PRACTICAL TIPS ON ASSESSING ENDOCRINE DISRUPTING PROPERTIES

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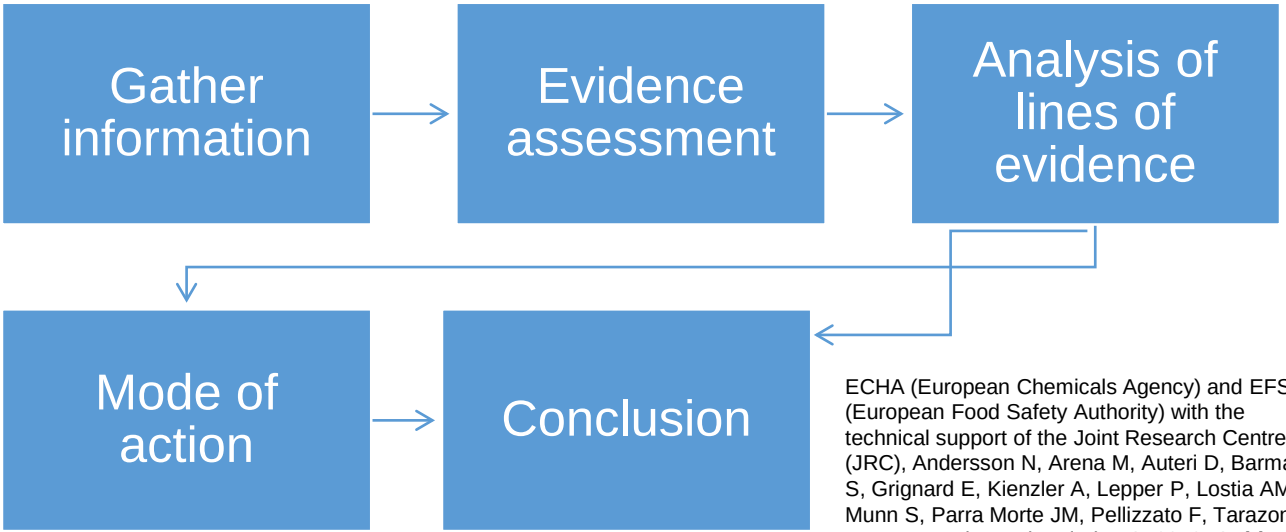
ED ASSESSMENT FOR ACTIVE SUBSTANCES



ECHA (European Chemicals Agency) and EFSA (European Food Safety Authority) with the technical support of the Joint Research Centre (JRC), Andersson N, Arena M, Auteri D, Barmaz S, Grignard E, Kienzler A, Lepper P, Lostia AM, Munn S, Parra Morte JM, Pellizzato F, Tarazona J, Terron A and Van der Linden S, 2018. **Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009**

LITERATURE SEARCH

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Information sources

consult more than 2 databases

…“reasonable efforts to locate all sources of relevant scientific peer-reviewed open literature and provide their reasons for choosing such sources..” (EFSA, 2011)

Justify the selected information source

Search

Systematic: single concept or targeted literature search

Search strategy

to retrieve as much potentially relevant scientific peer-reviewed open literature as possible

combination of search terms

Search terms

include synonyms, lab codes, trivial names

related to ED endpoints

Selection of articles

Clearly establish relevance criteria for acceptance/rejection of open literature studies

Filter based on abstracts and/or full study reports

Documentation

Document the steps of your literature search

Selection of articles

Reliability (e.g. Klimisch Scores)

Summarize and incorporate findings in your dossier (http://www.oecd.org/ehs/templates/)

EFSA (2011) Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009, EFSA Journal 2011;9(2) 2092

IN VITRO DATA

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TOXCAST

Several in-vitro tests/models relevant for ED

Limited number of these assays have metabolic capacity

Regular updates and improvements

OECD work

Detailed Review Paper on retinoid pathways under development

Draft TG Androgen Receptor Transactivation Assay (ARTA) 22Rv1/MMTVGR cell (“me-too”)

Update of TG 455 and 458 with the introduction of a metabolic step in the transactivation bioassay for ER/AR

Updated GD 150 on evaluation of chemicals for endocrine disruption (2018)

EU initiatives (EURL-ECVAM)

E.g. validation coordination of mechanistically informative alternative methods related to the detection of thyroid hormone disruption

https://ec.europa.eu/jrc/en/publication/eur-scientific-and-technical-research-reports/eurl-ecvam-status-report-development-validation-and-regulatory-acceptance-alternative-3

