



CEFIC Long-range Research Initiative Request for Proposals (RfP)

Title and Code Number:

Species comparison in liver-mediated thyroid and thyroid-related toxicities

Part 1: Characterization of liver-mediated thyroid toxicity in the rat. - **LRI-EMSG59**

Background

Many natural and synthetic chemicals are able to induce elevations in hepatic metabolism, typically manifesting as increased expression and activities of phase I and phase II enzymes. In addition to increased metabolism of xenobiotics, such increases in hepatic enzyme activities may also result in elevated clearance of endogenous substances, including thyroid hormones. This is particularly relevant for toxicology, as changes in thyroid hormone levels may subsequently lead to adverse effects in the thyroid itself and in a number of target tissues including the developing brain.

Historically the focus in this area has been directed towards the human relevance of liver-mediated thyroid cell hyperplasia and tumours observed in rodent toxicity studies. It is well accepted that rodents, in general, and rats in particular, are significantly more sensitive to this liver mediated thyroid toxicity than humans, due to species differences in thyroid hormone binding proteins and functional reserves of hormone in the thyroid. However, relevance of this mode of action to non-tumour outcomes in humans (e.g. developmental neurotoxicity) is now being challenged, particularly when exposure occurs at sensitive life stages (e.g. pre/post-natal time).

Thyroid hormones are regulated by both systemic (via the HPT axis) and local (e.g. via deiodinase activity) homeostatic mechanisms. However, the thresholds and quantitative linkage between induction of hepatic enzymes, reduction in circulating thyroid hormones, reduction in circulating foetal thyroid hormones, and tissue-specific thyroid hormone levels are not well understood, even in commonly used rodent laboratory models. Furthermore, the translation of thyroid-related findings from rodents to humans is complicated by a lack of quantitative understanding of the differences in species sensitivity. There is therefore a developing need to evaluate the (qualitative and/or quantitative) similarities and differences between species in thyroid toxicity when conducting safety assessments of chemicals causing effects on the thyroid mediated via liver enzyme induction.

Project Structure

Part 1 of this project will concentrate on characterizing dose-response profiles for liver enzyme induction, thyroid hormones, and thyroid-related effects, in the rat model for model compounds known to cause thyroid toxicity through a secondary, hepatic, mode of action.

Part 2 will develop a model (or models), using data generated in Part 1 of the project, to facilitate translation of outcomes in rodent toxicity studies to likely effects in humans accounting for species differences or similarities in this liver mediated thyroid adverse outcome pathways (AOPs).

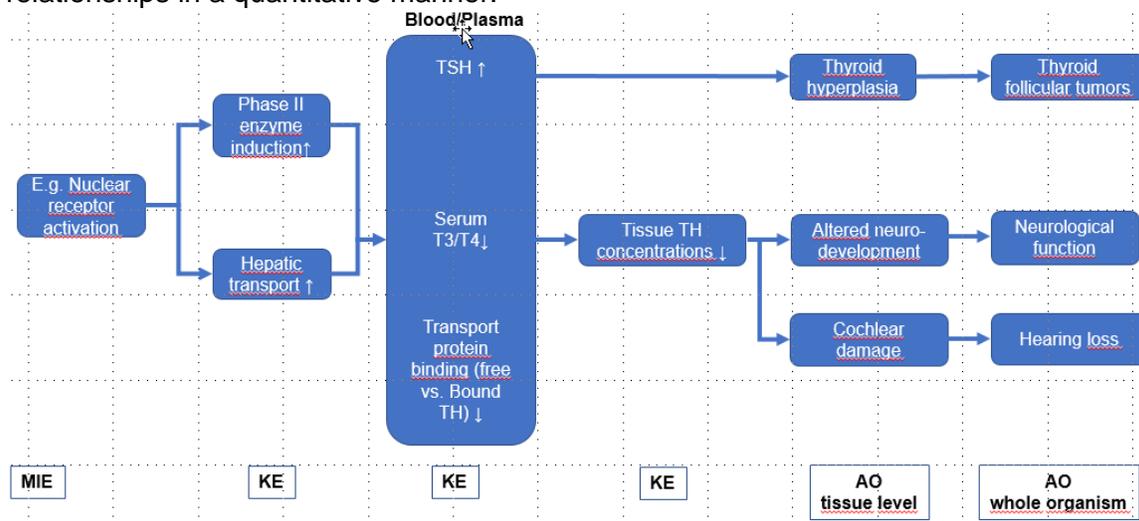
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This RfP is for Part 1 of the project, but it is anticipated that the successful applicant for Part 1 of the project will also oversee Part 2. It is therefore anticipated that Applicants for this RfP will provide a brief outline of how the data generated as Part 1 of this project will be used to deliver Part 2 of the project.

