



# SCREENED

SCREENING FOR ENDOCRINE DISRUPTORS

**A multistage model of thyroid gland function for screening endocrine-disrupting chemicals in a biologically sex-specific manner**

**[WWW.SCREENED-PROJECT.EU](http://WWW.SCREENED-PROJECT.EU)**



This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 825745.

## PROJECT OVERVIEW

Endocrine disruptors (EDs) are a class of chemicals used to produce materials commonly found in everyday life, such as some plastics, tin cans, electrical and household appliances, cosmetics, and pesticides, among others. EDs are, however, not without danger: these molecules interfere with the endocrine system, disrupting the physiological production and the target effects of hormones. In particular, EDs have proven effects on the reproductive system and impact on the occurrence of obesity, type 2 diabetes and cardiovascular diseases during aging.

There is also growing evidence that **EDs strongly interfere with thyroid function**. EDs cause changes in thyroid hormone concentration, the peripheral metabolism of these hormones and the signalling of their receptors. The mechanism by which they act on the thyroid axis is, however, still far from being understood. Models and assays currently used for safety assessment are strongly limited by the availability of adequate quantities of human thyroid tissue, the inability to recreate the complexity of the native thyroid gland, and the inability to predict the effects of EDs after low-dose exposure.

Information on thyroid hormone (TH) levels and the underlying mode of actions (MoA) leading to changes in TH signalling is not available for the majority of EDs. To date, Adverse Outcome Pathways (AOPs) focus on neurodevelopmental effects of EDs. In addition, no current molecular or cellular assay can clearly distinguish between sex-specific responses of the thyroid gland to EDs. Finally, virtually nothing is known about the effects, MoA and related AOP, of EDs on thyroid stem/progenitor cells, which role is critical in thyroid development, growth in postnatal life, and adaptation to thyroid injury.

**The EU project SCREENED aims to develop three-dimensional (3D) cell-based *in vitro* tests to better characterize the effects of EDs on the thyroid.** The solutions SCREENED develops will overcome the limitations of existing tests by being more sensitive at low-dose exposure to potential EDs and supporting the prediction of their toxicity on human health in a sex-specific manner.

**START DATE**

1 January 2019

**END DATE**

31 December 2023

**DURATION**

60 Months

**EU FUNDING**

5,655,088.75 €



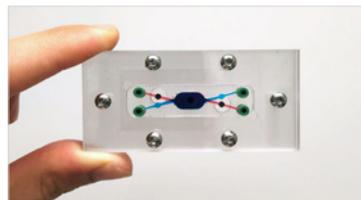
## THE PROJECT AND ITS CHALLENGES

The main challenge is to develop 3 different three-dimensional (3D) *in vitro* assays based on rodent and human 3D thyroid cell constructs. At different levels of anatomical complexity, these assays will increasingly mimic the structure and function of the native thyroid gland, ultimately achieving the replication of its vascular anatomy and morphogenetic characteristics:

- 1) a 3D organoid based on stem-cell derived thyroid cells,
- 2) a decellularized scaffold able to reproduce the biological composition of a native thyroid, repopulated by the 3D organoids,
- 3) a bioprinted construct with the 3D organoids able to mimic the spatial and geometrical architecture of a native thyroid.

These 3D assays will be hosted in a modular microbio reactor equipped with innovative sensing technology and enabling precise control of cell culture conditions. New superparamagnetic biocompatible and biomimetic particles will be used to produce “magnetic cells” to support precise spatiotemporal homing of the cells in the 3D decellularized and bioprinted constructs.

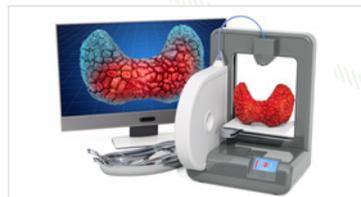
These 3D *in vitro* assays will be used to screen and comprehensively evaluate the effects of different EDs, at an unprecedented level of molecular detail thanks to an integrated omics approach. The major innovation of SCREENED will lie in the combination of thyroid 3D *in vitro* biological constructs that replicate the native thyroid gland at different levels of increasing complexity within a microbio reactor, coupled with proteogenomics analysis and biological modelling of underlying MoA and AOPs.



Microbio reactor equipped with sensing probes



Cell differentiation



Bioprinted thyroid



Proteogenomics analysis and biological modelling

## THE EXPECTED RESULTS

The 3D *in vitro* assays will be used to screen the effect of EDs on the thyroid function in a unique biological sex-specific approach. Their performance will be assessed individually, in comparison with each other, and against *in vivo* studies.

The 3D assays are expected to predict with more sensitivity and specificity the thyroid response to different classes of EDs at low doses, compared to classical 2D *in vitro* assays or *in vivo* models.

SCREENED is expected to provide Europe with powerful screening assays, able to reliably record toxic effects of known and new EDs in line with data from *in vivo* studies available through the consortium partners. As such, it would become an essential predictor of thyroid toxicity for a number of industrial sector products, spanning from consumer (e.g. food, cosmetics) to agrochemical products.



Supporting the “Adverse Outcome Pathway” (AOPs) concept along OECD guidelines, proteogenomics analysis and biological modelling of the underlying MoA will be used to gain a mechanistic understanding of the chain of events from exposure to adverse effects on thyroid development and function.

Based on the OECD guidelines on *in vitro* and *ex vivo* assays for the identification of modulators of thyroid hormone signaling, 8 blocks of assays have been identified to study the MoA and the potential AOP of EDs on the thyroid. Of these blocks, SCREENED will contribute to:

- Thyroid hormone synthesis, in particular in relation to tests for stem cell derived thyrocytes for which no assay is currently available
- Relevant short-term assays integration as a replacement of the thyroid gland explants since these cultures lack reproducibility due to different hormone levels in different animals.

For future uptake, SCREENED will engage in discussion with relevant stakeholder groups, including regulatory bodies and industry, to ensure that the assays are fit for purpose for EDs safety assessment.

## THE SCREENED CONSORTIUM

Assay development requires a multidisciplinary approach bringing together complementary expertises and research resources from basic stem cell research, thyroid biology and endocrinology, 3D cell technology, *in vivo* models, biomimetic materials, sensor technology, high-level toxicogenomics and -proteomics platforms, biostatistical analysis, and *in silico* modelling.

Nine European universities and companies from seven countries collaborate in an integrated, synergistic approach to deliver the promised results.

The SCREENED project coordinated by the Maastricht University is also being supported by two external groups, the International Advisory Board and the Stakeholder Group.



### PROJECT PARTNERS

- Universiteit Maastricht (Netherlands)
- Università degli Studi di Parma (Italy)
- Université libre de Bruxelles (Belgium)
- Consiglio Nazionale Delle Ricerche (Italy)
- Presens Precision Sensing GmbH (Germany)
- University College Dublin (Ireland)
- Atturos Limited (Ireland)
- ARTTIC (France)
- Cyprotex, an Evotec Company (UK)



## EURION CLUSTER

The SCREENED project is also part of the European Cluster EURION, which aims to improve the identification of Endocrine Disruptors. EURION Cluster is composed of eight research projects, all funded by the European Commission under the Horizon 2020 Research and Innovation programme. Each project focuses on a different aspect of new testing and screening methods to identify EDs. Being part of this cluster group allows the SCREENED project to optimise synergies with other projects of the same field, share expertise, and avoid overlaps in their research work.



[www.eurion-cluster.eu](http://www.eurion-cluster.eu)

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