Expert briefing: What have we learned from three years of in-depth active substance EDC assessments?

The 2018 Echa/Efsa guidance document on the identification of endocrine disruptors led to a steep learning curve for applicants and authorities under the BPR and PPPR, says Dr Daniela Fruth, expert regulatory toxicologist at consultant knoell

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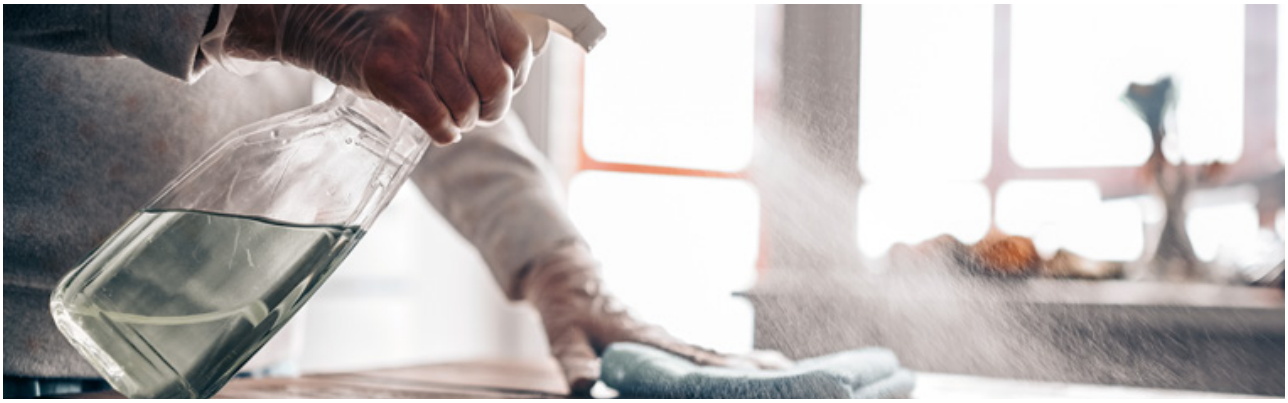

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The criteria were set after years of discussion, adhering to the WHO definition of 2002 that an EDC is "an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse effects in an intact organism, or its progeny, or (sub) populations". This definition restricts the assessment of potential endocrine disrupting-properties to a hazard-based approach, considering neither exposure nor risk. Authorisation of active substances identified as EDCs under the PPPR and BPR (professional uses) may only be granted if one of the derogation criteria defined under the respective regulation is met.

The Echa/Efsa guidance document on the identification of endocrine disruptors published in June 2018, was made immediately applicable, leading to a steep learning curve for applicants and authorities. To date, the guidance document is only applicable to biocides and plant protection products (PPPs) covering the oestrogen (E), androgen (A), thyroid (T) and steroidogenesis (S) modalities; their mechanism is well understood and accepted, so standardised test guidelines are available. However, since harmonisation across EU legislation is one of the goals of the EU chemicals strategy for sustainability, as per 'one substance, one assessment', the existing guidance document on the identification of endocrine disruptors, and criteria, are being used as a reference for other EU regulations.

EDC assessments under BPR and PPPR

Experiences and challenges

It is clear from experience gained over the past three years of active substance EDC assessments under the BPR and PPPR, that adhering to the guidance document's in-depth five-step process incurs an extensive workload for applicants and authorities.

The first step of the comprehensive assessment is gathering all available relevant and reliable information in an excel macro template that Efsa provides in its guidance (Appendix E). Relevant data comprises not only guideline studies requested under the respective regulatory framework, but also in silico screening and a comprehensive literature search. Depending on the substance, the literature search can return hundreds, or even thousands, of results requiring detailed evaluation for relevance and reliability.

The number of parameters retrieved from the substance dataset relevant for EDC assessment can easily lead

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to a data table of several hundreds of lines. Experience has shown that in order to ensure the high level of detail requested for Appendix E, the original study reports need to be checked; existing study summaries are of limited use. Consequently, from the first step of the EDC assessment (data gathering), the amount of work requiring (eco)toxicological expert knowledge is very high for the applicant performing the task – as well as for the evaluating authority later on in the process.

