

Where to start with testing Endocrine Disrupting Chemicals

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Introduction

Endocrine Disrupting Chemicals (EDCs) pose a risk to humans and wildlife due to their interference with hormone production, metabolism and regulation. The endocrine system consists of a network of glands, hormones and receptors and acts as a central communication network between the nervous system and biological systems involved in reproduction, metabolism, immune response and behaviour.

The assessment of endocrine disrupting (ED) properties is a requirement for active substances registered under the Biocidal

Products Regulation (BPR)¹ and the Plant Protection Products Regulation (PPPR)², has been adopted under the Classification and Labelling Regulation³ and is expected to be included in the REACH update in 2023⁴. These regulations prioritise endocrine disrupting properties to vertebrates, for substances that act via Estrogenic, Androgenic, Thyroid and Steroidogenic (EATS) modalities. Identification of those substances that may possess endocrine-disrupting properties, and which may require regulatory action, present a significant challenge.

What are the challenges to endocrine disruption assessment?

In vivo testing challenges

- Complexity: uses large numbers of animals, is expensive and lengthy timescales are required to complete and analyse studies.
- Laboratory capacity and experience is currently limited.
- High variability of key parameters measured (e.g. vitellogenin and reproduction).
- Multiple modes of action are often undifferentiated in most studies.
- Lacking guidance for interpretation.
- Potential for variability in species sensitivity.

Challenges in non-animal methods in fish and amphibians

- General lack of representation of complex biological processes and systems within the assays (e.g. absorption, distribution, metabolism and excretion (ADME)).
- Risk of false negatives or false positives.
- Validation studies are usually conducted using reference compounds which provide strong negative or positive outcomes. However, most 'real-world' chemicals tested for regulatory purposes will not provide such clear effects.
- Limited NAMs covering key pathways, especially for the thyroid modality.

How can Vitis Regulatory help?

Desk-based screening for ED properties



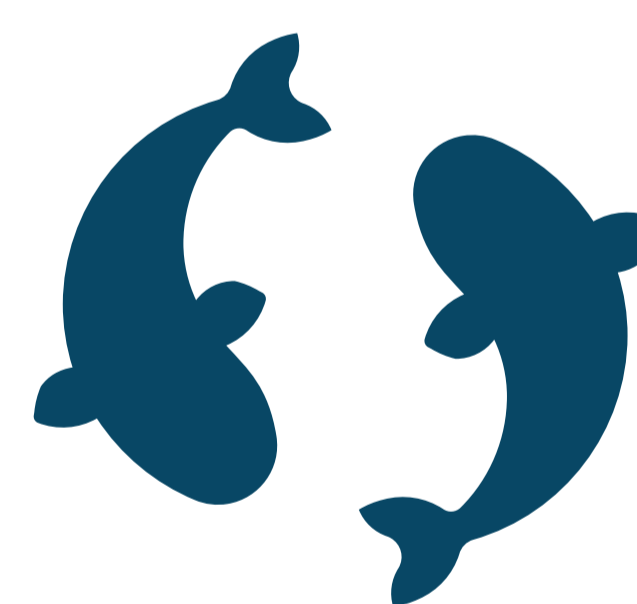
- Review of existing (eco)toxicology data in REACH dossiers.
- Comparison of substances against databases of known EDCs.
- Literature review.
- Data gap analysis.
- Data analysis from *in silico* tools to identify ED activity.

Targeted assessment of endocrine activity



- Testing strategy development.
- Placement and monitoring of targeted *in vitro* studies.
- Evaluation of *in vitro* and *in silico* data.
- Mode of action analysis.

Targeted assessment of endocrine adversity



- Testing strategy development.
- Placement and monitoring of targeted *in vivo* studies.
- Review of higher tier *in vivo* (eco)toxicology data.
- Interpretation of results in conjunction with available endocrine activity data.

Reporting on ED properties



- Interpret all data in line with available guidance documents to conclude on ED properties.
- Presentation of evidence for and against ED properties and modes of action for standalone purposes, or dossier submission.

References

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2. Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC. [Online]. [Accessed 30 March 2023]. Available from: <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32009R1107>.
3. European Commission Delegated Regulation amending Regulation (EC) No 1272/2008 as regards hazard classes and criteria for the classification, labelling and packaging of substances and mixtures. [Online]. [Accessed 30 March 2023]. Available from: <https://environment.ec.europa.eu/system/files/2022-12/Delegated%20Regulation%20amending%20Regulation%2012722008.pdf>.
4. European Commission REACH Regulation To protect human health and the environment against the harmful effects of substances. [Online]. Available at: https://environment.ec.europa.eu/topics/chemicals/reach-regulation_en.



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