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 Regulation[3] and is expected to be included in the REACH update in 2024[4]. 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?

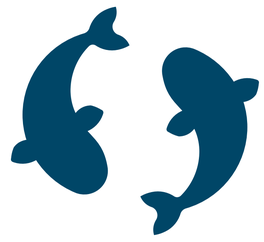
Desk-based screening for ED properties

- 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

1. Council Regulation (EC) No. 528/2012 of 22 May 2012 concerning the making available on the market and use of biocidal products. [Online]. [Accessed 15 April 2024]. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:02012R0528-20220415.

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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 15 April 2024]. 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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