Endocrine Disrupting Assessment for Plant Protection Products, Biocides and Industrial Chemicals in the EU – Challenges and Improving Points

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INTRODUCTION

All (ongoing) active substance registrations and renewals under the PPP and BPR require a full ED assessment. Co-formulants present in formulated products should be screened for ED and replaced if ED properties are confirmed. Furthermore, the European Commission is currently evaluating how the REACH annexes can be updated to include an ED assessment requirement. Companies can soon start including information on new hazard classes in their IUCLID dossiers, following the amendment of the Classification, Labelling and Packaging (CLP) Regulation.

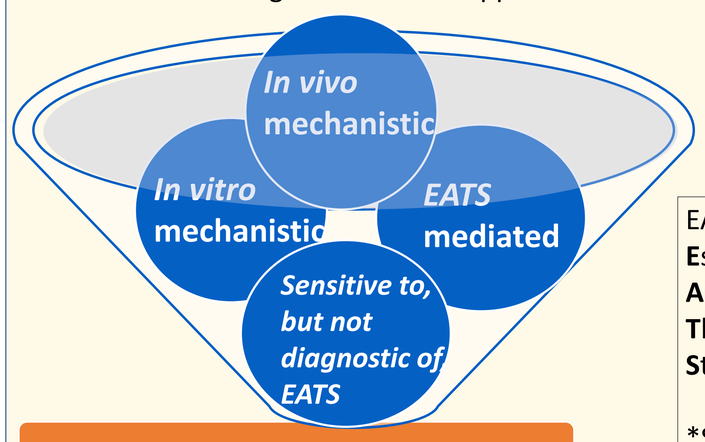
ACTIVE SUBSTANCES

PPP: Active substances, safeners, synergists
Biocides: Active substances

What criteria to assess?

Endocrine mode of action → **Consequences** → **Adverse effects**

How to assess? Weight of evidence approach[1]



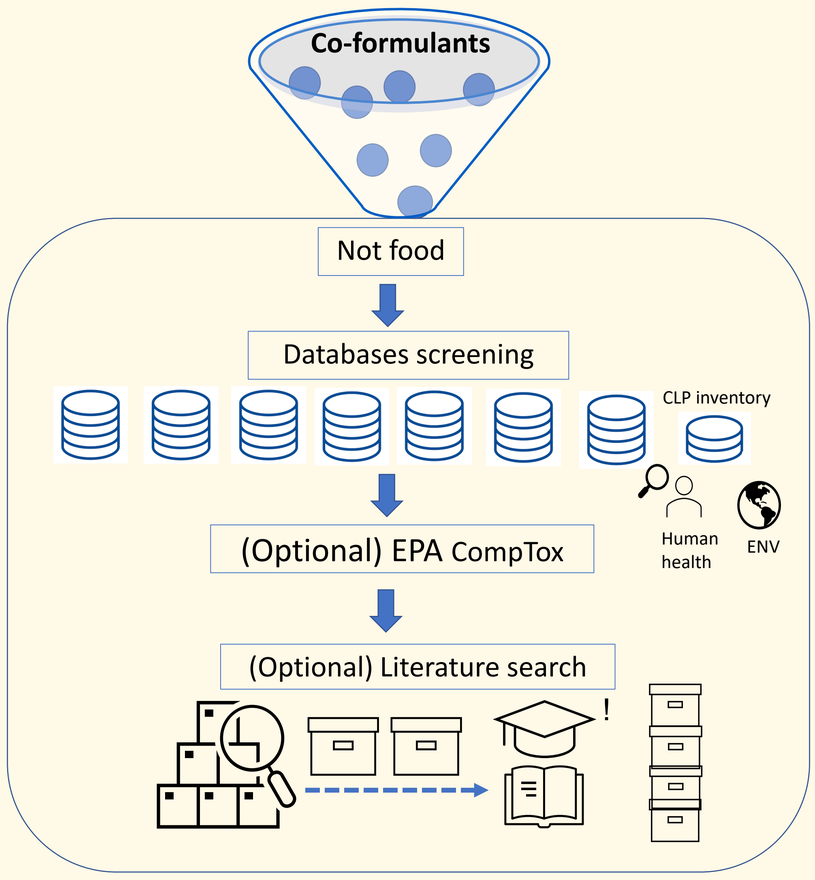
Gather information
Assess the evidence
Initial analysis of the evidence
Mode of action analysis
Conclusion

EATS mediated[1]*:
Estrogen-mediated activity
Androgen-mediated activity
Thyroid-related activity
Steroidogenesis-related activity

*Standardised test guidelines for *in vivo* and *in vitro* testing are available in OECD GD 150[2]. Available data can be reported and analysed using the Excel template prepared by ECHA and EFSA.

