Private & confidential: *Please be aware that the contents of this form may be made public resulting from the "Freedom of information Act". Personal details will not be released.*

G. Non-Technical Summary (NTS)

NOTE: The Secretary of State considers the provision of a non-technical summary (NTS) is an essential step towards greater openness and requires one to be provided as part of the licence application in every case. You should explain your proposed programme of work clearly using non-technical terms which can be understood by a lay reader. You should avoid confidential material or anything that would identify you, or others, or your place of work. Failure to address all aspects of the non-technical summary will render your application incomplete and lead to it being returned.

This summary will be published (examples of other summaries can be viewed on the Home Office website at www.gov.uk/research-and-testing-using-animals.

Word limit; 1000 words

Project Title	Control of arousal and autonomic output from the brain
Key Words	Obesity, Diabetes, Blood pressure, Sleep, Arousal
Expected duration of the project	5 year(s) 0 months

Purpose of the project (as in ASPA section 5C(3))

Purpose	
Yes	(a) basic research;
	(b) translational or applied research with one of the following aims:
Yes	(i) avoidance, prevention, diagnosis or treatment of disease, ill-health or other abnormality, or their effects, in man, animals or plants;
Yes	(ii) assessment, detection, regulation or modification of physiological conditions in man, animals or plants;
No	(iii) improvement of the welfare of animals or of the production conditions for animals reared for agricultural purposes.
No	(c) development, manufacture or testing of the quality, effectiveness and safety of drugs, foodstuffs and feedstuffs or any other substances or products, with one of the aims mentioned in paragraph (b);
No	(d) protection of the natural environment in the interests of the health or welfare of man or animals;
No	(e) research aimed at preserving the species of animal subjected to regulated procedures as part of the programme of work;
No	(f) higher education or training for the acquisition, maintenance or improvement of vocational skills;
No	(g) forensic inquiries.

Describe the aims and objectives of the project (e.g. the scientific unknowns or scientific/clinical needs being addressed):

In 2010, 26% of adults and 16% of children in the UK were classed as obese. A further 42% of men and 32% of women were overweight. Co-morbidities related to obesity, such as diabetes, high blood pressure and kidney disorders, create massive personal and public health problems, and are projected to cost the NHS £9.7 billion per annum by 2050. In order to find new ways to treat metabolic diseases we need to understand the balance between energy intake (the food that we eat) and the energy that we expend (for example, through exercise and adaptive thermogenesis). We aim to understand how dieting, exercise, sleep, blood glucose and blood pressure link to obesity, and how they might be manipulated separately and safely.

What are the potential benefits likely to derive from this project (how science could be advanced or humans or animals could benefit from the project)?

New approaches or interventions developed as a result of our studies, could potentially benefit those suffering with metabolic diseases such as obesity, diabetes and high blood pressure.

What types and approximate numbers of animals do you expect to use and over what period of time?

We expect to use around 6000 experimental mice over a 5-year period.

In the context of what you propose to do to the animals, what are the expected adverse effects and the likely/expected levels of severity? What will happen to the animals at the end?

Often, we need to do surgery on our mice in order to manipulate how the brain responds to different signals. Sometimes, mice will be given an injection (either under the skin, into a vein or directly into the brain) with minimal disturbance. We can carry out a range of physiological tests on the mice. Thus, we might put them in a scanner to see how much fat they have, measure their blood pressure, or measure their metabolic rate. Occasionally, we even train our mice to poke their noses into holes to break an infrared beam or to press a little lever, which provides them with a sugar reward. This can tell us about their motivation to eat. Invariably, the parameters we measure are very simple: for example, how much food do they eat or how much sugar is circulating in their bloodstream. For the latter, we shall take pin-prick samples of blood from their tail and measure these in a sugar monitor, rather similar to how a diabetic patient would. These procedures will cause some minor discomfort. In this case, we carry out the surgery with the mice under general anaesthetic, plus we give the mice pain killers and sometimes local anaesthetics, to make sure that they do not feel any pain during recovery. The mice recover very rapidly, so they can be returned to their home cages to carry on living as usual. At the end of the study, all the mice are killed humanely.

Application of the 3Rs

Replacement

State why you need to use animals and why you cannot use non-protected animal alternatives

Replacement

It is difficult to study appetite and body weight in anything other than a normally-behaving mouse. However, we can still find out a lot about brain cells by studying them isolated from the rest of the body, in brain slices in a dish.

Reduction

Explain how you will ensure the use of minimum numbers of animals

Reduction

For individual experiments in this project, data provided from similar studies in the past or from pilot studies, allows us to make precise calculations of the minimum number of animals we will need to provide robust results. When a strain is not being used regularly, we reduce the colony to a minimum or we end their breeding, having first cryopreserved sperm or eggs for future regeneration.

Refinement

Explain the choice of animals and why the animal model(s) you will use are the most refined, having regard to the objectives. Explain the general measures you will take to minimise welfare costs (harms) to the animals.

Refinement

To minimise any adverse effects, such as stress, we like to handle our mice (often daily) in order to get them used to being picked up. We also do a range of physiological tests on the mice, sometimes in their home cages, but often after acclimatising them to other cages.

We carry out surgery with the mice under general anaesthetic, and give the mice pain killers and sometimes local anaesthetics, to make sure they do not feel any pain during recovery. The mice recover very rapidly, so they can be returned to their home cages to carry on living as usual.

We use remote radiotelemetry, which is where, during surgery, we implant a small radiotransmitter under the skin or in the abdomen of the mouse. Later, these devices allow us to monitor things like body temperature, blood pressure and brain activity without having to disturb the mice.

We now use transgenic mice to identify, control or record the activity of individual cell types in the brain. This allows us to determine how different cells respond to stimuli and how they communicate with each other without using the very invasive old techniques. Since we can manipulate the mice while they are still in their home cage, we can record their normal behaviour, whether they are secreting hormones, or if their metabolism is changed, with minimal disturbance. To do this, we breed mice that have so-called “designer receptors” expressed in just a single cell type. The designer receptors lay dormant and the mice behave as usual. But, by then giving the mice a “designer drug” or by shining a light through an optic fibre, we can activate or inhibit selective brain cells, while studying changes in behaviour or physiology. It is now even possible to see and record the activity of specific brain cells in freely moving mice, using tiny camera lenses attached to the mouse’s head.