EFSA/ECHA (2018) GUIDANCE FOR THE IDENTIFICATION OF ENDOCRINE DISRUPTORS (ED): LOOKING BACK AFTER THE FIRST 3 YEARS OF IMPLEMENTATION

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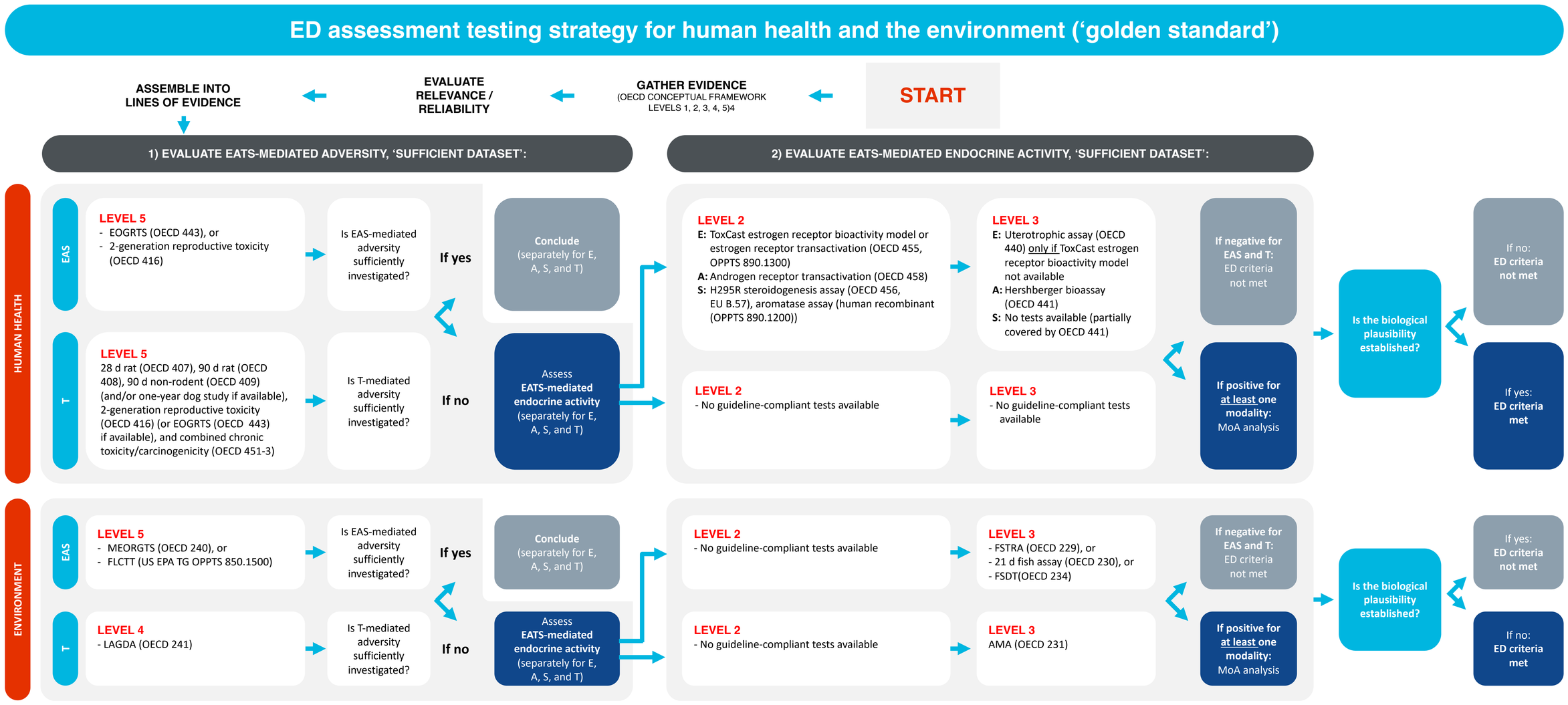
Introduction

Guidance for the assessment of endocrine disrupting (ED) properties under the **Biocidal Products** and **Plant Protection Product Regulations** (BPR and PPPR) was published in 2018 by the European Food Safety Authorities (EFSA) and the European Chemicals Agency (ECHA)[1]. Adaptations of the European Chemicals and Classification & Labelling Regulations (REACH[2] and CLP[3]) are planned, in line with the EFSA/ECHA guidance. Today, there is no guidance for the ED assessment of **chemicals**, **cosmetics**, **pharmaceuticals**, and other types of substances but the ECHA/EFSA guidance may be used to frame also these evaluations.

In the European regulatory context, effects on the endocrine system are evaluated considering the estrogen (E), androgen (A), thyroid (T), and steroidogenesis (S) pathways, commonly referred to as the **'EATS modalities'**.

This poster looks at some of the issues encountered over the past three years when conducting guideline-compliant ED assessments across various types of chemistries.

