CEFIC Long-Range Research Initiative

Request for Proposals (RfP)

LRI Project code: LRI-EMSG56

Title: The capacity of the endocrine system to cope with combined exposure to exogenous endocrine active substances at environmentally relevant concentrations

Deadline: 31 August 2010

Background:

There is concern expressed at international level that current risk assessment methodologies may be insufficient to protect against combined exposure to endocrine active chemicals, even when the individual exposures may be several orders below the no observed adverse effect level. A good example of this concern is a report prepared by Kortenkamp on the state of the art on Mixture toxicity. (1) This concern is based on a hypothesis that the endocrine system is uniquely sensitive to low doses of exogenous hormonally active substances. The experimental demonstration of additivity at relatively low doses is taken to imply the absence of a safe level of exposure.

Objectives:

The purpose of the research will be to investigate two alternative hypotheses.

Hypothesis 1: As omnivores, humans have evolved to cope with varying amounts of exogenous endocrine active substances such as phytoestrogens. The homeostatic mechanisms have the capacity to adapt to the relatively low levels of endocrine active substances found in the environment. Chemicals acting by the same mechanism can be accounted for within existing risk assessment procedures.

Hypothesis 2: As there are biologically active levels of endogenous endocrines circulating in humans, relatively small doses of exogenous endocrine substances can lead to adverse perturbations of the endocrine system. They can have especially damaging effects at sensitive periods such as organ development. The simultaneous presence of low levels of a large number of substances acting by the same mechanism can have effects that cannot be predicted by existing risk assessment procedures.

The focus of the research will require that:

1. An experimental whole animal model of homeostasis in mammalian regulation of sex hormones is described and demonstrated. The capacity of the processes by

which exogenous endocrine active chemicals and their concentrations and relevant thresholds are accounted for by the model needs to adequately described

2. The point of departure for pathological change is defined and anchored into the experimental design. The experimental demonstration will need to develop sensitive markers of endocrine activity close to, but below, the point of departure for pathological change.
3. Suitable dose ranges of exogenous endocrine active chemicals, (natural and synthetic) should be tested to explore the ability of the endocrine system to compensate below the dose causing adverse changes and whether the response is the same between synthetic and natural chemicals. As the focus of this project is on low dose effects, the doses tested will need to be a compromise between realistic environmental exposure levels and the sensitivity of the model.
4. Taking into account possible kinetic complexities, it would be useful to examine how this model responds to simultaneous exposure to different endocrine active substances and varying exposure levels. This will be a second phase of the project, depending on the demonstration of a sufficiently sensitive model of endocrine homeostasis.

It is essential that the principal demonstrations are performed in intact animal systems, although the model may be initially constructed with *in vitro* methodology if this is more efficient.

Scope:

The Principal Investigator will be required to submit a progress report at six monthly intervals during the course of the programme. At the end of the project a detailed review of the research, and its accomplishments, will be provided by the Principal Investigator. It is expected that the results will be published in peer-reviewed journals and the investigators are encouraged to present their preliminary findings in appropriate scientific meetings.

Budget and Timing:

The project is divided into two separate sections. The first section includes the development of the whole animal model and testing it with single endocrine active substances to demonstrate the homeostatic principle. The first phase is anticipated to have a duration of one and a half years with a budget of 300k€. If this model is successful, the second part will be considered in which the effect of a combined exposure to endocrine active chemicals on the homeostatic model will be evaluated. The submission will have to cover both parts one and two, however the initial contract will only cover part one, with a possible extension for part two, pending development of a successful model. The anticipated duration of the second phase is also one and a half years and the expected budget will also be 300k€.

References:

1. Kortenkamp A. State of the art report on mixture toxicity. In: The School of Pharmacy UoL, ed. London, 2009.