Once all relevant and reliable data have been gathered, the lines of evidence (LoE) are assembled for the respective modalities (EATS). Although Appendix E includes a macro for automatic generation of the LoE, the workload entailed should not be underestimated as the description and interpretation of potential effects need to be performed manually.

Assembling and especially assessing the LoE, as well as developing a testing strategy in case EATS-parameters have not been sufficiently investigated, are a core step of the EDC assessment requiring expert knowledge.

To date, most active substances have failed to meet the guidance document's definition of "sufficient investigation" for EATS-mediated adversity and endocrine activity. Therefore, additional in vitro and vertebrate studies have been requested and a testing strategy needs to be developed. Testing strategies should be set up using a tiered approach, mostly starting with investigations of endocrine activity, and considering potential worldwide interests and data requirements. In any case, the proposed testing strategy should be discussed with the competent authority which may involve the EDC expert group.

Additional vertebrate tests lead not only to tremendous animal sacrifice and expense, but also to delayed active substance assessments. This is thanks to the limited number of experts performing these assessments, as well as a lack of laboratory capacity – not every laboratory is able to perform EDC studies. Ecotoxicity studies are particularly affected, resulting in delays of more than a year. Furthermore, due to the tiered approach, additional studies might be required as a follow-up.

According to information that Echa collected on 92 of 147 active substances under evaluation:

- competent authorities (CAs) have identified the EDC assessment as a bottleneck for finalisation of biocidal active substance assessments;
- for at least 40% of active substances, no conclusion has yet been reached on whether further information is needed; and
- for 90% of the active substances, evaluation of the endocrine disrupting-properties has not been finalised, mainly due to lack of data and insufficient expert resources at CA level.

Update of information requirements under BPR

Organisation - BPR

One reason for the lack of EDC-related data is that most studies required for sufficient investigation of EATS-modalities are not part of the core data set under BPR and PPPR. In order to address this, information requirements under the BPR have been updated and are also due under the PPPR. The updates affect the toxicology and ecotoxicology sections of the BPR. The dataset needed for sufficient investigation of EATS-mediated parameters, as well as the assessment of endocrine disrupting-properties, have been included as core information requirements.

These updated BPR information requirements guarantee that all data requested by the guidance document to conclude on endocrine disrupting-properties will be available for future assessments. Nevertheless, additional vertebrate testing is shown. Therefore, it is crucial that alternative test methods are developed further and accepted in the regulatory process.

Inclusion of Annex I in the Echa/Efsa endocrine disruptor guidance document

In general, alternative methods are not accepted as stand-alone data for "sufficient investigation" of EATS modalities for human health (except the ToxCast oestrogen receptor model) and non-target organisms (NTOs), according to the Echa/Efsa guidance document. However, the recent inclusion of Annex A3 introduced the alternative Level 3 xenopus eleutheroembryonic thyroid assay (XETA; OECD 248) to the testing strategy for NTOs. The purpose of Annex A is not to replace any section of the guidance document, but to clarify under which circumstances the XETA may be considered as an alternative to the amphibian metamorphosis assay (AMA) for sufficient investigation of T-related endocrine activity.

- Case 1: endocrine disruption criteria for T-modality are not met; and
- Case 2: endocrine disruption criteria for T-modality are met for humans but not for mammalian NTOs and the mode of action is not related to thyroid hormone synthesis.

In practice, inclusion of the XETA in the testing strategy can be challenging. The testing strategy for NTOs is planned in parallel to the on-going evaluation of mammalian data to save time in the face of scarce laboratory testing slots. Moreover, the XETA is not specifically included in

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the updated Annex II to the BPR. This, in addition to the number of conditions in Annex A when the XETA can be considered a sufficient alternative to the AMA, might limit its applicability, especially with regard to dossier renewals.

Developments related to the EU chemicals strategy

The European Commission has proposed "to establish legally binding hazard identification" of EDCs, horizontally across EU legislation, and based on the existing criteria under the BPR and PPPR. It has also put forward acting "to review and strengthen the information requirements across legislation" to ban EDCs from consumer uses – unless proven essential for society.

EDC-related updates are already being heavily discussed for CLP and REACH which build the cornerstones of the EU chemicals regulation system.

