chemical watch news & insight

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What are the challenges navigating endocrine disruption assessment in the EU?

ED assessment remains a complex and challenging task. Yuzhu (Celia) Wei, Lydia Bouwman and Ingrid Sterenborg, experts in regulatory services at Triskelion, share experiences and discuss points of attention under the PPPR, BPR and REACH

CHEMICAL WATCH INSIGHT Expert Focus | 14 August 2024

Endocrine disrupting chemicals (EDCs) can interfere with hormonal systems, causing harmful effects in both humans and wildlife. With intensive scientific work on the presence and impact of EDCs, the EU has made its legislative framework regulating EDCs increasingly stringent.

Since 2018, endocrine disruption (ED) assessment has been a requirement for the approval of plant protection and biocidal products in the EU. These assessments are applicable to both active and non-active substances, such as co-formulants, safeners and synergists. In April 2023, the delegated regulation on the classification, labelling and packaging (CLP) of chemicals entered into force, which introduces new hazard classes for endocrine disruptors. Since then, ED assessment has gained significant attention in the regulation of industrial chemicals under the 'REACH' framework.

Although multiple guidance and test guidelines were published in the last two decades, ED assessment remains challenging for scientists, authorities and industries, considering that the hormonal system is a complex network which is not yet fully understood. In addition, the properties of certain substances such as unknown or variable composition, complex reaction products or biological materials (UVCBs) and polymers may complicate the process.

Below, we share our experiences, faced challenges, and potential solutions regarding ED assessment under the plant protection products regulation (PPPR), biocidal products regulation (BPR) and the regulation of industrial chemicals (REACH) in the EU.

Active substances under PPPR and BPR

According to the ECHA and EFSA guidance on the identification of endocrine disruptors published in June 2018, active substances in plant protection and biocidal products should be considered as having endocrine disruption properties if they meet all the following criteria:

- endocrine mode of action;
- adverse effects; and
- the adverse effect is a consequence of the endocrine mode of action.

These criteria should be evaluated using a weight-of-evidence approach, in which different types of information (eg guideline studies, *in silico* screening and literature search) are gathered and assessed.

Non-active substances under PPPR and BPR

Safeners and synergists contained in plant protection products are evaluated following the same endocrine disruption criteria used for active substances. Co-formulants that have ED properties are considered unacceptable and are listed in the Annex II of the PPPR.

For biocidal products, a screening assessment on ED properties is required for the co-formulants. The steps and challenges are described in an article we wrote for Chemical Watch News & Insight in 2022. In summary, all co-formulants must be screened in a number of ED databases. Non-conclusive ED properties in the screened databases will lead to a literature search that requires a wide range of specialist knowledge and may end with debatable conclusions.

Few improvements have been made to assessment in the past two years. However, the authorities suggest using more databases (such as the Japanese ED database and the Denmark ED-list) than the one mentioned in the current guidance. This so-called "screening" approach leads to a high workload, especially when each co-formulant needs to be individually screened using multiple databases. Based on our experience from the past two years (and using IT knowledge), these databases can be merged into an Excel spreadsheet, which significantly speeds up the process.

CLP and REACH

Four new ED hazard classes were introduced in the CLP regulation (1272/2008/EC) last year via delegated regulation 2023/707/EU. Two ED categories were defined for human health and two for the environment. For substances placed on the market before 1 May 2025, a 24-month transitional period applies. In this case, the new classification and labelling should be used before 1 November 2026. For substances placed on the market after 1 May 2025, the new classification and labelling is mandatory immediately.

At present, there is no requirement to perform an ED assessment for industrial chemicals under REACH. However, endocrine disruptors can be identified as SVHCs alongside chemicals known to cause cancer, mutations and/or toxicity to reproduction (CMR).

More studies are expected on the ED potential of industrial chemicals. Here, one of the most discussed chemical groups is the polymer group, which may fall within the REACH regulation according to ECHA guidance for monomers and polymers (2023). How should the ED potential of polymers be tested? In our view (before relevant guidance becomes available), the testing approaches – and challenges – can be similar to those of UVCB substances, described below.

