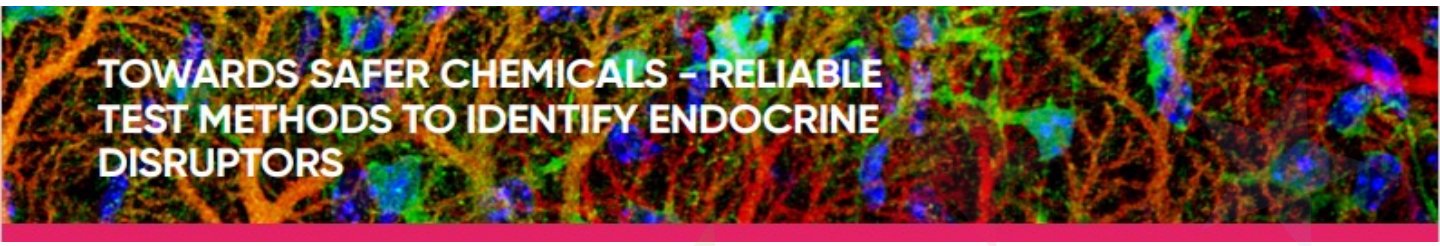
EURION

European Cluster to Improve Identification of Endocrine Disruptors

POLICY BRIEF | JUNE 2024



This policy brief summarizes the results of the EURION cluster, a collaboration between eight research projects dedicated to provide **new testing and screening methods** to identify **endocrine disrupting chemicals (EDCs)**, funded under the European Union's Horizon 2020 Research and Innovation programme.

The research in EURION focused on four endocrine-related health domains: **thyroid hormone system disruption** (ATHENA, ERGO, SCREENED), **metabolic disorders** (EDCMET, GOLIATH, OBERON), **developmental neurotoxicity** (ENDpoiNTs) and **female fertility** (FREIA).

KEY MESSAGES

- Research in EURION has resulted in more than 100 new test methods and new endpoints in existing test methods to identify possible EDCs, as well as 35 computational models and tools.
- Around 40 of these methods are currently tested in multiple laboratories to determine their robustness.
- 11 EURION methods are on the OECD (Organisation for Economic Co-operation and Development) workplan for further development and potential implementation in regulatory test strategies.
- Advanced technologies, including organ-on-a-chip models and omics-techniques, nowadays are well-established and we envision their use in regulatory settings.
- EURION has generated data from human studies that links EDC exposure to changes in thyroid hormone patterns in expectant mothers, developmental neurotoxicity, clinical metabolic outcomes and female fertility problems.
- EURION findings have contributed to the development and fine-tuning of at least 40 Adverse Outcome Pathways (AOPs), which can support EDC identification in regulatory processes.
- The EURION data show that endocrine disrupting effects are chemical-specific, involve a broad variety in (molecular) targets, and can affect multiple hormonal pathways in a species-, age- and sex-dependent manner.
- EURION shows that, in some cases, it is possible to extrapolate endocrine disrupting effects across vertebrate classes, which allows a combined human health and environmental assessment of endocrine disruptors.
- EURION addressed important gaps in regulatory identification of EDCs. To fully exploit these efforts, shorter science-to-policy implementation and additional funding for validation and implementation of test methods are highly recommended.

THYROID HORMONE SYSTEM

Thyroid hormones control functions such as development and homeostasis in all vertebrates. Disruption of the thyroid hormone system in pregnant women can lead to adverse neurodevelopmental outcomes in their children.

In amphibians, transformation from tadpole to frog is disturbed in developing fish, eyes, swim bladder and neurodevelopment are affected.

EURION outcomes show that:

- Mild-to-moderate iodine insufficiency in pregnancy exacerbates the effects of chemicals that disrupt the thyroid hormone system.
- Changes in thyroid hormone thyroxine (T4) concentrations should be regarded as an adverse outcome in and of itself.