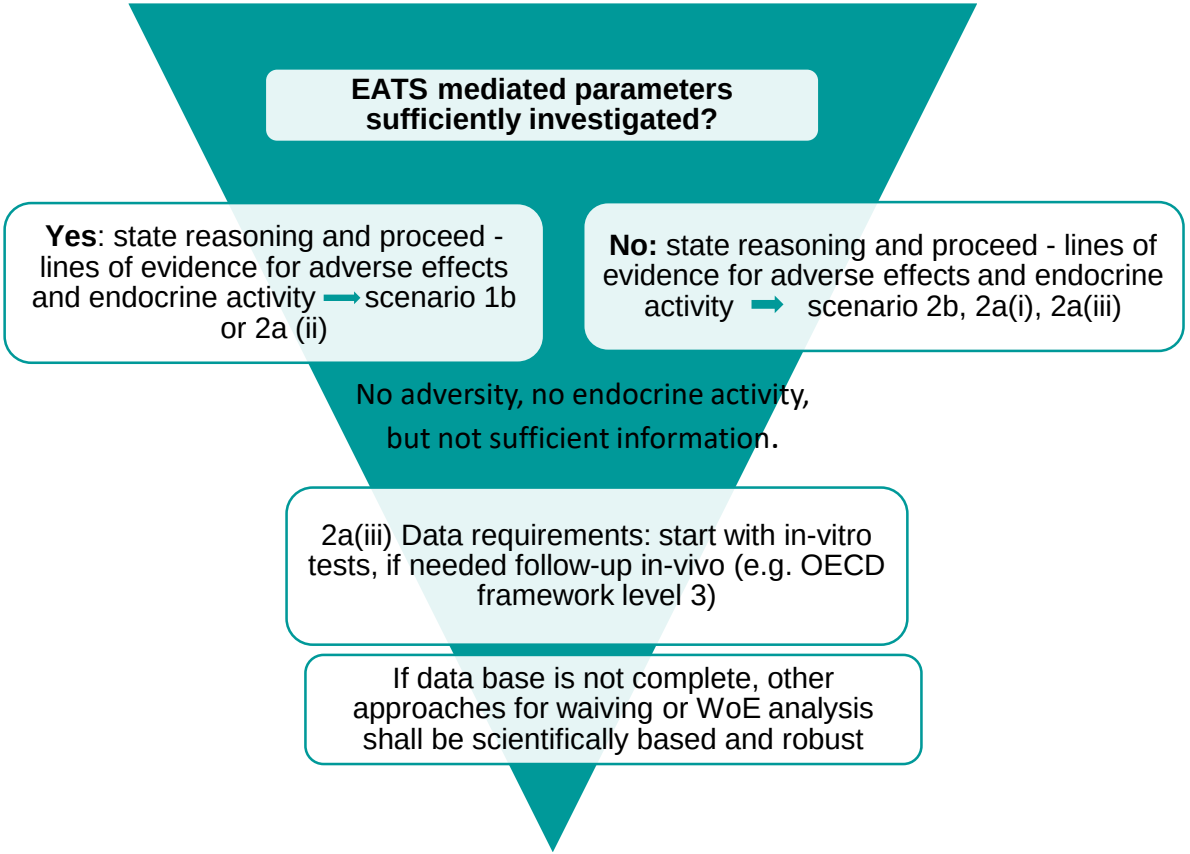
DATA GATHERING (GUIDELINE) STUDIES

- Outline of dataset considered for (eco)toxicology assessment
- In vivo mechanistic, In vitro mechanistic, EATS-mediated, Sensitive to, but not diagnostic of EATS, General adversity
- Compilation of the Excel Template (cf. Appendix E of the ED Guidance)
- Look into all original study reports
- Report clinical chemistry changes that could be related to ED (e.g. cholesterol)
- Report also findings “sensitive, but not diagnostic of EATS” (e.g. heart weight)
- Report magnitudes of effects (e.g. body weight, organ weight changes)
- Report no effects
- Report findings for different generation/life stages/sexes
- Graphical presentation of study findings (optional)

FOLLOW THE ED GUIDANCE

- Follow the ED Guidance during ED assessment(s)
- Do not conclude that ED criteria are not met only based on check of the available data, if adversity or activity have not been addressed in an adequate way
- Possible data gaps need to be identified
- In some cases waiving of additional tests possible – please consult with Competent Authority

ASSESSMENT ACCORDING TO ED MODALITIES



ED ADVERSITY: EXAMPLE THYROID

- Histopathological changes
- Thyroid hormone alterations indicate a „potential concern for neurodevelopment“
- Does not always lead to classification (cf. classification limits, definition of adversity)
- Consider toxicokinetic information and species differences
- Not to dismiss rat specific data without experimental proof of non-relevance to humans
- Effects secondary to other toxicity (e.g. systemic toxicity)

MODE OF ACTION (MoA) ANALYSIS

- Only relevant if endocrine adversity or endocrine activity was observed
- Level of detail and work on the MoA analysis can vary depending on method and/or observed effects
- Further clarifying information in consultation with the eCA
- Multiple MoA possible: address one by one (by same/different modalities, but can be complex/not possible due to crosstalks)
- Alternative non-endocrine MoA always require a comparative MoA analysis
- Graphical presentation of study findings/dose/species supporting the comparative MoA analysis
- Address uncertainties of the (postulated) MoA analysis
- If weight of evidence (WoE) and MoA analysis for one EATS modality leads to the conclusion that ED criteria are met ED assessment could stop

ED ASSESSMENT ENVIRONMENT

General

Even if human health ED criteria are met, an assessment for non-target organisms has to be performed. But it is expected, that in that case no further testing will be requested.

