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Introduction to the ED assessment strategy

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European Food Safety Authority

Contents

Background for guidance

- ED criteria laid down in Commission Delegated Regulation **(EU) No 2017/2100** for **Biocidal Products** (BPs) and Commission Regulation (EU) No **2018/605** for **Plant Protection Products (PPPs)**

- EFSA and ECHA were mandated to provide technical guidance on the implementation of the ED criteria applicable in the context of the BP and PPP Regulations

Scope of the Guidance

- Provide technical guidance for the implementation of the ED criteria to applicants, risk assessors

- Covers endocrine modes of action caused by estrogen, androgen, thyroid and steroidogenic (**EATS**) modalities

  ⇨ However, available information on potential non-EATS endocrine disrupting modes of action also needs to be followed-up

- Focuses on ED effects in vertebrates; i.e. mammals, fish, amphibians

Assessment strategy: general

- The guidance document, in order to establish whether the ED criteria are fulfilled, describes how:
  - ✓ To gather, evaluate and consider all relevant information for the assessment
  - ✓ To apply a weight of evidence (WoE) approach
  - ✓ To conduct a mode of action (MoA) analysis

- 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.

Assessment strategy: OECD GD 150

The assessment strategy is based on the OECD GD 150 which lists the OECD TGs and help to the interpretation of the results

The parameters relevant for ED identification are grouped in four groups:
(Grouping based on OECD GD 150 & JRC screening methodology to identify potential EDs)

1 ***In vitro mechanistic*** (OECD CF level 2)

2 ***In vivo mechanistic*** (OECD CF level 3)

Provide information on endocrine activity

3 ***EATS-mediated*** (OECD CF levels 4 & 5)

4 ***Sensitive to, but not diagnostic of, EATS*** (OECD CF levels 4 & 5)

