Breaking down the wall between human health and environmental testing of endocrine disrupters EndocRine Guideline Optimisation (ERGO)

Henrik Holbech[1], Harald Hasler-Sheetal[1], Jürgen Arning[2], Dries Knapen[3], Lucia Vergauwen[3], Gerrit Schüürmann[4], Thomas Braunbeck[5] , Lisa Baumann[5], Frédéric Flamant[6], Marieke Reuver[7]

[1]University of Southern Denmark, Campusvej 55, 5230 Odense M, Denmark
[2]Umweltbundesamt, Woerlitzer Platz 1, 06844 Dessau-Rosslau, Germany
[3]University of Antwerp, Universiteitsplein 1, 2610 Wilrijk, Belgium
[4]Helmholtz-Zentrum Fuer Umweltforschung GMBH-UFZ, Permoser Strasse 15, 04318, Leipzig, Germany
[5]University of Heidelberg, Seminarstrasse 2, 69117 Heidelberg, Germany
[6]Ecole Normale Normale Superieure de Lyon, Parvis Rene Descartes 15, 69342, Lyon, France
[7]AquaTT UETP Ltd, Pleasants Street Olympic House Unit, 8 Dublin, Ireland
E-mail contact: hol@biology.sdu.dk

1. Introduction

Recently, international workshops and projects arranged by the EU have identified gaps in the testing of suspected EDCs[1-3]. Regulators are therefore requesting better tests and approaches for assessment of the hazards and risks of EDCs to protect human health and the environment. Another challenge identified by the EU and OECD[4] is that regulatory procedures for identification and assessment of EDCs are separated for human health and the environment in both EU and other international legislations. Consequently, useful data obtained from non-mammalian vertebrate tests (fish and amphibians) are disregarded, or not given sufficient weight, in human health assessments and vice versa even though the endocrine system is highly conserved among vertebrate classes. Among other gaps, The workshops pointed out thyroid disruption (TD) as a focus area, because existing vertebrate in vivo tests are not protective enough and validated in vitro tests for TD are not yet available.

An EU call: SC1-BHC-27-2018: “New testing and screening methods to identify endocrine disrupting chemicals” under the Horizon 2020 funding program ended up funding 8 projects addresing the identified gaps in the testing of EDCs. Here we present the overall goals, ideas and tasks of a research network clustering all 8 projects and we goes into details with one of the projects named ERGO.

The ERGO project will break down the wall between mammalian and non-mammalian vertebrate regulatory testing by identifying, developing and aligning thyroid-related B/E for linkage of effects between different vertebrate classes (Figure 1). To achieve this, an AOP network covering various modes of TD in multiple vertebrate classes will be developed. An AOP starts from a molecular initiating event (MIE) and outlines the sequence of key events (KE) leading to a relevant adverse outcome at the organism or population level. The AOP network will provide the scientifically plausible and evidence-based foundation for the selection of B/E and assays in lower vertebrates predictive of human health outcomes. These assays will be prioritized for validation in ERGO.

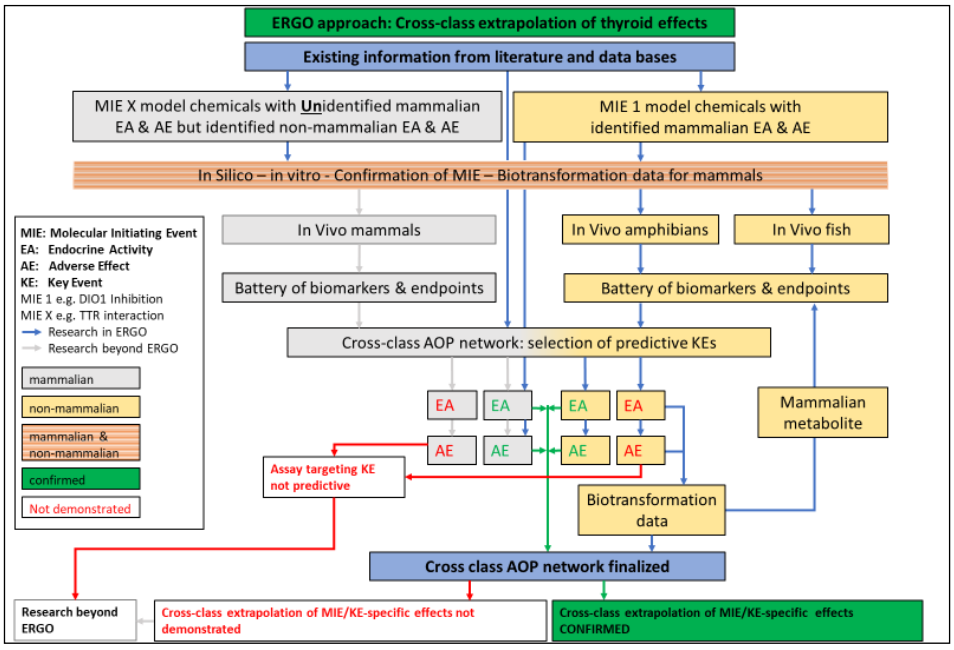

Figure 1: ERGO approach for testing and cross-class extrapolation of TD effects between mammalian and non-mammalian TGs. Based on existing information,

chemicals with known MIE, KE, EA and AE in mammals will be investigated in silico, in vitro and in vivo in fish and amphibians. A battery of B/E will be tested for EA and AE in the in vivo studies. Biotransformation data will be obtained when EA and/or AE cannot be confirmed. All existing and new data will be used for AOP network development. Chemicals with unknown effects in mammals, but known EA and AE in non-mammalian vertebrates will be investigated in silico, in vitro and for differences in biotransformation.

