorate (ASPI), to help it assess the impact of multiple procedures administered over a period of time and the cumulative severity experienced by the animals in such procedures. The use of nonhuman primates in neuroscience research will be considered in this review but it is likely that the conclusions will have implications for assessing cumulative severity in other areas of research.

The APC notes that the timing of this review is additionally relevant as there is an emphasis on lifetime experiences of animals together with the requirement for retrospective reporting in the new EU Directive (2010/63/EU).

Directive 2010/63/EU requires that the assignment of the severity category shall take into account any intervention or manipulation of an animal within a defined procedure and that it shall be based on the most severe effects likely to be experienced by an individual animal after applying all refinement techniques. The Directive also highlights the need to consider the lifetime experience of animals in making decisions and points out that "…long-lasting moderate pain, suffering or distress…shall be classified as severe"

A paper outlining the current system of severity limits and bands, together with the relevant implications of Directive 2010/63/EU, is attached at Annex C.

Terms of Reference
The aim of this review is to consider how an assessment can be made of the cumulative severity experienced by animals undergoing multiple procedures over a prolonged period of time.

The review will encompass the following:

1. Consideration of the criteria by which to assess cumulative severity in non-human primates.

2. Consideration of the latest research to into understanding the cumulative severity experienced by animals undergoing commonly used procedures. This research may include physiological and behavioural studies.

3. The implications of considering cumulative severity for future project licence applications and implications of retrospective reporting under Directive 2010/63/EU.

4. Ethical considerations of cumulative severity.

Scope
1. The scope be confined to procedures involving non-human primates, concentrating on neuroscience research, but may include other research fields as appropriate.

2. The scope will include, but not be limited to the consideration of the following procedures:
    - Behavioural constraints and demands
    - Surgery and anaesthesia, including possible post-operative sequellae
    - Restrictions of food and water.

3. This review will concentrate on scientific procedures involving animals undertaken in Great Britain as covered by the Animals (Scientific Procedures) Act 1986.

Mode of operation
The review will be conducted by the Animal Procedures Committee, and led by its Primate Sub-Committee.

The review will be informed by a review of the literature on non-human primate cumulative suffering in the context of neuroscience research and related fields.

The review will consult widely, via meetings, interviews and correspondence with stakeholders, including researchers in the field, research funders and welfare organisations. Other parties who wish to submit evidence to the

review will be encouraged to do so, initially by a published invitation to make written submissions.

Representatives of the Animals Scientific Procedures Inspectorate (ASPI) will take part in the review, particularly the evidence gathering sessions, including attending meetings with stakeholders and participating in discussions. However, the findings of this review will be exclusively those of the Animal Procedures Committee and ASPI will provide its advice separately to the Secretary State, independent of the APC.

Proposed Timing

Terms of Reference finalised: February
Announcement and call for written evidence: March
Literature review – scheduled for March to May
Meetings, including with researchers, research funders, welfare interests and other stakeholders: March – June
Discussion of preliminary findings: June (APC meeting)
Draft report: September
Finalised report submitted to Home Office Ministers: November 2011.

Annexes:

Annex A: Referral of project licences to the APC
Annex B: Guidance to Project Licence Applicants referred to the APC Applications sub-committee
Annex C: The UK system of Severity Classification and Directive 2010/63

Annex A

Referral of project licences to the APC.

The APC sees applications for project licences that involve:

- the use of wild-caught non-human primates
- the use of cats, dogs, equidae (the horse family) or non-human primates in procedures of substantial severity
- a substantial severity banding (classification of suffering of an 'average' animal) or major animal welfare or ethical implications, involving:
  (a) xenotransplantation (surgical transferral from one animal to another of a different species) of whole organs or
  (b) chronic pain models or
  (c) study of the central nervous system
- applications of any kind raising novel or contentious issues, or giving rise to serious societal concerns

The APC advises the Home Secretary on such applications, offering advice on whether they should be granted and, if so, on any particular conditions they should have.