EURION contributes to improved testing for EDC-mediated thyroid hormone system disruption through:

- Insights into thyroid hormone patterns associated with chemical exposure.
- Biomarkers and endpoints for thyroid hormone system disruption in cells and living organisms.
- Multiple AOPs and AOP networks to facilitate extrapolation across fish, amphibians and mammals, including humans.
- Optimised analytical methods to measure thyroid hormone concentrations in neuronal tissues.
- Closed gaps between human and environmental toxicology research.
- Improved in vitro-in vivo extrapolation for thyroid hormone system disrupting chemicals.
- Advanced 3D cell models of thyroid follicles that display increased sensitivity compared to 2D cultures.

DEVELOPMENTAL NEUROTOXICITY

Hormonal pathways are involved in key events regulating brain development. Hence, endocrine disruptors interfering with these pathways can induce developmental neurotoxicity.

Hormonal pathways important for neurodevelopment are mostly different from the ones usually tested in the context of endocrine disruption.

Research in EURION has contributed to improved testing for endocrine disruption-induced developmental neurotoxicity by:

- Pinpointing hormonal pathways relevant for neurodevelopment.
- Generating high throughput assays, which are in pre-validation phase and will be submitted to the OECD test guideline programme.
- Integrating omics data across in vitro and in vivo test systems and epidemiological studies to identify biomarkers linking endocrine disruption to neurodevelopmental outcomes.
- Constructing over ten novel elements in AOPs and one novel AOP network based on EURION data to plausibly and causally link endocrine disruption to developmental neurotoxicity.

METABOLIC DISORDERS

Exposure to chemicals with endocrine disrupting effects may result in metabolic disruption, which plays a role in diseases such as obesity, diabetes, and fatty liver disease among others.

The research data generated in EURION shows that:

- Chemicals that disrupt metabolic processes can be linked to an increase of obesity at the population level among other metabolic pathologies.
- Human cell and zebrafish models are predictive of metabolic disruption, and can be applied for both human health and environmental EDC assessment.
- Chemicals that disrupt metabolic processes can also be identified as known or suspected EDCs.

Accomplishments from EURION to improve testing for EDC-mediated metabolic disorders include:

- Four methods to the level of pre-validation: steatosis assay in hepatic cells, PPAR-alpha and –gamma reporter cell assays, human mesenchymal stem cell differentiation to white adipocytes assay.
- A selection of reference chemicals for (pre)validation, and optimisation of test methods related to metabolic disorders.
- Augmentation of the established CYP induction assay in hepatocytes to include EDCs.
- Pancreatic alpha and beta cell models for identification of endocrine disruptors.

FEMALE FERTILITY

Hormones are crucial for the development, maturation and function of the female reproductive system. Exposure to EDCs during these life stages can negatively impact a woman's reproductive health, including fertility.

EURION research findings show that:

- Mammary gland development and neuropeptide release in the brain are more sensitive endpoints in rodent studies than those currently used to assess EDC effects on female reproduction.
- Fatty acid metabolism and steroid hormone biosynthesis are sensitive targets for EDCs in human ovaries, and may be captured by expanding the current steroidogenesis assay.

EURION outcomes create opportunities for developing superior tests compared to those currently used to assess EDC effects on females, and to protect female reproductive health, including:

- 16 putative AOPs, 4 QSAR models, and molecular biomarkers of EDC-mediated female reproductive toxicity.
- New methods to screen for changes in number of corpora lutea and assess effects on hypothalamic neuropeptide release in rodent studies.
- Proposals submitted to the OECD for inclusion of the mammary gland in rodent studies, and expansion of H295R steroidogenesis assay (OECD TG 456).
- Identification of lifestyle factors associated with EDC exposure and reduced ovarian response to fertility treatment in adult women.

BACKGROUND EURION

In 2002, the World Health Organisation (WHO) defined an endocrine disruptor as "an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations."

We are exposed to EDCs daily via the air, dust, food and water, or via our skin. EDCs can be transferred from the mother to the developing foetus or child through the placenta and breast milk.

Exposure to EDCs may disturb normal hormone signalling and cause adverse health effects. Therefore, identification, classification and regulation of EDCs is crucial to protect human and environmental health.

Current regulatory test strategies do not cover the whole spectrum of EDC-mediated health effects.