2. Materials and methods

To achieve its goals of providing stakeholders and businesses with better tools and strategies needed to ensure improved management of EDCs, ERGO has four overarching objectives:

1) Investigate, develop and validate thyroid biomarkers and endpoints (B/E) predicting effects across vertebrate classes for inclusion in new in vitro and existing in vivo OECD test guidelines (TGs) for improved identification and safer assessment of thyroid disrupting chemicals.

2) Develop an Adverse Outcome Pathway (AOP) network across vertebrate classes for identification of thyroid B/E applicable for assessment of cross-class thyroid disrupting key events (KE).

3) Transform new data, tools and understanding into a harmonized IATA testing strategy for regulation of endocrine disrupting chemicals (EDC) by inclusion of stakeholders at the global level in the incorporation of the cross-vertebrate class testing approach.

4) Publish a guidance document on extrapolation of thyroid disrupting (TD) effects across mammalian, fish and amphibian OECD TGs.

3. Results and discussion

The result of ERGO will be compiled in a comprehensive data warehouse (Figure 2).

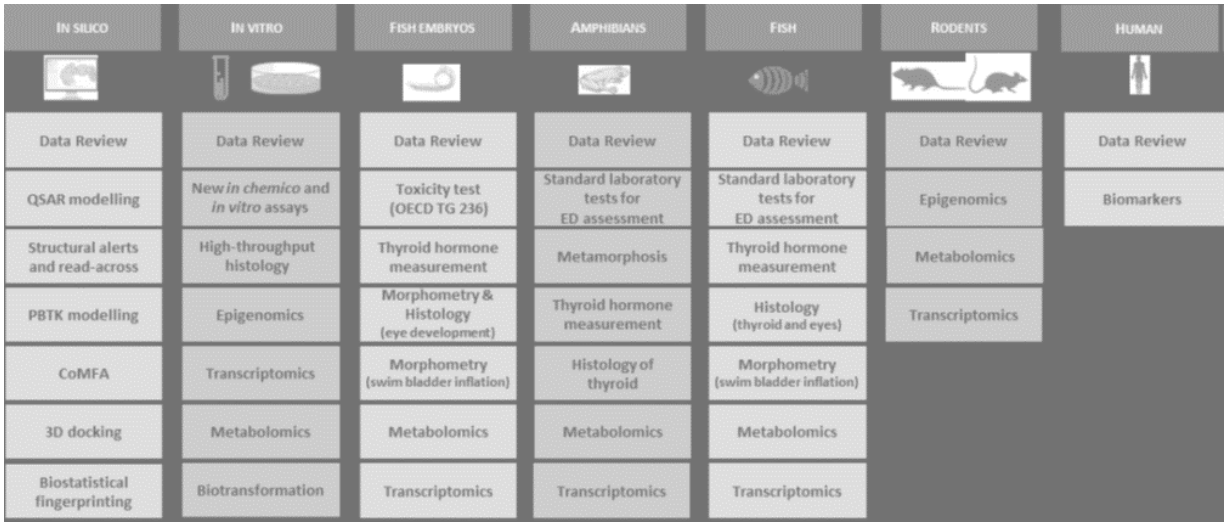

Figure 2: ERGO develops a comprehensive data warehouse composed of different kinds of cross-vertebrate class, in silico, invitro, in vivo samples and cell-lines samples combined with many state-of-the-art analytical methods.

4. Conclusions

ERGO is a coordinated attempt to contribute filling the gaps in the field of TD. It will allow to identify both disturbance of the thyroid axis and its potential adverse effects in different vertebrate classes. ERGO is expected to improve methodologies for using cell tests and fish and amphibian assays for early screening of substances and to develop new in silico models for predicting internal dose of TDCs to design physiologically based toxicokinetic modelling (PBTK) models and to link MIEs with AE within an AOP network.

5. References

[1] European Commission, D.-G. f. t. E. Supporting the organisation of a workshop on thyroid disruption –Final Report. (2017).

[2] Bopp S, N. M., Halder M, Munn S Expert survey on identification of gaps in available test methods for evaluation of endocrine disruptors. (2017).

[3] European Commission, D.-G. f. t. E. Setting priorities for further development and validation of test methods and testing approaches for evaluating endocrine disruptors. (2018).

[4] OECD. Guidance Document 150 on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption (2018 version). (2018).