Provide information on potentially adverse effects

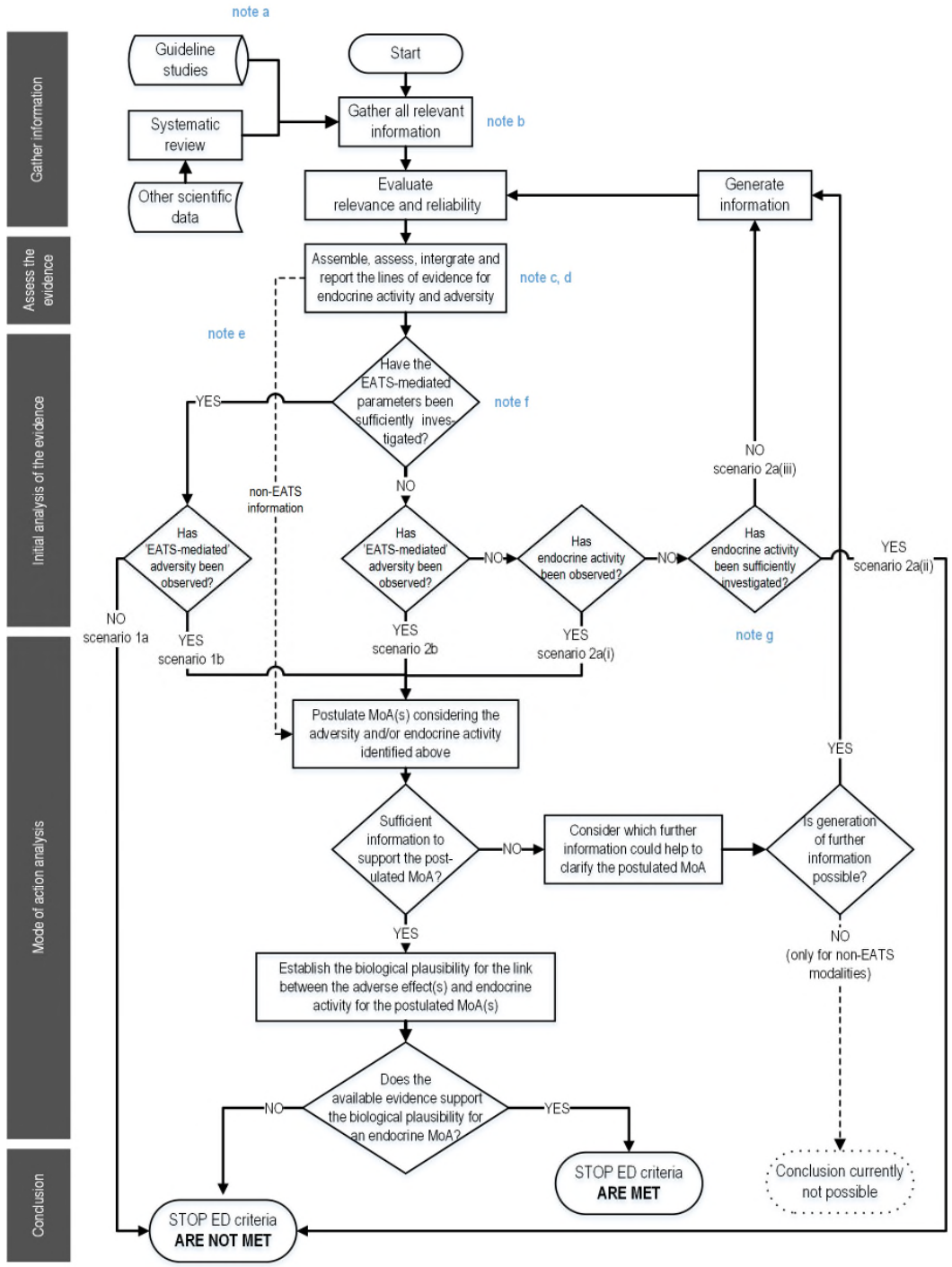
1. Gather

2. Assess

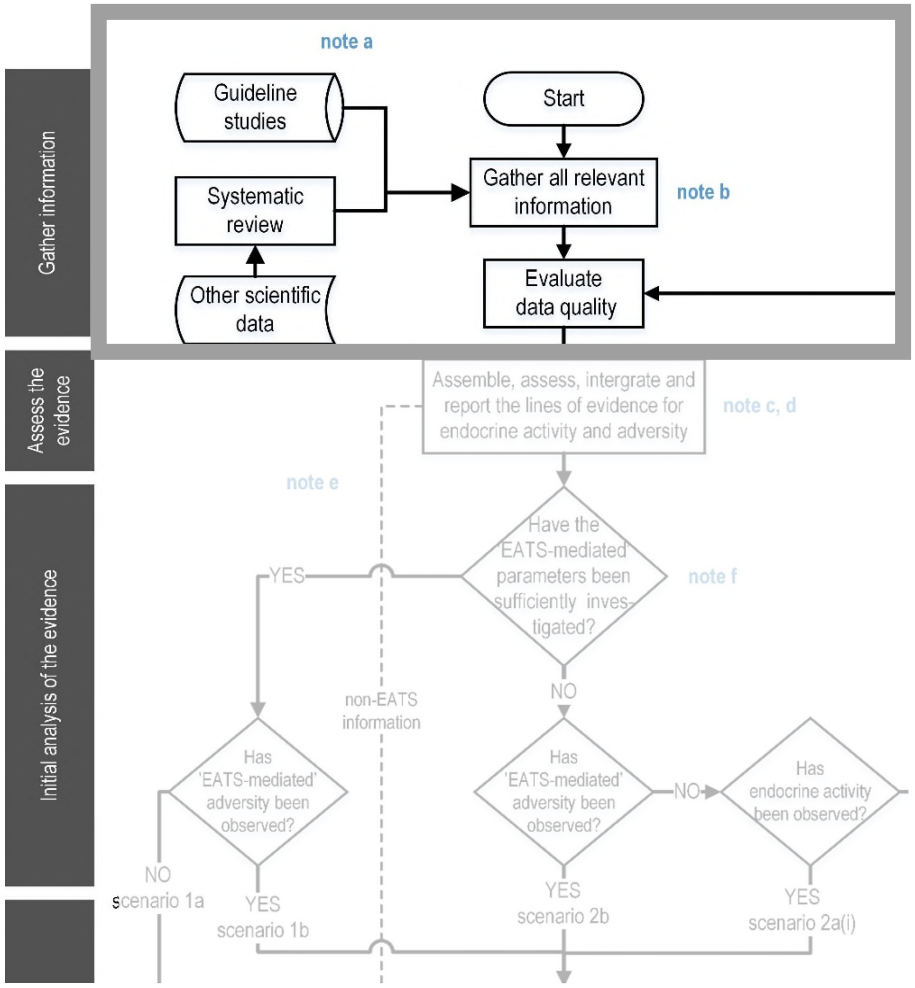
3. Initial analysis

4. MoA analysis

5. Conclusion



Gather and evaluate all relevant information



All relevant information must be considered:

- guideline studies
- other scientific data selected through systematic review (App F)

