13 February 2019

EFSA-EChA-JRC Guidance for the identification of endocrine disruptors

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Introduction

- ED criteria laid down in **Commission Delegated Regulation (EU) No 2017/2100** for BP and **Commission Regulation (EU) No 2018/605** for PPP.
- EFSA and ECHA (European Chemicals Agency responsible for biocides) were mandated to provide technical guidance on the implementation of the ED criteria applicable in the context of the Biocides and Plant Protection Products Regulations.

ED criteria (1)

Assessment of ED criteria necessary deals with both humans and non-target organisms

Section A — ED properties with respect to humans

Section B — ED properties with respect to non-target organisms

(point 1)
ED criteria (definition of what constitutes an endocrine disruptor)

(point 2)
How to determine whether the criteria are met

ED criteria (2): definition of endocrine disruptor

*a)**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;*

*b)it has an endocrine mode of action, i.e. **it alters the function(s) of the endocrine system**; and*

*c)**the adverse effect is a consequence** of the endocrine mode of action.'*

- '**Endocrine mode of action**' = 'endocrine activity'
  - Term 'endocrine mode of action' in point (c) includes both the endocrine activity, the adverse effect(s) and a biologically plausible link between
- Points (b) and (c) should be understood as:
  - it shows endocrine activity, i.e. it has the potential to alter the function(s) of the endocrine system;
  - the substance has an endocrine disrupting mode of action, i.e. there is a biologically plausible link between the adverse effect and the endocrine activity..

ED criteria (3): how to conduct risk assessment

Point (2) of the ED criteria specifies the information to be considered when determining ED properties, and how to assess this information.

- Assessment based on
  All available relevant scientific data
  - Data requirement: guideline studies/systematic literature data
- **Weight of evidence approach** to be applied for the assessment, considering factors such as:
  - Relevance of the study design for the assessment of adverse effects and endocrine activity
  - Positive and negative results (i.e. consistency of the results)
  - Coherence of the (pattern) of results within and between studies and across species
  - Biological plausibility of the link between the endocrine activity and the adverse effects, i.e. the endocrine mode of action

Scope of the Guidance

- 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.
- But does not dismiss non-EATS modalities and invertebrates

Assessment strategy: general

- The guidance document describes how to gather, evaluate and consider all relevant information for the assessment, conduct a mode of action (MoA) analysis, and apply a weight of evidence (WoE) approach, in order to establish whether the ED criteria are fulfilled.
- The guidance recommend to consider the data in an holistic approach but start the analysis on the mammalian data and draw a conclusion based on those before performing and/or requesting more data on other non-target organisms
- The guidance gives the possibility to identify a.s. for which an ED assessment is not needed.

STEPWISE APPROACH

Assessment strategy: OECD GD 150

The Guidance is based on the OECD Conceptual Framework for testing and assessment of endocrine disruptors (OECD GD 150) which lists the OECD TGs and help to the interpretation of the results

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 and conclusion: overview

- 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 dataset for performing the ED assessment is given for both adversity and endocrine activity
- When adverse effects and/or endocrine activity are identified, the MoA analysis is necessary to demonstrate the biologically plausible link between the two.
- 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.

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