Code Number and Title:
LRI-ECO35: Assessment of potential endocrine activity in fish – elucidation of the role of liver toxicity in the vitellogenin response.

Background

Vitellogenin (VTG), a yolk pre-cursor protein, is a key biomarker in fish endocrine screening and testing. Industry is required to run fish tests incorporating the measurement of VTG to assess potential endocrine activity in fish (cf OECD test guidelines 229, 230, 234 and the proposed medaka extended one generation test). Reduced female VTG can be associated with endocrine modes-of-action (e.g. inhibition of steroidogenesis), while in males the increase in VTG may indicate estrogenicity. Such effects might be indicative of endocrine activity that would require further higher tier testing. These tests are expensive both in terms of resources and animal use. However, VTG levels can also be affected by systemic toxicity [1, 2] and, more specifically, by liver toxicity since the liver is the site of VTG synthesis [3]. Two mechanisms can be envisaged, either direct damage to the liver (i.e. degenerative changes) or liver enlargement and/or other signs of altered liver metabolism (i.e. increased hepatocellular vacuolization) accompanied by induction of biotransformation enzymes leading to increased hormone clearance. Both these mechanisms have the potential to affect VTG synthesis.

The liver is affected by many chemicals (industrial chemicals, pesticides and pharmaceuticals) due to its major role in metabolism [4]. Therefore, liver toxicity could lead to decreased VTG levels by many substances undergoing endocrine screening and testing. Consequently, there is the potential for many chemicals to be incorrectly labelled as endocrine active *in vivo* from the results of such fish tests. A greater understanding of the role of non-endocrine modes of action, specifically fish liver toxicity, in the scientific and regulatory community will assist in a better evaluation of substances, reduced testing needs, reduced animal use and improved regulatory outcomes.

We envisage the RfP to address potential liver toxicity in a small fish model used for regulatory testing (fathead minnow, medaka etc). Investigative work into liver-mediated toxicity, covering a range of potential modes of action, and effects on VTG levels and reproduction, should be proposed. The development of additional diagnostic tools (either global or specific) would also be of interest. Chemical selection criteria should be outlined in the RfP. It is anticipated that an Adverse Outcome Pathway (AOP) could be developed from the data generated for one or more modes of action.

Scope and Objectives

Investigate if VTG can be affected by liver toxicity in fish. In particular:

1. Investigate whether VTG can be affected by non-endocrine modes of action, specifically fish liver toxicity
2. Develop specific or global diagnostic tools for liver-mediated toxicity in fish in order to distinguish between endocrine and non-endocrine mediated effects
3. Develop an Adverse Outcome Pathway (AOP) for liver toxicity mediated reproductive dysfunction in fish

Deliverables

The final report shall contain an executive summary (2 pages max), a main part (max. 50 pages) and a detailed bibliography. It is expected that the findings will be developed into at least one peer reviewed publication, following poster(s) and presentation(s) at suitable scientific conference(s) and where possible an AOP for submission to the OECD.

Cost and Timing

Start in 2015, duration 18-24 months
Budget in the order of €250,000

Partnering/Co-funding

Applicants should provide an indication of additional partners and funding opportunities that can be appropriately leveraged as part of their proposal. Partners can include, but are not limited to, industry, government/regulatory organizations, research institutes, etc. Statements from potential partners should be included in the proposal package.

Fit with LRI objectives/Possible regulatory and policy impact involvements/ Dissemination

Applicants should provide information on how their proposal is aligned with LRI objectives. Furthermore, an indication on how the results could influence regulatory and policy areas should be provided.
Dissemination plans should also be laid down.

References

[1] Hutchinson T, Bögi C, Winter M, Owens J. 2009. Benefits of the maximum tolerated dose (MTD) and maximum tolerated concentration (MTC) concept in aquatic toxicology. *Aquatic Toxicology* 91:197-202.
[2] Wheeler J, Panter G, Weltje L, KLThorpe. 2013. Test concentration setting for fish *in vivo* endocrine screening assays. *Chemosphere* 92:1067–1076.
[3] Wheeler J, Gimeno S, Crane M, Lopez-Juez E, Morritt D. 2005. Vitellogenin: A review of analytical methods to detect (anti) estrogenic activity in fish. *Toxicology Mechanisms and Methods* 15:293-306.
[4] Cullen JM. 2005. Mechanistic classification of liver injury. *Toxicologic Pathology* 33:6-8.

DEADLINE FOR SUBMISSIONS: 6 Sept 2015

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