Disruption of thyroid regulation associated with adverse effects of environmental pollutants

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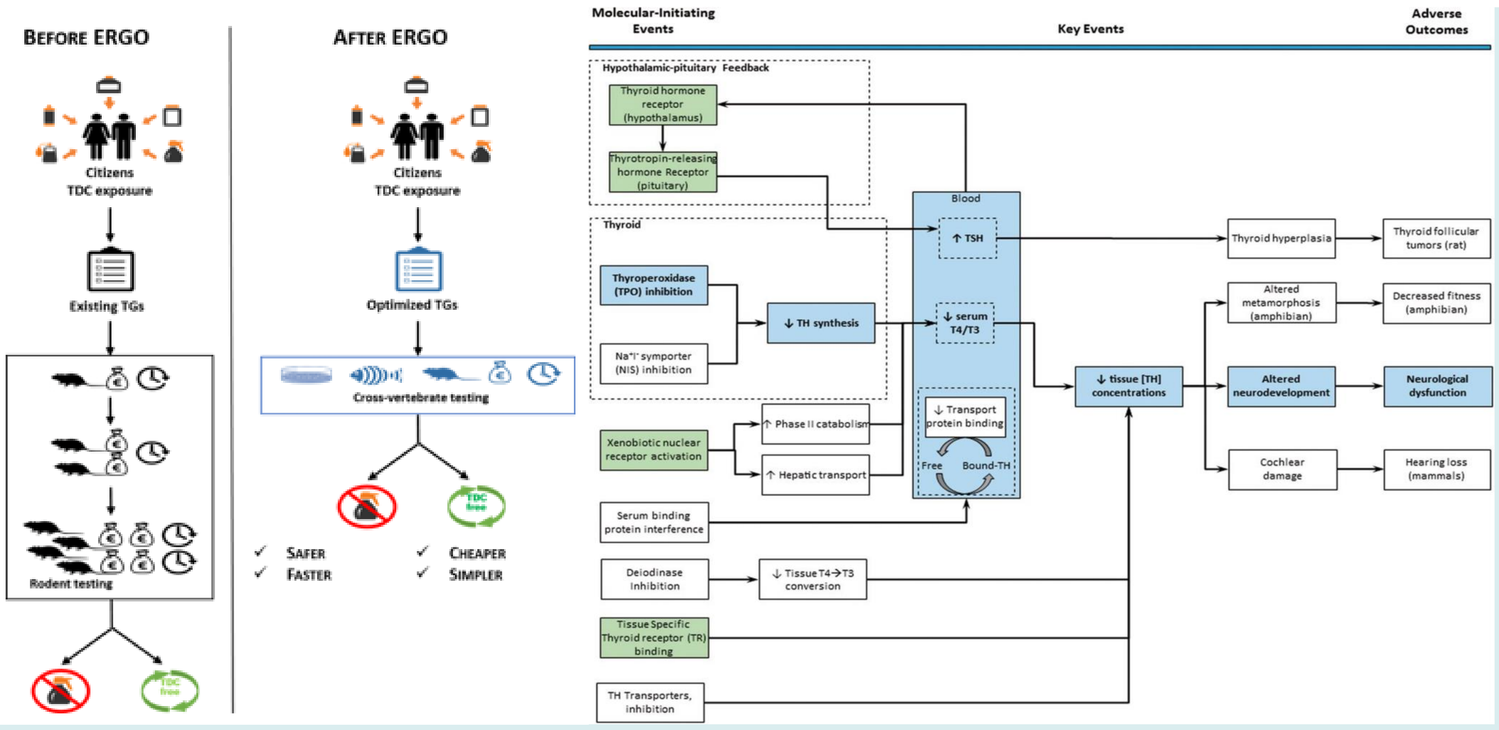

Figure 1 Aims of the ERGO project and a combined adverse outcome pathway (AOP) network integrated from several putative adverse outcome pathways (AOPs) for thyroid hormone (TH) disruption. A Molecular Initiating Event (MIE) is the initial interaction between a molecule and a biomolecule or biosystem that can be causally linked to an outcome via a pathway. MIEs proceed to key events, and then to adverse outcomes.

Methods

Nthy-ori (human) and FRTL-5 (rat) cell lines are used to build thyroid in vitro models. Human neural stem cell is used to build Thyroid hormone (TH) responsive in vitro model.

The expression of genes and proteins relevant for MIEs in in vitro models are characterized through qPCR and western blot.

TH metabolization: AZ-AhR Stable HepG2 Luciferase Reporter Cell Line is used for the assessment of interaction of samples with selected nuclear receptor - aryl hydrocarbon receptor (AhR) that is a ligand-activated transcriptional factor that regulates genes implicated in chemical metabolism.