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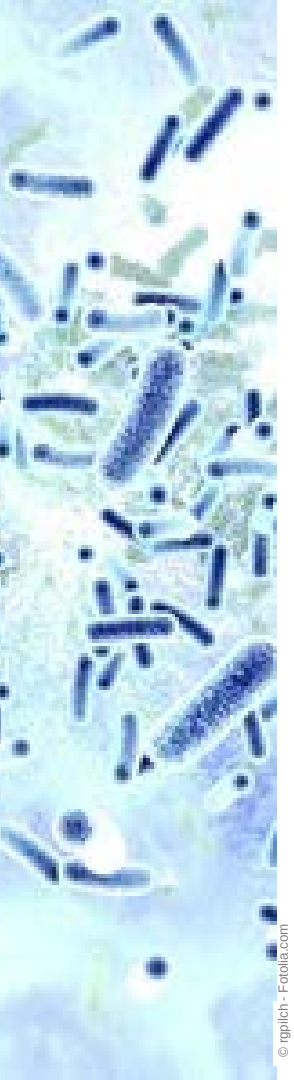
ED sufficiently investigated?

Chronic daphnia tests according to existing protocols are not usable for ED identification

Fish full life cycle test does not cover all EATS mediated parameters, especially if no sex-ratio (and vitellogenin) is reported

Choice of test concentration suitable for detection of ED relevant parameters (based on acute and chronic effect concentrations)

Follow the testing regime in the ED guidance (e.g. fish: short time reproduction (OECD TG 229), sexual development (TG 234), amphibia: AMA (TG 231), LAGDA (TG 241)



ED ASSESSMENT BIOCIDAL PRODUCTS

- During the evaluation phase to consider the ED criteria for both:

  (a) the active substance(s) included in the product; and

  (b) the 'co-formulants' (non-active substances)

- evaluating bodies have to decide whether there is a need to evaluate a specific non-active substance in detail and, if necessary, to ask additional information to the applicant for the appropriate assessment
- …only occur where there are **indications** that a non-active substance may have ED properties based on the existing knowledge and the available scientific information…. *(CA-March18-Doc.7.3.b-final)*
- Guidance was developed for applicants based on a proposal by UK and agreed by the Coordination Group in 2019

INSTRUCTIONS FOR APPLICANTS

approved at CG 34 2019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A. Checking EU Decisions on ED properties

- under REACH?
- under the BPR?
- under the PPPR?


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B. Excluding food/ foodstuff materials

- Defined as „food“ under Article 2 of Regulation (EC) No 178/2002 (General Food Law Regulation)


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C. „ Indications" of ED properties

- EU priority lists
- REACH registration data
- US databases (USEPA Comptox including EDSP 21)
- Classification
- Literature search

ED INDICATIONS CO-FORMULANTS

- Document different steps for each co-formulant (including date of query of databases)
- Literature search (publication of last 2 years, specific search terms)
- QSAR and Toxcast models could supplement the assessment
- Reporting template

Substance name	CAS number	Classification	Identified as ED in				Food/food-stuff	ED alert found in			
			BPR/ PPPR	REACH Substance Evaluation	CORAP	EU priority list		USEPA EDSP 21	US EPA ToxCast	REACH registration dossier	Inter-nation programmes

ED ASSESSMENT BIOCIDAL PRODUCT

If a concern has been identified …

conclusion on whether or not that co-formulant is considered to have ED properties supported by: dedicated testing, read across, justification etc., as appropriate.

Summary that addresses each co-formulant

informs if and on what basis the co-formulants are considered to have or have not ED properties

Co-formulants with identified ED properties

are Substances of Concern

Instructions/guidance

is not legally binding

CONCLUSIONS

- Information gathering and documentation (Excel spreadsheet) key for the evaluation
- If MoA analysis is necessary check all possible hypotheses
- If other „lead-toxicity“ is observed a comparative MoA assessment is required
- Report all uncertainties
- Co-formulants are assessed for „indications“ of ED properties
- Use the listed information sources
- Carefully check detailed evaluations by (inter)national authorities/bodies
- If new data are generated/required always consult with the Competent Authority

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