CLP

In March, the competent authorities sub-group on endocrine disruption (CASG-ED) discussed a draft proposal for inclusion of separate EDC hazard classes for human health and the environment, based on the existing EDC identification criteria and guidance document under the BPR and PPPR. Two categories of hazard class are proposed:

- category 1 – known or presumed endocrine disruptors; and
- category 2 – suspected endocrine disruptors.

Clarification has yet to be provided on the exact definition and required evidence (studies) to support classification.

Interestingly, generic concentration limits are proposed for the classification of mixtures, contradicting the current approach under the BPR, where no thresholds are applicable for identification of a biocidal product as an EDC.

The indicative plan for a draft proposal for revision of CLP was postponed to 2022 to allow stakeholders (member states, NGOs and industry) more time to develop their positions. After adoption of the criteria under CLP they will be proposed under the Globally Harmonized System (GHS) of classification and labelling. This approach has sparked concerns from industry and some member states that fear it could undermine global harmonisation and hamper worldwide trade.

REACH

Under the EU chemicals strategy, EDCs shall be included in REACH as a separate category of substance of very high concern (SVHC) under Article 57. Currently, EDCs can be identified as SVHCs under Article 57f alongside chemicals causing cancer, mutations and reproductive toxicity on condition that they raise an "equivalent level of concern". Substances identified as an SVHC might be subject to authorisation/restriction.

Last October initial thoughts on updating the REACH Annexes (I and VII to X) for additional data requirements, based on the learnings from the Echa/Efsa guidance document, were presented at a CASG-ED meeting and further discussed in March. In general, the additional EDC-specific studies proposed for the update of data requirements correspond to those suggested in the guidance document, but the level of detail depends on the tonnage band. The indicative aim for completion of the update is 2022. An impact assessment and an open public consultation will be carried out beforehand.

The planned updates are expected to increase workload – to what extent depends on the information requirements agreed on in the final version. Based on experience under the BPR and PPPR, more vertebrate testing is likely despite the fact that animal testing must be the last resort. Since laboratory and expert capacities needed for complex studies and their assessments are already scarce due to increased testing under the BPR and PPPR, these constraints are likely to be intensified.

Conclusion

In general, the assessment of EDC properties is a dynamic regulatory field gaining even more momentum after publication of the EU's chemicals strategy. Based on the experience of EDC assessment under the 2018 guidance document, it can be concluded that the assessments delay the active substance authorisation process. Justification for non-submission of additional vertebrate studies listed in the guidance document are only accepted in exceptional cases. Thanks to strict adherence to the studies listed for "sufficient investigation" of EATS-modalities, additional (mostly vertebrate) testing will consume laboratory capacities leading to delays for ecotoxicity NTO testing in particular, as well as drive very high use of animals. Moreover, since expert knowledge is required throughout the process from data gathering to concluding on potential EDC properties, both authorities and applicants face capacity challenges.

For future assessments, close collaboration of (eco) toxicologists is essential to ensure a complete EDC assessment and a reasonable testing strategy, if required, as well as discussion of the strategy with the authority. The workload related to the EDC assessment should not be underestimated but rather regarded as a "small dossier within the dossier".

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The planned updates to the CLP and REACH Regulations will mean further time and resource constraints since additional testing will be required. All affected parties should therefore follow the ongoing processes closely in order to react in a timely manner – and involve experts where necessary.

The views expressed in this article are those of the author and are not necessarily shared by Chemical Watch.

Footnotes

1 COMMISSION DELEGATED REGULATION (EU) 2017/2100 of 4 September 2017 setting out scientific criteria for the determination of endocrine-disrupting properties pursuant to Regulation (EU) No 528/2012 of the European Parliament and Council
2 COMMISSION REGULATION (EU) 2018/605 of 19 April 2018 amending Annex II to Regulation (EC) No 1107/2009 by setting out scientific criteria for the determination of endocrine disrupting-properties
3 Annex A to the Echa/Efsa ED GD (09/04/2021): Use of the XETA in the assessment strategy of the Echa/Efsa Guidance

FURTHER INFORMATION

Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009, Echa/Efsa, June 2018

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