Annex B

Guidance to Project Licence Applicants referred to the APC Applications sub-committee

This guidance has been prepared by the APC Applications sub-committee (ASC) to help those with project licence applications referred to the APC understand and prepare for ASC review of the application. It gives some background to the review and sets out some questions commonly asked or project licence applicants.

Background

It is the duty of the APC to advise the Secretary of State (SoS) on such matters concerned with the Animals (Scientific Procedures) Act 1986 and her functions under it, as the Committee may determine or as may be referred to the Committee by the SoS.

The APC has requested, and the SoS agreed to, referral of specific categories project licence applications consideration and advice.

Since 2004, the categories of application to be referred include:

1. Any involving the proposed use of wild-caught non-human primates;
2. Any involving the proposed use of cats, dogs, equidae or non-human primates in protocols of substantial severity;
3. Any with a substantial severity banding, or major animal welfare or ethical implications, involving a) xenotransplantation of whole organs, b) chronic pain models, or c) study of the central nervous system;
4. Applications of any kind raising novel or contentious issues, or giving rise to serious societal concerns (for example, any application involving the genetic modification of non-human primates or embryo aggregation chimaeras involving dissimilar species).

Typically, the applicant is invited to meet with members of the ASC to discuss the application in person. ASC members are scientists and non-scientists (www.apc.gov.uk/aboutapc/workgroups.htm). The ASC does not wish to create additional work for project licence applicants, but has found very helpful if applicants prepare the following in advance of the meeting:

1. A lay summary of the proposed project written so as to be readily comprehensible by a member of the general public (see Abstract section of the Project licence application form http://scienceandresearch.homeoffice.gov.uk/animal-research/publications-and-reference/publications/licences/project-licences/).

2. A schematic (e.g. graph, flow chart, GANTT chart) showing the number and scheduling (and if possible, relative severity) of all procedures involved in the project that impact on the welfare of the animals.

Preparation of these documents is, of course, voluntary, but assists the ASC to understand and explore the scientific justification for the project procedures and their costs to the animals.

Invariably, the ASC wishes to estimate the total suffering experienced by the animals on the project, during their whole life-times, and to rationalise this against the expected benefits.

Common questions asked of applicants

Background, objectives and benefits

- What are the key objectives of the project, and the likely benefits (e.g. in terms of scientific knowledge, human or animal health, the 3Rs)?
- How does the project relate to progress made under previous or current project licences?
- To what extent has previous research (*in vivo/in vitro*) and existing data, literature and knowledge influenced the licence application? How has unnecessary duplication of previous work been avoided?
- What is the likelihood of achieving the project objectives, and what factors are critical for success?
- What are the key ethical issues?

Experimental design and the 3Rs

- How was the experimental design decided, and how have each of the 3Rs been integrated into the entire plan of work?
- Why is it necessary to use animals to achieve the project objectives? Why are non-animal alternatives unsuitable?
- What is the justification for use of the particular animal species/model?
- Was the advice of a statistician taken on minimising the number of animals to be used per experiment, and the appropriate methods for data analysis?
- How else has animal use been optimised?

Scientific procedures and animal welfare

- What is the justification for the particular scientific procedures to be used, and what are their effects on the animals involved?
- How many animals will undergo each procedure?
- How will pain, suffering, distress or lasting harm be avoided, recognised, alleviated and managed?
- Will anaesthesia and analgesia be used? Has advice been taken on the most appropriate agents and regimens?
- How frequently and by whom are the animals monitored before, during and after each procedure?
- What are the relevant clinical signs and the humane endpoints that will be applied?
- How are the animals acclimatised to, or trained to co-operate with, procedures?
- What are the standards of animal accommodation, environmental enrichment and care?
- Will single housing of animals be necessary?
- From where will the animals be sourced?
- What will happen to the animals when the work is completed?
- What is the rationale for nomination of the project severity band?

February 2011 **Annex C**

The UK system of Severity Classification and Directive 2010/63.

In considering the concept of cumulative severity, it is important to understand the current UK system of severity classification, and the changes being implemented by the new Directive 2010/63/EU. There are two elements to the current UK system – severity limits and severity bands.

What is a severity limit?

