PhD position

Hypothalamic-pituitary-gonadal axis modelling in zebrafish (Danio rerio) for understanding and predicting effect of endocrine disrupting chemicals

Deadline for applications: **30th April 2015.**

Several chemicals possess the ability of modulating the endocrine systems, associated with reproductive and developmental dysfunctions, and abnormal levels of circulating steroids hormones. There have been increasing concerns regarding these endocrine disruptor compounds (EDCs) and their potential harmful effects on humans and wildlife, including fish. Among model species for ecotoxicological investigations, zebrafish (*Danio rerio*) is a vertebrate organism extensively used in hazard and risk assessment of EDCs.

Mathematical models can provide the framework in which the effects on many endpoints and the cross regulations between these endpoints can be integrated, and then, to understand the physiological impacts of EDCs on fish. In this PhD project, we propose to develop and to integrate a hypothalamic-pituitary-gonadal (HPG) axis model for male and female zebrafish to assess impact of EDCs on HPG functioning.

The first step of the PhD project will consist in generating original experimental data. A special attention will be paid to biological variables that play a key role in the HPG functioning (e.g., steroidal hormones, expression of gonadotropins and their receptors). These data will be used to develop a model that will predict the kinetic of the steroid hormones under physiological conditions as well as in fish exposed to model compound(s).

A Physiologically-based pharmacokinetic model (PBPK) for zebrafish previously developed at the INERIS will serve as a foundation for the development of the HPG model for male and female zebrafish

The PhD student will be in charge of defining the hypothesis of the model using published information on the physiology in zebrafish and existing HPG model in fish. Then, the model will be developed, analysed and calibrate using the data produced in this project and data that can be gathered following an extensive bibliographic research.

Finally, the predictive performances of the model will be tested using available literature for zebrafish exposed to a some endocrine disruptors targeting the HPG axis. This model could be also used to relate levels of hormones and effects observed on zebrafish reproduction.

Schedule planned

Year 1	Year 2	Year 3
- Definition of the model hypothesis - Experimental design to assist the model calibration taking into account the existing data in literature and in our laboratory, - Experiment in control conditions, - Sample analysis	- Development and calibration of the HPG model in control conditions, - Experiment on 17β-oestradiol, - Sample analysis, - First publication describing the data obtained	- Model calibration, analysis and test of predictive capacity, - Second publications describing the HPG model, - PhD manuscript redaction.

Profile of the candidate

The candidate should have a master's degree in endocrinology / physiology and have a strong interest in modelling approach. You should preferably have experience in ecotoxicological research, and affinity for working with fish. The candidate must be proficient in spoken and written English, and have good communication skills. Moreover, the candidate will have to demonstrate of being able to work as a part of a team or individually and have a strong interest in a scientific career.

Organisation

The work will be carried out at the unit METO (Models for ecotoxicology and toxicology) at INERIS, 30 min from Paris by train. Further details about INERIS can be found at http://www.ineris.fr/en. The experimental part of this PhD project will be performed in close collaboration with the ECOT unit (in vitro and in vivo ecotoxicology unit).

The unit METO is involved in the development of mathematical models supporting (eco)toxicological risk assessment. More precisely, we develop QSAR and PBPK models to assess kinetics and effects on individuals. Current projects are focusing on PBPK models for EDCs like phthalates, PCBs, HAPs and pesticides (atrazine and anti-androgenic pesticides). We also develop population dynamics models to integrate effects measured on individuals at population levels and to assess long term effects on populations (multigeneration and mesocosms studies, with a focus on evolution and carrying capacity).

The METO unit dispose of all necessary computing resources to deal with the calibration of complex models and the numerical simulation of agent-based models.

The ECOT unit acquire strong skills and expertise since more than 15 years research on the mode of action and effect of EDCs on fish endocrinology and reproduction. The unit is equipped with state-of-the-art fish facility comprising multi-rack systems and several stand-alone systems for maintenance and breeding of wild-type and transgenic zebrafish lines. The zebrafish facility is well-equipped with fish exposure systems under controlled temperature and photoperiod including flow through exposure systems. The unit is also equipped with biochemical, molecular laboratories and imaging platform.

Informal enquiries about the position can be directed to:

Beaudouin Rémy, INERIS, Unité METO, Parc Alata, BP2, 60550 Verneuil en Halatte, remy.beaudouin@ineris.fr.

Brion François, INERIS, Unité ECOT, Parc Alata, BP2, 60550 Verneuil en Halatte, françois.brion@ineris.fr.