Assessing Endocrine-Disrupting Properties of Active Substances in Plant Protection Products in the Light of Current Insights and Demands

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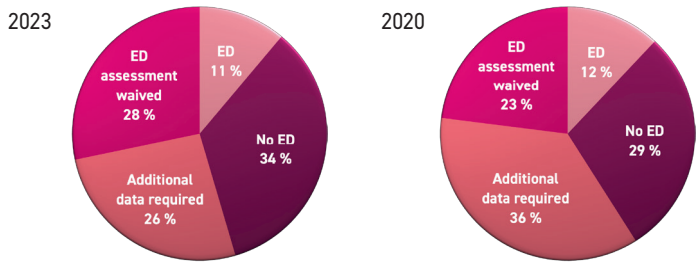
Introduction

Since the introduction of new scientific criteria for the identification of endocrine-disrupting (ED) properties in the European Union in 2018, EFSA has assessed more than 100 pesticide active substances (a.s.) for potential ED properties. From the 106 a.s., which are either in the evaluation process or have already been evaluated by EFSA, 12 a.s. (12/106 a.s.) were (preliminarily) concluded to be endocrine-disrupting chemicals (EDC) based on the available data for the human health (HH) part. Within this group, 5/12 a.s. were also considered as EDC for non-target organisms (NTO). A total of 5/12 a.s. were classified as EDC due to effects on the thyroid (T) modality and 2/12 a.s. were considered as EDC due to effects on the estrogen, androgen, steroidogenesis (EAS) modalities. 1/12 a.s. was considered as EDC due to effects on EATS-modalities. For 4/12 a.s. an EFSA conclusion is not yet available. Overall, 36/106 a.s. were concluded not to be an EDC for humans. For 28/106 a.s., additional data were requested with regard to HH. For the remaining 30/106 a.s., the ED assessment was waived for the HH part. Furthermore, for 3 a.s. the performance of the assessment was not applicable (3/109) (EFSA, 2023).

Legal background

- 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
- Commission Implementing Regulation (EU) 2018/1659 of 7 November 2018 amending Implementing Regulation (EU) No 844/2012 in view of the scientific criteria for the determination of endocrine disrupting properties introduced by Regulation (EU) 2018/605

(Preliminary) conclusions by EFSA on the ED properties (HH) of an a.s.



Regulatory background

- Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009 (ED Guidance Document) (ECHA and EFSA, 2018)
- Administrative guidance on submission of dossiers and assessment reports for the peer-review of pesticide active substances (EFSA, 2019) – Appendix I
- Technical report on the outcome of the pesticides peer review meeting on general recurring issues in mammalian toxicology (EFSA, 2020)
- OECD Series on Testing and Assessment Revised Guidance Document 150 on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption (OECD, 2018)
- Respective test guidelines (OECD, US EPA)

Necessary steps for the ED assessment in line with the ED Guidance Document (ECHA and EFSA, 2018)*

Data gathering
- Appendix E (*in vivo* and *in vitro* information)
- Appendix D.1 (database information)
- Appendix D.2 (*in silico* information)
- Systematic literature search

Testing proposal, if required
- EAS/T-mediated adversity sufficiently investigated?
- EAS/T-related endocrine activity sufficiently investigated?
- Generation of mechanistic information in the context of a mode of action (MoA) analysis

MoA analysis, if required
- By means of the adverse outcome pathway (AOP) concept (*via* AOPwiki and specific literature search)
- Generation of supporting evidence
- Dose and temporal concordance assessment
- Analysis of potential alternative MoA

Overall assessment (Appendix I)
- Weight of evidence (WoE) assessment
- Selection of relevant scenario
- Separate conclusion for HH and NTO and overall conclusion
- Outcome:
  - No EDC
  - EDC
  - No conclusion can be drawn and/or additional data have to be generated

* As a first step, options for waiving the ED assessment should be checked.

Potential testing strategies for the T-modality

- Developmental neurotoxicity (DNT) study (OECD TG 426)
- Guidance for thyroid assays in pregnant animals, fetuses and postnatal animals, and adult animals (US EPA, 2015), also known as 'comparative thyroid assay' (CTA)
- In line with Appendix A of the ED Guidance Document (ECHA and EFSA, 2018):
  - Thyroid hormone (TH) and thyroid-stimulating hormone (TSH) measurement
  - Analysis of different potential molecular initiating events (MIE)
  - Hepatic enzyme induction and subsequently increased TH clearance

SCC experience

- Since the introduction of the new scientific criteria in 2018, SCC GmbH has been involved in the assessment of the ED properties of more than 20 pesticide and biocidal a.s.
- Our services include but are not limited to:
  - Complete data gathering
  - Analysis of sufficiency of the dataset
  - Testing strategy proposal and study monitoring
  - MoA analyses
  - Position papers on specific ED topics, *e.g.* dose and temporal concordance assessment
  - *Etc.*

Conclusion and outlook

- 5 years after the implementation of the scientific criteria, authorities expect the industry to be well prepared for the assessment; all relevant data must be available at the time of submission, stop-of-the-clock possibilities will only be applicable in rare cases.
- Due to the complexity of the assessment sufficient time needs to be scheduled, also in case further data must be generated. It should be kept in mind that the necessity of further data might just come up during the MoA analysis.
- The ED assessment is a task which demands close exchange between experts of different fields, such as toxicology, ecotoxicology, *in silico* toxicology, regulatory affairs, ...
- Regulatory overview is also absolutely needed for the overall strategy and in order to foresee possible consequences.

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