TH synthesis: Enzyme inhibition assays about TPO (Thyroid peroxidase) will be performed to evaluate the interaction of samples with the ability of TPO enzyme that has a strong relation to the TH synthesis.

TH transport: thyroxine-transthyretin (T4-TTR) binding assay is performed, thyroxine-transthyretin carries TH in the blood.

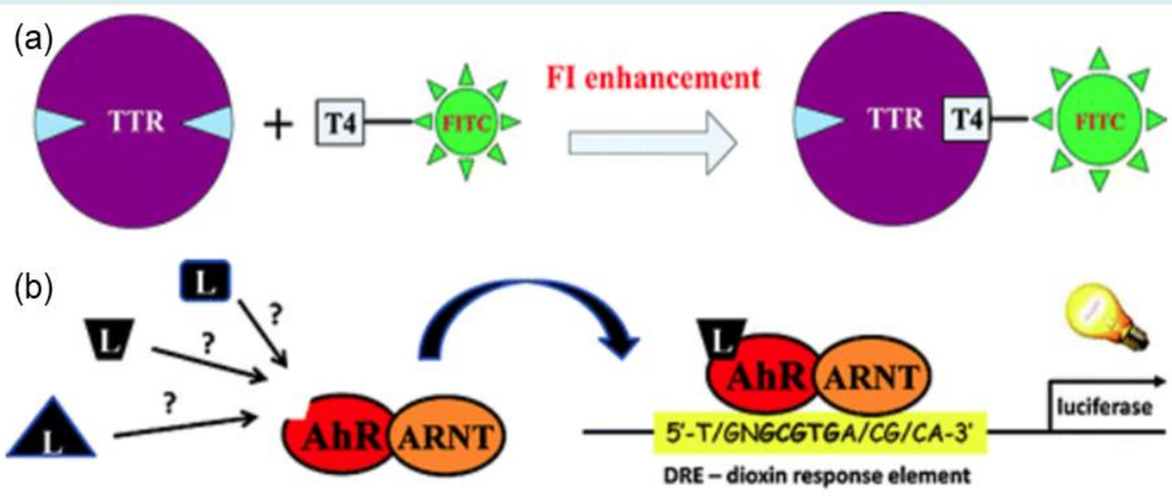

Figure 2 Mechanisms of (a) TTR assay and (b) AZ-AhR assay

Current Results

20 ERGO prioritized chemicals were tested in the AZ-AhR assay and TPO assay. None of 20 ERGO prioritized chemicals could active AhR. In the TPO assay, Triclosan (TCS), Bisphenol A (BPA) and 6-propylthiouracil inhibited TPO enzymatic activity.

20 ERGO prioritized chemicals

BPA	2,2-Bis(4-hydroxyphenyl)propane (Bisphenol A)	TBBPA	Tetrabromobisphenol A
PTU	6-propylthiouracil	TPP	Triphenyl phosphate
BDE47	2,2′,4,4′-Tetrabromodiphenyl ether	TDCPP	Tris(1,3-dichloro-2-propyl) phosphate
BDE99	2,2′,4,4′,5-Pentabromodiphenyl ether	CBZ	Carbamazepine
DBP	Dibutylphthalate	T3	3,3′,5-Triiodo-L-thyronine
PFOS	Perfluorooctane sulfonate	T4	3,3′,5,5″-Tetraiodo-L-thyronine
HBCD	Hexabromocyclododecane	DON	Deoxynivalenol
IOP	Iopanoic acid	TCS	Triclosan
PFOA	Perfluorooctanoic acid	BP2	2,2′-4,4′-tetrahydroxy benzophenone
PCL	Perchlorate	AMP	Ampicillin

Introduction and aims

Thyroid Disrupting Chemicals (TDCs) can induce disruption of thyroid hormone signaling in human, which can be linked with many human health problems such as neurodevelopmental disorders (autism, attention deficit hyperactivity disorder (ADHD) and learning disabilities) in children, thyroid neoplasms, thyroid autoimmune disorders and increased cardiovascular risk due to altered lipid metabolism in adults. The PhD project is a part of Horizon 2020 ERGO (EndocRine Guideline Optimization) project, improving identification and hazard assessment of TDCs for the protection of human health and the environment by breaking down the wall that currently exists between the different research fields that investigate adverse effects of TDCs in different vertebrate classes.

