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 project clearly using non-technical terms which will be understandable to 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 may 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 http://scienceandresearch.homeoffice.gov.uk/animal-research/).

(WORD LIMIT: 1000 WORDS)

Please complete the following:

<table>
<thead>
<tr>
<th>Project Title (max. 50 characters)</th>
<th>Metabolic disease – mechanisms and therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Key Words (max. 5 words)</td>
<td>Metabolism, heart, mitochondria, diabetes, obesity</td>
</tr>
<tr>
<td>Expected duration of the project (yrs)</td>
<td>5</td>
</tr>
<tr>
<td>Purpose of the project as in ASPA section 5C(3) (Mark all boxes that apply)</td>
<td></td>
</tr>
</tbody>
</table>
  
  - Basic research
  
  - Translational and applied research
  
  - Regulatory use and routine production
  
  - Protection of the natural environment in the interests of the health or welfare of humans or animals
  
  - Preservation of species
  
  - Higher education or training
  
  - Forensic enquiries
  
  - Maintenance of colonies of genetically altered animals

Describe the objectives of the project (e.g. the scientific unknowns or scientific/clinical needs being addressed) | The project aims to elucidate the mechanisms of common metabolic diseases such as diabetes, obesity and heart failure. It also aims to investigate possible novel therapeutic strategies, including via dietary manipulation, that aim to improve tissue energy levels and therefore function of the tissue, organ and whole body.

---

1 At least one additional purpose must be selected with this option.

The Home Office, in line with the rest of HMG, has implemented the Government Security Classification (GSC). Details of the GSC can be found at https://www.gov.uk/government/publications/government-security-classifications. Please note that documents and emails you receive may contain specific handling instructions.

Handling Instructions: Contains personal sensitive information, subject to confidentiality requirements under the Data Protection Act. This should only be circulated in accordance with ASPA Guidance and stored in a locked secure location.

All government information may be subject to an FOI request and subsequent assessment.
<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>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)?</td>
<td>The incidence of chronic metabolic disease in the developed world continues to increase, associated with the rise in obesity. With no cure currently available for many of these diseases, including type 2 diabetes and cardiovascular disease, it is vital that we develop a greater understanding of the biological mechanisms underlying these diseases and the high mortality rates associated with them. In so doing, we can understand why mortality associated with these conditions is currently so unacceptably high, as well as identifying possible targets of new therapies that could positively impact on patients’ health, improving survival and quality of life. This study has the potential to benefit millions of people worldwide with these conditions by a) identifying novel therapeutic targets, and b) working with stakeholders, including health charities and industry to move our findings into public health advice or therapeutics.</td>
</tr>
<tr>
<td>What species and approximate numbers of animals do you expect to use over what period of time?</td>
<td>Rats and mice. We would estimate a total of 2200 animals over the course of this work.</td>
</tr>
<tr>
<td>In the context of what you propose to do to the animals, what are the expected adverse effects and the likely/expected level of severity? What will happen to the animals at the end?</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td></td>
</tr>
<tr>
<td>We will study some animal models of diabetes and obesity, as well as animals exposed to low atmospheric oxygen conditions (such as a person might experience at high altitude) as low tissue oxygen levels are a key feature of many of these conditions (including obesity, diabetes and heart failure). These animals will have their diets altered (whilst continuing to provide adequate nutrition for normal health) and may be injected with drugs or other substances that could improve their condition. The mice may be provided with running wheels in their cages to test their capacity for exercise, but they will not be forced to run and as this exercise aspect is voluntary it can enrich their environments. We may also measure blood pressure in animals with a tail cuff. The majority of animals in this project will experience mild conditions, but in a small number of animals e.g. some models of disease they could experience a more moderate degree of discomfort. Generally expected outcomes in these animals include increased tiredness and lethargy. Some animals may lose appetite and thus body weight, but this would be expected to be temporary and will be closely monitored. At the end of procedures animals will be killed by a humane method and their bodily tissues collected to provide a significant amount of data for further analysis.</td>
<td></td>
</tr>
</tbody>
</table>

The Home Office, in line with the rest of HMG, has implemented the Government Security Classification (GSC). Details of the GSC can be found at [https://www.gov.uk/government/publications/government-security-classifications](https://www.gov.uk/government/publications/government-security-classifications). Please note that documents and emails you receive may contain specific handling instructions.

Handling Instructions: Contains personal sensitive information, subject to confidentiality requirements under the Data Protection Act. This should only be circulated in accordance with ASPA Guidance and stored in a locked secure location.

All government information may be subject to an FOI request and subsequent assessment.

Version 1.5
**Application of the 3Rs**

**1. Replacement**
State why you need to use animals and why you cannot use non-animal alternatives

The complex nature of metabolic disease requires an interplay between numerous tissues e.g. heart, liver, fat, skeletal muscle, and as such it is not possible to study such systemic conditions in cultured cells. Moreover, cultured cells do not exhibit the functional properties of tissues inside the body (e.g. cultured heart cells do not contract against blood pressures, as the heart muscle does). It is also not viable to collect samples of some internal organs (such as heart and liver) from human subjects (particularly healthy humans who would not be undertaking invasive operations), and so we must use animals in order to be able to collect such organs and to study the function of them.

**2. Reduction**
Explain how you will assure the use of minimum numbers of animals

From each animal, multiple tissues will be collected and analysed to ensure that the best use is made out of every single animal used and total numbers therefore minimised. Wherever possible, we use cells or human subjects rather than animals, for instance we can take fat or muscle biopsies and blood samples from humans without causing any lasting harm, and despite their functional limitations we can use cultured cells to understand some genetic pathways.

**3. Refinement**
Explain the choice of species 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.

Rats and mice are the least sentient animals which are appropriate for the study of mammalian metabolism. Established disease models (including genetically-modified animals) are available for the study of diabetes and obesity. The choice of models will be determined by a) those that best represent the human condition, b) those that allow us to address a particularly scientific question, and c) those that minimise distress/harm to the animal. Welfare costs will be minimised by careful selection of models used, as well as regular monitoring and scoring of individual animals with the application of early humane endpoints such that animals are humanely killed to avoid unnecessary suffering.

**For Office Use Only**

<table>
<thead>
<tr>
<th>Will the project be subject to Retrospective Assessment?</th>
<th>Yes</th>
<th>No</th>
<th>Date due:</th>
</tr>
</thead>
</table>

---

The Home Office, in line with the rest of HMG, has implemented the Government Security Classification (GSC). Details of the GSC can be found at [https://www.gov.uk/government/publications/government-security-classifications](https://www.gov.uk/government/publications/government-security-classifications). Please note that documents and emails you receive may contain specific handling instructions.

Handling Instructions: Contains personal sensitive information, subject to confidentiality requirements under the Data Protection Act. This should only be circulated in accordance with ASPA Guidance and stored in a locked secure location.

All government information may be subject to an FOI request and subsequent assessment.