Home Office

NON-TECHNICAL SUMMARY

Environmental programming of phenotype during pregnancy and early life

Project duration

5 years 0 months

Project purpose

- (a) Basic research
- (b) Translational or applied research with one of the following aims:
  - (i) Avoidance, prevention, diagnosis or treatment of disease, ill-health or abnormality, or their effects, in man, animals or plants.
  - (ii) Assessment, detection, regulation or modification of physiological conditions in man, animals or plants.
  - (iii) Improvement of the welfare of animals or of the production conditions for animals reared for agricultural purposes.

Key words

Pregnancy, Development, Environment

Retrospective assessment

The Secretary of State has determined that a retrospective assessment of this licence is not required.

Objectives and benefits

Description of the project's objectives, for example the scientific unknowns or clinical or scientific needs it's addressing.

What's the aim of this project?

Observations in human populations and experimental studies on animals have shown that poor environmental conditions during pregnancy and early development are related to degenerative conditions later in life, like high blood pressure and diabetes, that shorten lifespan. Interestingly, it is not only the offspring of adverse pregnancy that are at future risk. Studies have also shown that mothers whom have had a complicated pregnancy (e.g. preeclampsia) may themselves be at greater risk of cardiorespiratory disease after giving birth. Thereofore, the overall purpose of the project is to identify the mechanisms by which environmental conditions before and during pregnancy, and in early life, alter the physiology of the mother and her offspring with the ultimate goal of improving pregnancy outcome and long term health in both mother and offspring, thereby markedly enhancing benefits. In particular, the study will investigate environmental challenges, such as low oxygen levels seen in pregnancy at high altitude or with poor placental development, inadequate or inappropriate nutrition and raised levels of stress hormones that are common features of human pregnancies with complications needing clinical monitoring. The project is designed to answer the following key questions.

1. What are the mechanisms by which environmental conditions during pregnancy and early life alter the mother and her offspring from the level of the gene to the whole living animal?

2. What are the consequences of these environmentally induced changes for the disease risk of the mother and offspring in later life?

3. Do environmental challenges before pregnancy alter the maternal responses to subsequent environmental conditions and the ensuing risk of maternal and offspring ill health?

4. Are there therapeutic interventions either during pregnancy or after birth that can prevent the detrimental outcomes for the mother and offspring of a poor environment during pregnancy and early life?

Potential benefits likely to derive from the project, for example how science might be advanced or how humans, animals or the environment might benefit - these could be short-term benefits within the duration of the project or long-term benefits that accrue after the project has finished.

What are the potential benefits that will derive from this project?

The output of the programme of work will largely be in the form of published scientific data, which will be used by researchers, clinicians (doctors and veterinary surgeons), health professionals in the field (eg midwives, nurses, health visitors) and, potentially, in the long-term by government and professional agencies. More specifically, the data are likely to be used to

•   Design experiments by the scientific community to dis-cover fundamental biological principles, to further opti-mise human health and animal welfare, to diminish the burden of disease in the mother and the offspring and to reduce and refine the use of animals in experimental procedures.
•   Identify environmental conditions during early life with and without potential health risks for the mother and offspring.
•   Design new methods of recording data which improve animal welfare and reduce animal use.
•   Initiate epidemiological studies in human populations on the basis of the results of the

experimental studies.
•   Advise clinicians and health professionals on parameters to monitor, treatments to give or avoid and on potential clinical trials.

Overall, the results will advance understanding of the basic biological processes governing mammalian development with benefits in reducing health care costs, increasing livestock productivity and more generally in raising awareness of the early life origins of adult health and disease.

Species and numbers of animals expected to be used

What types and approximate numbers of animals will you use over the course of this project?

We will be using sheep, rats and mice in the pregnant and non-pregnant state with studies of the mother and fetus during pregnancy and of newborns, juveniles and adults at different stages of development. Mice may be genetically altered to study the effect of specific genes on the response to environmental challenges.
Numbers of animals likely to be used over the 5 years of the licence are 880 sheep, 800 rats and 8000 mice.

Predicted harms

Typical procedures done to animals, for example injections or surgical procedures, including duration of the experiment and number of procedures.

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?