Effects of ERGO prioritized chemicals will be characterized on thyroid-responsive biomarkers and different endpoints. The project is involved in studies concerned with

(i) the development and pre-validation of a battery of in vitro methods covering the prioritized molecular initiating events of endocrine disruptive chemicals affecting thyroid hormone (TH) signaling (e.g. biochemical and cell culture-based assays),

(ii) characterization of the toxic potential of model compounds as well as complex environmental samples relevant to human exposure, identification of mixture effect drivers.

Future

Identification and optimization of novel endpoints and biomarkers

Developing high-throughput assessment assays of prioritized MIEs in the in vitro models based on the results of gene and proteins expression.

Cross-species comparison for sensitivity of effects on prioritized molecular initiating events in the thyroid disruption.

Modelling the effects of detected exposure mixtures.

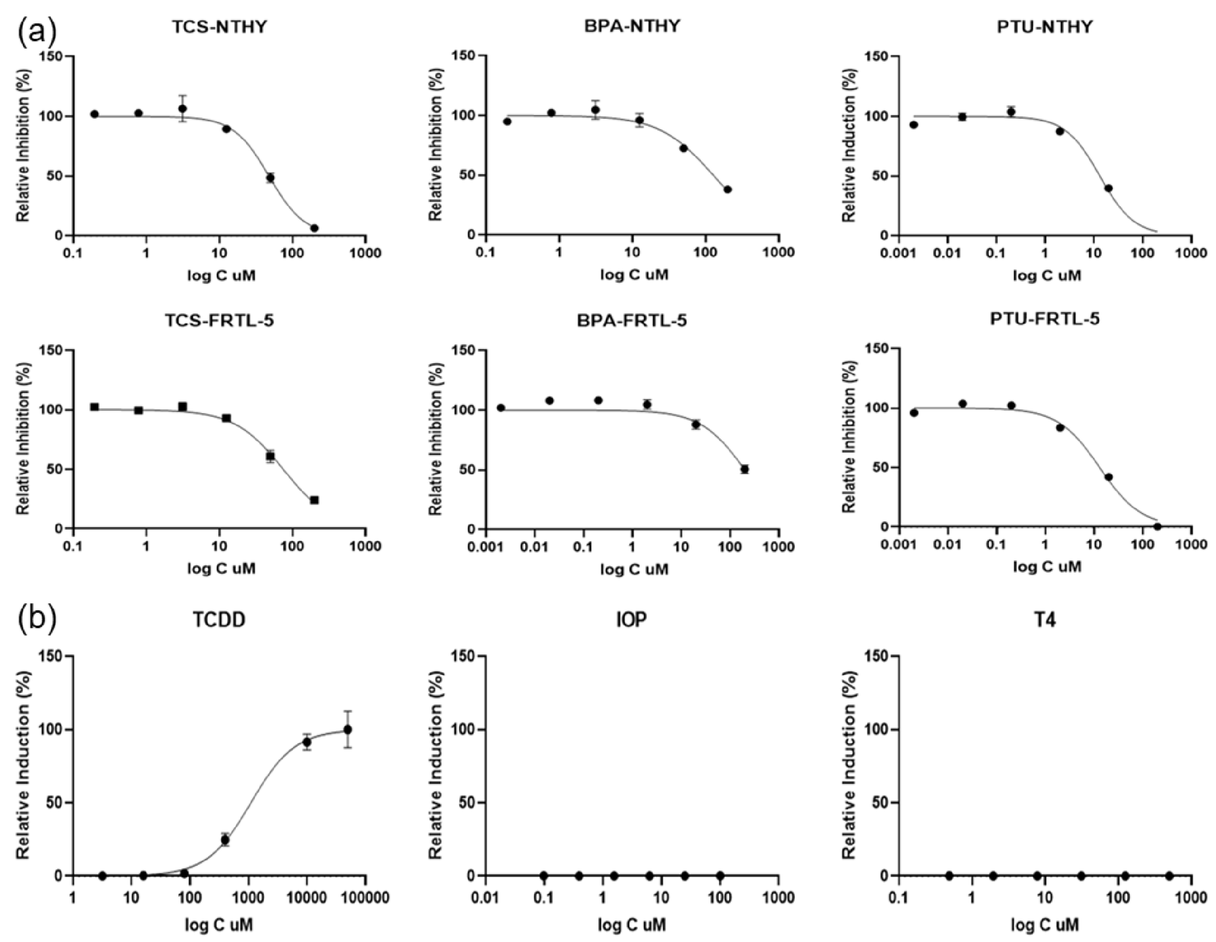

Figure 3 (a) TPO inhibition results for TCS, BPA and PTU from Nthy-ori (human) and FRTL-5 (rat) cell lines; (b) AZ-AhR results for TCDD (positive control), IOP and T4.

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