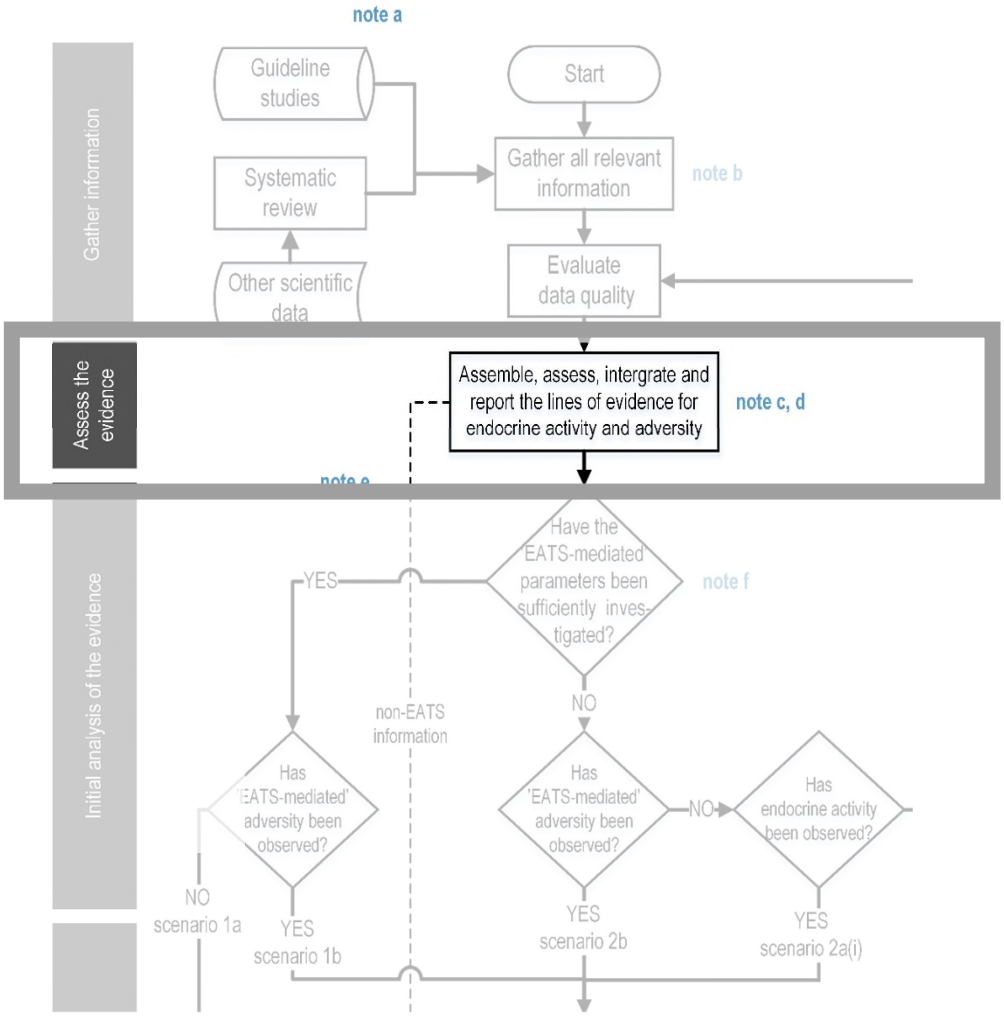
❖ To support the gathering of information→ App E

❖ Evaluation of data quality e.g. relevance and reliability

❖ From reliable studies assign all parameters relevant for ED assessment to the groups:

- *In vivo* mechanistic
- *In vitro* mechanistic
- EATS-mediated
- Sensitive to, but not diagnostic of, EATS