The severity limit applies to a protocol (procedure or series of related procedures applied to an animal) and is determined by the upper limit of the expected adverse effects that may be encountered by a protected animal, taking into account all appropriate measures, including those specified in the licence, which must be used to avoid and control adverse effects. It represents the worst potential outcome likely to occur to any animal subjected to the protocol. It is possible that none, or only a very small proportion, of the animals will actually experience severity approaching this limit.

There are four levels of severity limit: unclassified, mild, moderate, and substantial. During studies, licence holders are required to ensure that animals are appropriately monitored and cared for and that they take effective precautions to prevent, or reduce to the minimum consistent with the scientific objective, any pain, suffering, distress or lasting harm. The suffering of the animals has to be maintained within the severity limit specified, and within the constraints of the described adverse effects or the Home Office must be promptly notified should this be, or be likely to be, exceeded.

The unclassified limit applies to protocols performed entirely under general anaesthesia from which the animal does not recover consciousness. This includes the preparation and use of decerebrated animals.

The mild limit applies to protocols where only minor or transient welfare problems are expected. Many mild protocols involve no more than dosing by injection and blood sampling. A severity limit of mild may be appropriate if procedures which may be more severe are stopped, or effective controls are provided, before the animal suffers more than minor adverse effects.

The moderate severity limit includes those protocols where it is accepted that animals may experience a noticeable degree of pain, suffering, distress or lasting harm even when appropriate care and attention is provided. Most surgical procedures with recovery fall into this category.

The substantial severity limit includes those protocols which may cause a major departure from the animal's usual state of health or well-being with significant or prolonged animal suffering. For example, this would include animal models producing the full, uncontrolled, clinical signs associated with Parkinson's disease, some vaccine challenge studies where serious clinical disease may result and major surgery.

A complex case by case analysis is required for determination of severity limits. The concept of cumulative severity over the lifetime of an animal makes this evaluation even more complex.

What is a severity band?

The assessment of the severity band applies prospectively to the project as a whole and considers the likely adverse effects on all of the animals likely to be used in all the procedures within the project. It includes consideration of the nature, extent and duration of the likely pain, suffering, distress or lasting harm which is likely to be caused, the proportion of animals expected to reach the severity limit of each protocol, and the actions to be taken to relieve the suffering.

It is based on the overall level of suffering likely to be experienced by every animal which is estimated to be used in the project, not just the single worst possible case. It follows therefore that, for example, a project licence assessed overall as being of mild or moderate severity band may include one or more procedures (protocols) assessed as having a substantial limit.

The severity band is thus indicative of the "average" degree of suffering expected to be experienced by the animals in the project. Approximately 3% of projects are banded as unclassified, 36% as mild, 59% as moderate, and 2% as substantial.

A severity band is not a requirement of the Animals (Scientific Procedures) Act but is used as an administrative tool to give an indication of the likely overall severity experienced by the animals used in a particular project. Severity bands are not currently used outside the UK and will not be part of Directive 2010/63/EU.

What will change under Directive 2010/63?

The new Directive 2010/63/EU will introduce severity classification to all EU Member States. In July 2009, the Commission convened an Expert Working Group tasked to provide scientific-technical information on severity classification in support of the new directive. Experts were nominated by each EU Member State as well as a number representing relevant European organisations. The resulting report[1] defines four categories of severity: non-recovery, mild, moderate and severe.

Assignment of category is based upon the most severe effects likely to be experienced by an individual animal after applying all appropriate refinement techniques. Examples of different types of procedures falling into each category were agreed by the experts and published with the report which forms Annex VIII of the directive. Under the directive, an animal subjected to long lasting mild pain, suffering or distress will be classified, cumulatively, as suffering moderately, and likewise long lasting moderate pain, suffering or distress will, cumulatively, represent severe (substantial) severity.

[1] http://ec.europa.eu/environment/chemicals/lab_animals/pdf/report_ewg.pdf

This system of severity categories will be applied in the EU Member States when the directive is fully implemented in January 2013. A system of retrospective reporting will also be applied from January 2014 which will provide information on the actual severity experienced by the animals, taking into consideration the lifetime experience.