To address this, the European Commission organised a European expert workshop in 2017 with the objectives to i) identify gaps in test methods; ii) identify ways to address those gaps; and iii) prioritise further development and validation of test methods and testing approaches to identify EDCs.

This resulted in a call for research projects under the Horizon 2020 Research and Innovation program: SC1-BHC-27-2018 'New testing and screening methods to identify endocrine disrupting chemicals (EDCs)'. Eight proposals received funding, totalling 50M Euro EU contribution.

To optimise synergies and avoid overlaps between the projects, it was decided the projects would form a cluster, with support from an international advisory panel. Being part of this cluster has allowed the projects to collaborate and share expertise, thereby maximising their impact.

The EURION cluster was launched on 1 January 2019. The final results of EURION are presented on 13 and 14 June 2024 in Brussels.

INPUT INTO POLICY PROCESSES

In the European Union, criteria for the identification of chemicals that have endocrine disrupting properties are provided in the Biocidal Products Regulation (BPR), the Plant Protection Product Regulation (PPPR) and the Classification, Labelling and Packaging (CLP) regulation. Additional regulatory provisions for endocrine disruptors are covered under REACH, the Regulation on cosmetics, and under EU legislation on food contact materials.

In 2018, ECHA and EFSA, with support from JRC, published a guidance document on how to identify and classify chemicals as an EDC in the context of PPPR and BPR, and this is also used as basis in other regulations.

The assessment strategy is based on three conditions in the EDC criteria – adversity, endocrine activity and a biologically plausible link between the two – and applies both for humans and the environment. EDC assessment starts with gathering all available relevant information, which includes data from internationally agreed study protocols as well as data from the scientific literature. Then, an evaluation is carried out to explain how a chemical causes the observed endocrine activity and/or adverse effect.

Collectively, EURION has provided new and improved test methods, novel endpoints and better insights into EDC-mediated health effects, which have the potential to support identification of EDCs in line with the assessment strategy, in all regulatory frameworks.

To maximise the impact of EURION and to better protect human health and environmental species:

- Support is needed for faster validation and implementation of robust scientific findings into accepted test methods for EDC identification practices.
- EDC identification would benefit from a more holistic approach, rather than focusing on single organs and endpoints in single species.
- EDC assessment practices across regulations should regularly be reviewed to evolve (combined) human health and environmental assessment.

Recommendations to effectuate EURION results:

- Provide financial support for (pre)validation tests, i.e. extensive multi-laboratory tests with multiple chemicals, of EURION test methods to facilitate faster acceptance of new test methods.
- Update test requirements in chemical regulations and the EFSA/ECHA/JRC guidance for EDC identification to include newly developed tests, as well as descriptions on how test results from human and environmental health assessment can be used to support one another.
- When an EDC is associated with one adverse health outcome, other effects cannot be excluded. Citizens should be provided with science-based actionable information on how to reduce exposure to EDCs.
- Organise roundtable discussions between policy makers, risk asessors and academics to close the gap between regulatory needs and scientific innovations.

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PROJECT ACRONYMS, *in alphabetical order*

ATHENA	Assays for the identification of Thyroid Hormone axis - disrupting chemicals: Elaborating Novel Assessment strategies
EDCMET	Metabolic effects of Endocrine Disrupting Chemicals: Novel testing METhods and adverse outcome pathways
ENDpoiNTs	Novel testing methods for endocrine disruption linked to developmental neurotoxicity
ERGO	Breaking down the wall between human health and environmental testing of endocrine disrupters: EndocRine Guideline Optimisation
FREIA	Female Reproductive toxicity of EDCs: a human evidence-based screening and Identification Approach
GOLIATH	Beating Goliath: Generation Of NoveL, Integrated and Internationally Harmonised Approaches for Testing Metabolism Disrupting Compounds
OBERON	An integrative strategy of testing systems for identification of EDs related to metabolic disorders
SCREENED	A multistage model of thyroid gland function for screening endocrine-disrupting chemicals in a biologically sex-specific manner

OBERON

freia PROJECT

ERGO

SCREENED

GOLIATH

athena

edcmet

ENDpoiNTs

FIND OUT MORE

eurion-cluster.eu

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