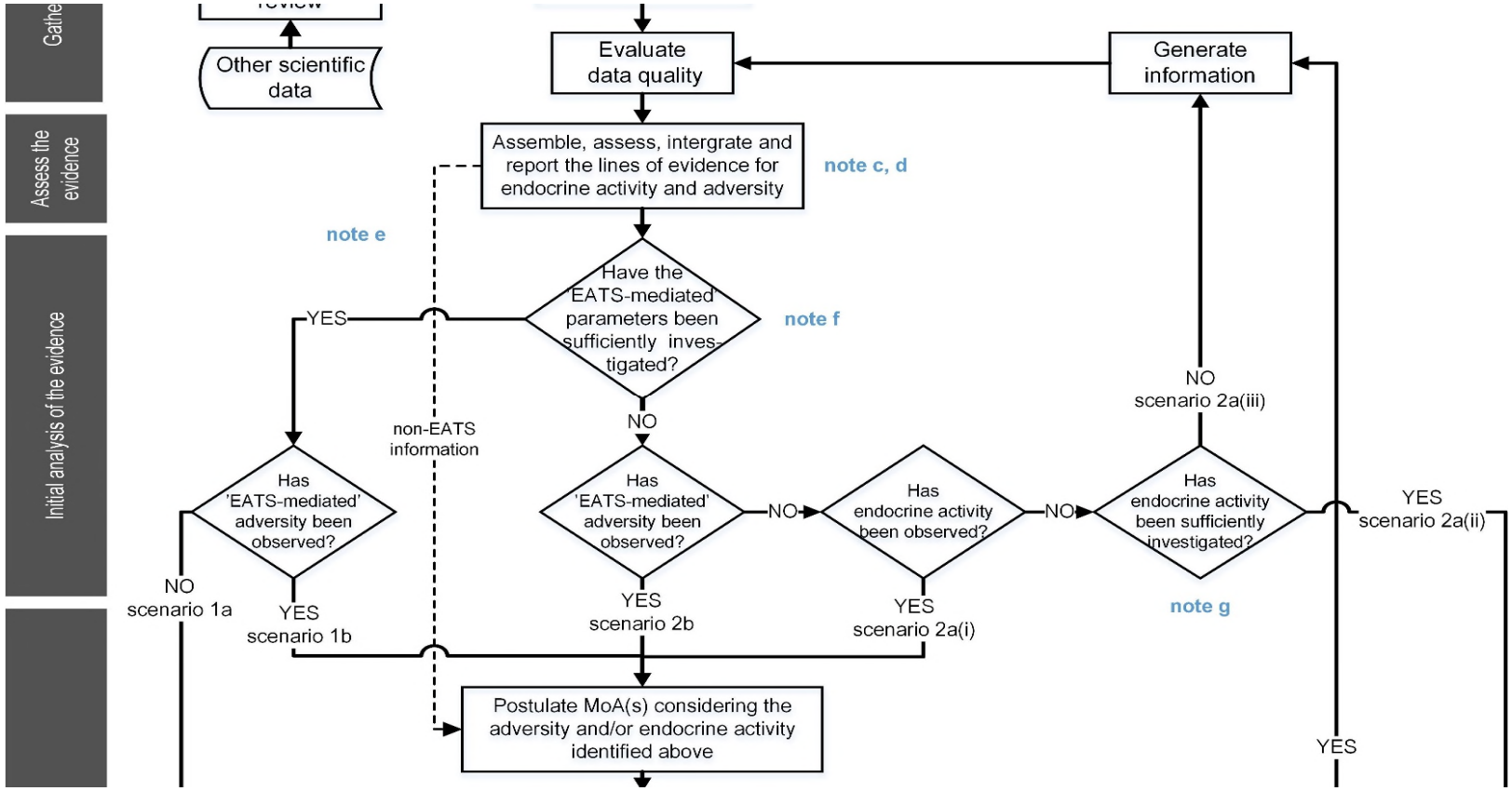
Assemble, assess and integrate the lines of evidence



Assemble all available data and integrate it into lines of evidence based on the grouping:

- **Lines of evidence for adversity** from:
  - 'EATS mediated' parameters
  - 'sensitive to, but not diagnostic of, EATS' parameters
- **Lines of evidence for endocrine activity** from:
  - '*in vitro* mechanistic' parameters
  - '*in vivo* mechanistic' parameters
  - 'EATS mediated'-parameters

Initial analysis of the evidence



Are 'EATS-mediated' parameters sufficient investigated?

For humans & mammals

'EAS-mediated' parameters

- foreseen to be investigated in a two generation reproductive toxicity study (**OECD TG 416**) measured

or

- foreseen to be investigated in an extended one generation reproductive toxicity study (**OECD FTG 443;** EOGRTS) measured

'T-mediated' parameters

- foreseen to be investigated in the required standard studies for repeated dose toxicity, reproductive toxicity and carcinogenicity.

For non-target organisms

'EAS-mediated' parameters

- foreseen to be measured in the Medaka extended one-generation test (MEOGRT, OECD TG 240)