Objectives

The aim of the Part 1 of the project is to fully characterize maternal (gestation and lactation), foetal and pup thyroid and thyroid related endpoints in a dose response manner in the rat. This will serve as the basis for further investigation to better evaluate similarities and differences between mammalian species in liver mediated thyroid toxicity.

Therefore Part 1 of the project will concentrate mainly on the MIE and the first three key events (KE), which are common to the AOPs below as well as determining the key event relationships in a quantitative manner.



Project Objective

To quantitatively establish the link between MIE, hepatic key events, plasma thyroid hormones, and tissue level thyroid hormones, in pregnant rats and their foetuses/offspring using model liver enzyme inducers.

Scope

The project should investigate liver mediated thyroid toxicity in the rat using relevant reference chemicals. Parameters to investigate should include liver enzyme induction, particularly phase II enzymes (enzyme activities and gene transcripts), plasma hormone levels for T3, T4 and TSH (+ pituitary TSH beta transcript) with associated pharmacokinetics parameters (e.g. T4 hormone clearance). In addition the toxicokinetic characteristics of the reference chemicals used should also be investigated. Relevant target tissue histopathology and concentration of unbound fraction of hormones should

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also be considered. Points of departure of key events (eg phase II enzyme induction and plasma hormone levels) should be identified from appropriate dose-response studies. Selected target tissues (e.g. brain) from foetuses/offspring from rat should be preserved in an appropriate manner to allow any further analysis if required after the termination of the present Part 1 of the project.

The output of this work shall be formally written up as a scientific report, and delivered to interested CEFIC stakeholders as an oral presentation. It is expected that the findings will be developed into at least one peer reviewed publication, following oral and poster presentation at suitable scientific conference(s).

Cost and Timing

Start in Q1 2019

Duration: 18 months

Budget in the order of 600.000€

The Part 2 budget and timing are not yet defined and will depend, in part, of the results of Part 1

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 the fit of their proposal with LRI objectives and an indication on how and where they could play a role in the regulatory and policy areas. Dissemination plans should also be laid down. At least one article related to the research project shall be published in the open access literature.

References

A literature review of the current state of the science regarding species differences in the control of, and response to, thyroid hormone perturbations. Part 1: a human health perspective. Regulatory Science Associates Report sponsored by ECPA <http://cefic-lri.org/wp-content/uploads/2018/06/RSA-Draft-Thyroid-State-of-Science-Review-v4.pdf>

Implementing Developmental Thyroid Toxicity Guidance into practice: what is working, what is not and how can we do better. Abby A. Li et al. manuscript in preparation



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Evaluation of interspecies differences in susceptibility to thyroid perturbation. Thomas A. Lewandowski, SOT 2018 Poster # 2827/P350. http://cefic-lri.org/wp-content/uploads/2018/06/SOT_2018_Lewandowski_thyroid.pdf

DEADLINE FOR SUBMISSIONS: 2 September 2018

Please see www.cefic-lri.org for general LRI objectives information, project proposal form and further guidance for grant applications.