Mothers and their offspring will be exposed to environmental challenges before and after birth, with and without therapeutic interventions. The challenges will involve overnutrition to achieve obesity, low oxygen levels to mimic conditions at high altitude and with poor placental development, reduced food intake and altered dietary composition to reflect the diversity of human nutrition worldwide and overexposure to stress hormones as seen with transport, isolation, emotional distress or certain clinical conditions and treatments. The interventions will involve, for example, administration of nutritional supplements, drugs and anti-oxidants. The consequences of these challenges and interventions for key physiological systems will be determined in the mother and her offspring before and after birth and, in rodents, across generations after mating. Physiological systems to be monitored include the cardiovascular, metabolic, hormone, respiratory and nervous systems together with the placenta. Measurements of the physiological variables (eg. blood pressure and flow, use of nutrients such as sugar and fat and the secretion of hormones) will be made in normal and challenged offspring and their mothers using measuring devices and indwelling catheters inserted surgically under general anaesthesia. Data collection may involve blood sampling and giving substances by different routes including under the skin, into the blood stream or via devices implanted surgically as well as confining the animals in sampling or metabolism pens for variable periods of time. With a new focus on the mother as well as the offspring, greater instrumentation during surgical procedures is necessary. Greater instrumentation leads to prolonged surgery and slows the post-surgical recovery. Adverse

effects are rare, even in surgically instrumented animals, and any discomfort associated with surgery is minimised by use of pain relief, close monitoring and appropriate veterinary care. All animals are inspected regularly. Most of animals including those pregnant and their unborn young will be killed at the end of the experiment by humane methods to collect tissues such as the heart, liver, lungs and brain for biochemical and other analyses to explain the changes observed in the living animal induced by the environmental challenges. Those animals allowed to give birth as part of the study do so uneventfully but if problems arise during delivery veterinary assistance is sought.

Replacement

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

As interactions between mother, placenta and offspring involve many factors that change frequently during the course of pregnancy, environmental control of development can only be determined by using living animals, which coupled with analyses of tissues and organs after death allows a comprehensive, integrated assessment of development from the gene to the level of whole living animal.

Reduction

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

We minimise animal use in a number of ways. First, all protocols start with the least invasive procedures on small numbers of animals and, then, progress to additional numbers or more extensive investigations only on the basis of positive results. Secondly, using advice from expert statisticians and preliminary studies, advanced statistical calculations are used to determine minimum numbers required for statistical significance for any given study. In farm species, 4-7 animals are used per treatment group, whereas, in rodents the number is 8-10 to allow for variations in litter size and sex ratios. Thirdly, when animals cannot be studied as originally intended due for example to catheter blockage, they are not wasted as the animal will still provide tissues for further analyses. Finally, in addition to the requirements of the planned study, a wide range of tissues is collected following death to provide material for later use by the group and other researchers, thus minimising the unnecessary use of further animals for experimental purposes. Collectively, these approaches maximise the data gained from each animal while minimising animal usage in the long term by providing archival tissue for additional collaborative studies and evaluation of new analytical techniques.

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.

The project uses three species (sheep, rats and mice), each of which provides a unique element while collectively allowing identification of unifying mechanisms relevant to health and disease across

different species that are also likely to be relevant to human populations. Farm animals, unlike rodents, are large enough to be studied in detail in the uterus and subsequently across multiple physiological systems, whereas rats and mice with their short lifespans are good for identifying critical periods of development and intergenerational consequences of environmental change. Mice can also be manipulated genetically, allowing identification of specific gene effects and targets for therapeutic intervention. These three species also differ in litter size, placental structure, nutrition, metabolic constraints and mechanisms of pregnancy maintenance.   These differences means that we can identify common and unique mechanisms by which the environment affects development across species with direct relevance to the human population and to the general welfare of each species.

Using veterinary advice, we ensure that we use best practise for all surgical, anaesthetic and experimental techniques. This reduces surgery and post-operative recovery times and leads to the collection of better data. All animals are monitored daily and particularly closely post-surgery for food and water intake, demeanour and wellbeing determined by blood parameters where possible. During the course of the last project licence we have implemented remote wireless recording of a wider range of maternal and fetal physiological parameters eg blood and other fluid pressures, blood flow, which allows continuous measurements to be made in the unrestrained state while the ewe has free movement within a pen. Previously animals would have been confined to a metabolism cage which restricted an animal's free movement for longer periods during data collection. When the study requires blood samples on a regular basis during physiological assessment, the ewes s are held for several hours in a sampling pen which allows the animal to stand, sit and turn around with access to food and water before return to their larger home pen which allows greater freedom of movement. All animals are acclimatised to the sampling procedures and experimental environment for several days before experiments begin.