Challenges and potential solutions in testing

Non-animal testing information

The in vitro assays listed in *OECD Document 150* provide key information for the ED assessment. In addition, QSAR model prediction and read-across to other substances, based on the similarities in the structure/receptors, can be used as well. These options avoid animal sacrifice and high costs and accelerate the regulatory process.

However, for some complex active substances, such as UVBCs, the QSAR toolbox usually contains little information on the identified constituents, hence it does not provide sufficient evidence to predict the ED properties of the UVCB substance. Since not all mechanisms of endocrine disruption are well-understood, the read-across approach is likely to be used for concluding a substance is an endocrine disruptor, but it cannot be used to provide evidence that a substance does not have ED potential.

Even if the substance can be 'read across' to an abundant element in nature, the authorities may still ask for tests to better understand the element. For unidentifiable substances, eg some constituents of a UVCB, a non-testing strategy is inapplicable. According to an OECD report (2023) about EDCs in freshwater, they can have effects at concentrations as low as nanograms per litre, and in mixtures with other chemicals. This means that even if UVCB constituents account for minor percentages of the UVCB, they might exhibit ED potential that could dominate the classification of the entire substance. To cover the unidentifiable constituents or impurities, in most cases, the UVCB substance should be tested in guideline studies, either *in vitro* or *in vivo*.

Animal testing information

The focus in the ED assessment is the oestrogen, androgen, thyroid and steroidogenesis (EATS) mediated mode of action. This is because their mechanism is well understood (in line with the EFSA/ECHA guidance). Measured parameters that may contribute to the ED assessment, but are not mediated by EATS, are considered 'sensitive to, but not diagnostic of, EATS'. This type of information is usually difficult to evaluate due to the limited existing knowledge, which may warrant further investigation via literature search or end with non-conclusive ED properties.

For environmental aquatic studies with fish and amphibians, testing of a single substance is quite often already challenging because of possible issues with water solubility, choice of test concentrations and development and validation of analytical methods to measure concentrations in water.

For UVCBs, the water solubility of the different constituents should be considered when preparing water soluble concentrations. Most challenging, however, will be the choice of constituents to be analysed. Which constituents will be toxic, and which may possibly exhibit ED effects? Which constituents are sufficiently available in water to be analysed, and are these the constituents causing ED effects? How can we decide this when the composition of the UVCB is not (exactly) known? In our opinion, analysis of some of the different individual constituents often fails to add clarity to the questions above. Therefore, we would propose to reconsider performing mandatory analysis on constituents of UVCBs.

It is important that directors of ED studies, and regulatory experts, discuss the set-up of studies with UVCBs, mixtures and polymers to make sure they are suitable for regulatory purposes. In addition, the statistics to be used for the interpretation of results are complex. Therefore, statistical analysis of results should be performed, or at least be checked, by statisticians with knowledge of (environmental) toxicology studies. Similar challenges and solutions can be expected when performing animal testing on ED potential for other complex substances, such as mixtures and polymers.

Conclusion

Although the guidance for identifying EDCs in plant protection and biocidal products has been available for years, ED assessment remains a complex and challenging task for scientists, regulatory authorities and industry, especially for complex substances such as UVCBs and polymers. The introduction of new hazard classes for endocrine disruption represents a significant step forward in chemical regulation. Directors of ED studies and regulatory experts should discuss the set-up of studies with UVCBs, mixtures and polymers. As the regulatory landscape continues to evolve, addressing the challenges inherent in assessing the ED potential of substances will be key, in particular for complex substances..

The views expressed in this article are those of the authors and are not necessarily shared by Chemical Watch News & Insight.

FURTHER INFORMATION

EFSA/ECHA guidance →

OECD Document 150 →

OECD guidance for EDCs in freshwater →

ECHA guidance for monomers and polymers →