ED assessment testing strategy for human health and the environment ('golden standard')



(EOGRTS: Extended One Generation Reproductive Toxicity Study; H295R: Angiotensin-II-responsive steroid-producing adrenocortical cell line; MEORGTS: Medaka Extended One Generation Reproductive Toxicity Study; FLCTT: Fish Life Cycle Toxicity Test; FSDT: Fish Sexual Development Test; LAGDA: Larval Amphibian Growth and Development Assay; AMA: Amphibian Metamorphosis Assay)

Some of the practical and conceptual issues encountered

ISSUES AROUND DATA AVAILABILITY

'Sufficient dataset' not available for many substances. Initial evaluations often based on weight of evidence approaches using existing *in silico / in vitro/ in vivo* data and read across.

- *In silico* data allows to cover data gaps, support mode of action hypotheses, and create bridge between human health and the environment, **however** *in silico* predictions have limitations, e.g., tools not powered enough to cover ED endpoints.
- *In vitro* high throughput screening (HTS) data (e.g., US EPA ToxCast) represents important cornerstone of many ED assessments, **however** data not available for all substances and, when available, sometimes complicated to interpret due to high number of false positives/ negatives.
- *In vivo* data remains key element of all ED assessments. Studies usually available on species relevant for the evaluation of effects on human health, but testing (and sufficient background knowledge on biological mechanisms) often missing for environmentally relevant species. In some cases, a wealth of studies identified, but not guideline-compliant, and do not evaluate all required endpoints.
- Read across approaches (between substances or from human health to environment) often not accepted.

CONCEPTUAL ISSUES

Besides data availability, other issues may be faced when assessing the ED potential of substances with biocidal, pesticidal, and/or other applications:

- How to deal with substances that have specific properties possibly precluding systemic uptake / ED modes of action (e.g., strong irritants / corrosives, oxidants), or with complex compositions (e.g., UVCBs, plant extracts).
- How to differentiate and evaluate primary and secondary ED effects?
- How to handle substances that are naturally present in the environment and/or necessary for life, in the absence of specific guidance and consensus across legislative bodies?
- How to handle in situ generated substances?
- To what extent is read across possible between the human health and the environmental ED assessments?

Case study: ED assessment of substances naturally present in the environment

Certain substances used in biocidal, pesticidal, or other applications occur naturally in the environment, are essential for life, but at the same time fulfil the definition of an 'endocrine disruptor', as laid down in Regulation (EU) 2018/605 [5]. One example is iodine, an essential element that has a physiological function in thyroid hormone synthesis (i.e., intentionally interacts with the endocrine system). Both iodine deficiency and excess iodine can impair thyroid homeostasis/thyroid hormone levels. This is an endocrine effect but it would not be justified to conclude that iodine should be labelled as an endocrine disruptor, therefore excluding it from use as a biocide for example.

For biocidal and pesticidal naturally occurring active substances, a possible approach is to **demonstrate negligible risk under realistic worst-case use conditions**, thereby allowing use as per exemption to the exclusion criteria (Article 5 of Regulation (EU) No. 528/2012 [6] and Section 3.6.5. of Regulation (EC) No. 1107/2009 [7]). The approach and related possible pitfalls are laid out below:

1. Demonstrate/confirm essentiality (issue: not always obvious to show this due to lack of data)
2. Derive ED-related safety thresholds for human health and the environment (issues: lack of data, low dose effects, no clear guidance on how to derive such values for ED effects)
3. Gather information on levels present in the environment (drinking water, food, drugs, air, soil, water….) from natural and anthropogenic sources (issue: lack of reliable data)
4. Select levels that are relevant for human and environmental exposure assessment (issues: what value to choose: overall lowest, mean, …? Consider anthropogenic sources or not?)
5. Compare 'safe exposure level' to 'background level' and determine whether there is an ED concern for human health and the environment under the proposed use conditions

If the amounts of active substance potentially released into the environment through the considered uses are within naturally occurring background levels, a conclusion **of 'no concern with respect to human health and/or the environment'** could be proposed (issue: no clear guidance and possible contradictions across legislations).

References

1 EFSA/ECHA (2018). Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No. 528/2012 and (EC) No. 1107/2009. https://echa.europa.eu/documents/10162/23036412/bpr_guidance_identif_ed_en.pdf/1a4d2811-3faa-fe61-1de2-3cbce8fd4d95 (accessed August 2019).
2 Regulation (EC) No. 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No. 793/93 and Commission Regulation (EC) No. 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC.
3 Regulation (EC) No. 1272/200 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No. 1907/2006.
4 OECD (2018). Revised guidance document 150 on standardised test guidelines for evaluating chemicals for endocrine disruption, OECD Series on Testing and Assessment, OECD Publishing, Paris. https://doi.org/10.1787/9789264304741-en.
5 Regulation (EU) No. 2018/605 amending Annex II to Regulation (EC) No. 1107/2009 by setting out scientific criteria for the determination of endocrine disrupting properties.
6 Regulation (EU) No. 528/2012 concerning the making available on the market and use of biocidal products.
7 Regulation (EC) No. 1107/2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC.