Guidance for the identification of EDs in the context of the Biocides and Plant Protection Products Regulations

Joint EFSA/ECHA/JRC drafting team

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Outline

- Objectives of the guidance
- Scope of the guidance
- Content of the guidance
- ED criteria (relevant for the assessment strategy)
- Assessment strategy

Objective

- Provide technical guidance on the implementation of the ED criteria applicable in the context of the Biocides and Plant Protection Products Regulations ((EU) No 528/2012 & (EC) No 1107/2009)
  - Hazard properties that determine a substance as endocrine disruptor are (regulatory) context independent
  - Therefore, consistent ED criteria and identification of EDs on the basis of their hazard properties across regulatory frameworks is warranted and desirable

Scope of the Guidance

- The Guidance (like the ED criteria) is based on the WHO/IPCS definition of an endocrine disruptor (WHO/IPCS 2002)

"*An **endocrine disruptor** is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations*"

- The Guidance is based on the OECD Conceptual Framework for testing and assessment of endocrine disruptors (OECD GD 150) which provides lists the OECD TGs and help to the interpretation of the results
- Covers endocrine modes of action caused by estrogen, androgen, thyroid and steroidogenic (EATS) modalities
- Focuses on ED effects in vertebrates; i.e. mammals (incl. humans), fish, amphibians, birds and reptiles.

Content of the guidance

1. Introduction
2. Scope of the guidance
3. **Assessment strategy**
4. Information sources for endocrine disruptor identification
5. Recommendations
6. References

Appendices

A - Additional considerations on how to assess the potential for thyroid disruption
B - Recommendations for design, conduction and evaluation of hormonal studies
C - Information requirements under the BPR and PPPR
D - Databases, software tools and literature derived (Q)SARs
E - Excel template for reporting the available information relevant for ED assessment
F - Example on how to develop the search strategy protocol
G - Example of moa for non-target organisms (fish)

Assessment strategy: ED Criteria

Section A — ED properties for humans

Section B — ED properties for non-target organisms

1) ED criteria: **Definition of an endocrine disruptor**

- ✓ it shows an adverse effect in an intact organism or its progeny, which is a change in the morphology, physiology, growth, development, reproduction or life span of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress or an increase in susceptibility to other influences;
- ✓ it has an endocrine mode of action, i.e. it alters the function(s) of the endocrine system; and
- ✓ the adverse effect is a consequence of the endocrine mode of action.'

2) ED criteria: **How to identify an endocrine disruptor**

- ✓ Assessment based on 'all available relevant scientific data' e.g. data requirement
- ✓ Weight of evidence approach

Assessment strategy: OECD GD 150

The parameters relevant for ED identification are grouped to support the users of the guidance in the evaluation of the scientific evidence.
(Grouping based on OECD GD 150 & JRC screening methodology to identify potential EDs)

The four groups are:

- ✓ ***In vitro* mechanistic** *(OECD CF level 2);*
- ✓ ***In vivo* mechanistic** *(OECD CF level 3);*
- ✓ **EATS-mediated** (OECD CF levels 4 & 5)
  Provide information on potentially adverse effects, while at the same time (due to the nature of the effect and the existing knowledge) they are also considered indicative of an EATS MoA and thus (in the absence of other explanations) imply an underlying in vivo mechanistic explanation;
- ✓ **Sensitive to, but not diagnostic of, EATS** (OECD CF levels 4 & 5)
  Provide information on potentially adverse effects. However, due to the nature of the effect and the existing knowledge, these effects cannot be considered (exclusively) diagnostic of any one of the EATS modalities. Nevertheless, in the absence of more diagnostic parameters, these effects might provide indications of an endocrine MoA that might warrant further investigation.

Assessment strategy: initial analysis of the evidence

- Adverse effects observed for 'EATS-mediated' parameters drive the assessment. This is because these parameters provide both information on adversity and (knowledge on) endocrine activity.
- A definition of a sufficient dataset for performing the ED assessment is given for both adversity and endocrine activity

For example:

✓ If 'EATS - mediated' effects were sufficiently investigated and no adversity was identified

Conclude: ED criteria not met

✓ If 'EATS mediated'-effects are not sufficiently investigated

Consider the endocrine activity

Mode of action analysis

- ✓ When adverse effects and/or endocrine activity are identified, the MoA analysis is necessary to demonstrate the biologically plausible link between the two.

- ✓ The IPCS MoA framework has been considered in the guidance to address additional considerations which are necessary for ED assessment.

Applicability of the assessment strategy

- It applies to HH and non-target vertebrates (in a 'stepwise approach' to reduce vertebrate testing)
- It applies to non-EATS modalities, when clear effects are seen in the studies available in the dossier.
- It applies to non-target invertebrates when data are available

Conclusion on the ED criteria

- ✓ If the MoA analysis supports the biological plausibility of the link between the observed adverse effects and endocrine activity for at least one MoA among those postulated, the substance is considered to meet the ED criteria.

- ✓ If the biological plausibility of the link between the endocrine activity and the adverse effect(s) is not demonstrated for any of the postulated MoA(s), the substance is considered not to meet the ED criteria