CO-FORMULANTS

PPP: Check the EU list of unaccepted co-formulants for inclusion in plant protection products[3]
Biocides: Screening approach[4] as shown below

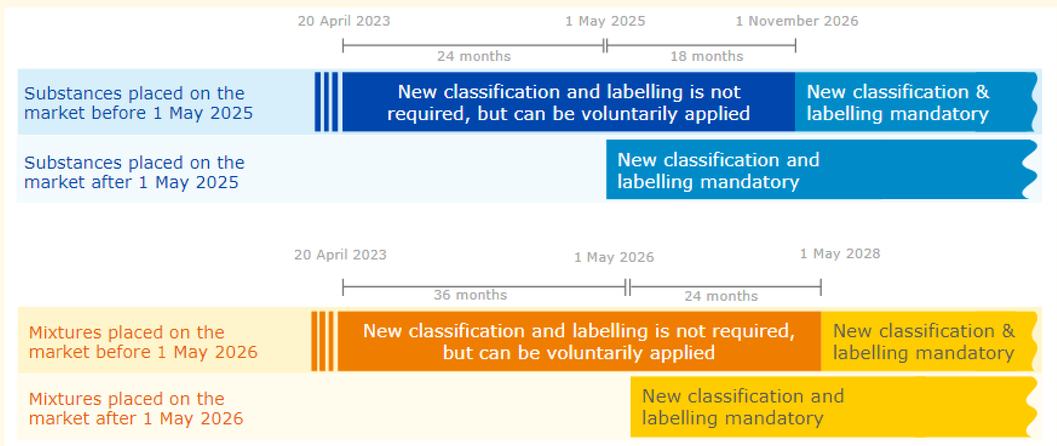


A harmonised approach for evaluating co-formulants is unavailable. In case the ED properties of a substance cannot be concluded based on the databases (e.g. some UVCB substances), a literature search and/or expert statement may be needed, which can be time-consuming and require expert knowledge.

CLASSIFICATION, LABELLING AND PACKAGING

New EU hazard statements are in force as of 20 April 2023

Hazard class and category code	Hazard statement code	Hazard statement
ED HH 1	EUH380	May cause endocrine disruption in humans
ED HH 2	EUH381	Suspected of causing endocrine disruption in humans
ED ENV 1	EUH430	May cause endocrine disruption in the environment
ED ENV 2	EUH431	Suspected of causing endocrine disruption in the environment



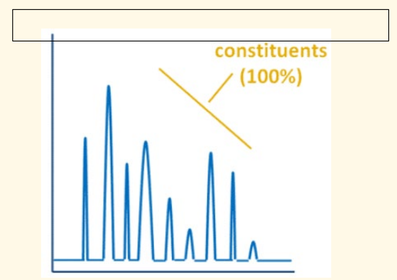
Picture source: ECHA website

EXAMPLE

How to handle "difficult" substances?
In general, a weight-of-evidence approach should be used, which considers all available information to conclude on the ED properties of a substance. UVCB's are used as an example but more or less the same would apply to mixtures, polymers, etc.:

Testing strategy (OECD GD 150)
Challenges with *in-vivo* testing:

- Choice of test concentrations: Should the top dose be sufficiently high to give clear systemic effects (i.e. non-endocrine specific toxicity) or not? If yes, what does this mean for a UVCB?
- Water Accommodated Fractions: Most UVCB's are not (completely) soluble in water. What is actually tested in aqueous studies?
- Analytical method development and validation: Which components of the UVCB will be measured? Can one or more analytical methods be developed and how can any effects be related to the measured values?
- Statistical analysis of data: Statistical analysis of the various endpoints is difficult and needs expert judgement.



UVCB stands for unknown or variable composition, complex reaction products or of biological materials.
A UVCB substance has many different constituents, some of which may be unknown. The composition can be variable or difficult to predict.

Picture source: ECHA website

Non-testing strategy
Possibilities (*and challenges*)**:**

- Screening the UVCB substance and/or its identifiable constituents in the databases listed in the biocides regulation for co-formulants (*Limited information is expected*).
- Perform a literature search on the UVCB substance and/or its identifiable constituents for ED indication (*Limited information is expected*).
- Read across to other substances based on the similarities on the structure/receptors (*More difficult to prove non-ED than ED*).
- Perform QSAR model prediction for the UVCB substance and/or its identifiable constituents (*Depends on available information on constituents*).

REFERENCES
1. ECHA and EFSA 2018. Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC)No 1107/2009. doi: 10.2903j/.efsa.2018.5311
2. 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
3. EU commission 2021. COMMISSION REGULATION (EU) 2021/383 of 3 March 2021 amending Annex III to Regulation (EC) No 1107/2009 of the European Parliament and of the Council listing co-formulants which are not accepted for inclusion in plant protection products
4. ECHA 2021. Proposal to bridge the endocrine disruptor assessment of biocidal non-active substances with REACH screening and assessment. CA-March21-Doc.4.3

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