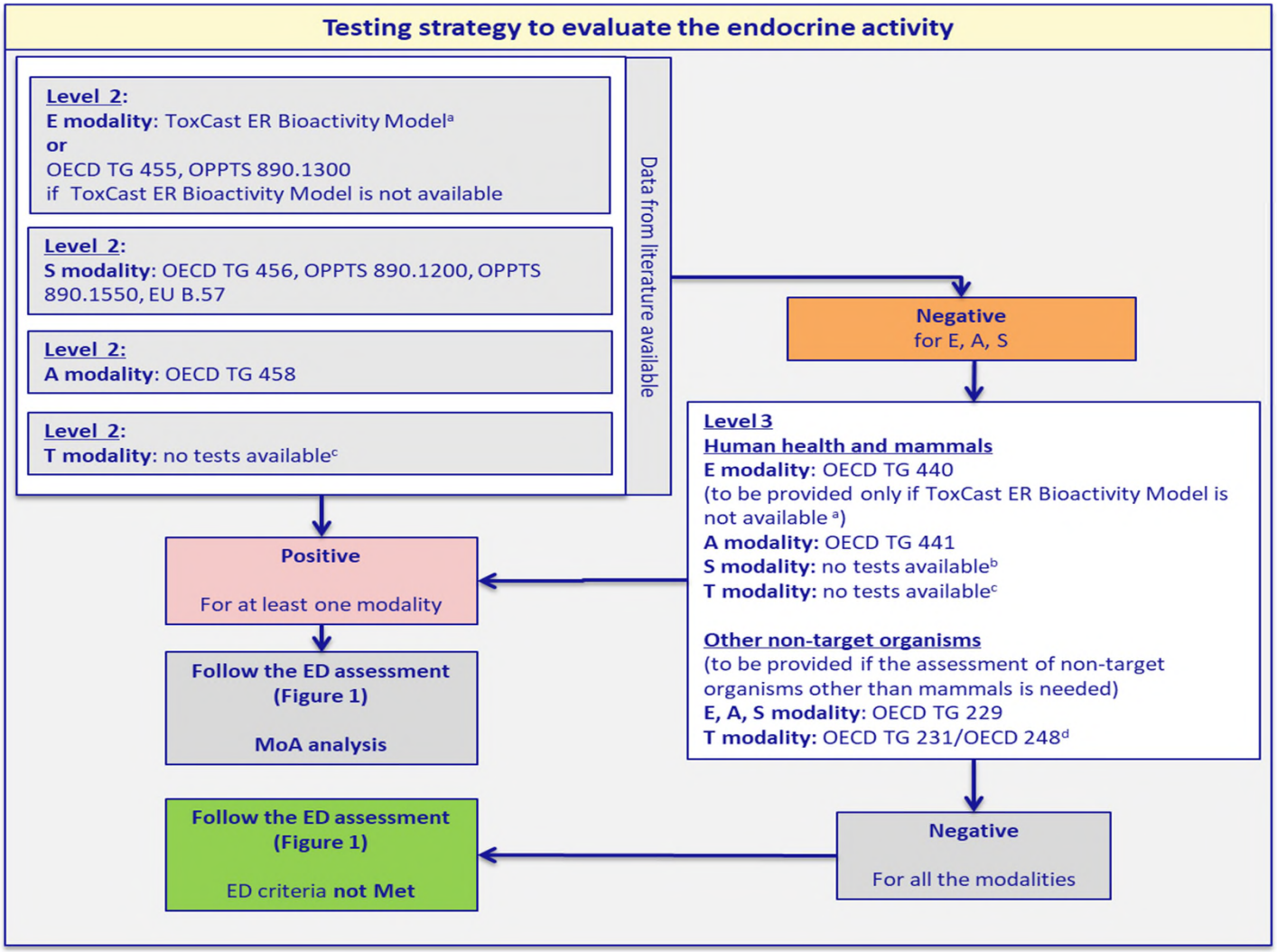
or

- a FLCTT covering all the 'EAS-mediated' parameters foreseen to be measured in the MEOGRT

'T-mediated' parameters

- foreseen to be investigated in the Larval amphibian growth and development assay (LAGDA; OECD TG 241)

Testing strategy for the ED activity



Is 'endocrine activity' sufficiently investigate

For humans & mammals

- **E-modality** – Output data from the ToxCast ER Bioactivity Model or 'Uterotrophic bioassay in rodents' (OECD test guideline 440).
- **A-modality** – 'Hershberger bioassay in rats' (OECD test guideline 441).
- **T-modality** – Thyroid parameters foreseen to be investigated in the required standard studies for repeated dose toxicity, reproductive toxicity and carcinogenicity (same as for T-mediated parameters).
- **S-modality** – 'H295R steroidogenesis assay' (OECD TG 456) **and** the 'aromatase assay (human recombinant)' (OPPTS 890.1200) carried out.

For non-target organisms

- E, A, S modalities - preferably the 'Fish short term reproduction assay' (FSTRA; OECD TG 229) should have been conducted

The 21-day fish assay OECD TG 230 is acceptable as well.

If data are already available covering the mechanistic parameters investigated in OECD TG 229 or OECD TG 230 (e.g. OECD TG 234), then those data could be used instead.

- T-modality - an 'Amphibian metamorphosis assay' (AMA; OECD TG 231) should have been conducted.

Initial analysis of the evidence

Outcomes

1)Conclude 'ED criteria not met' IF:

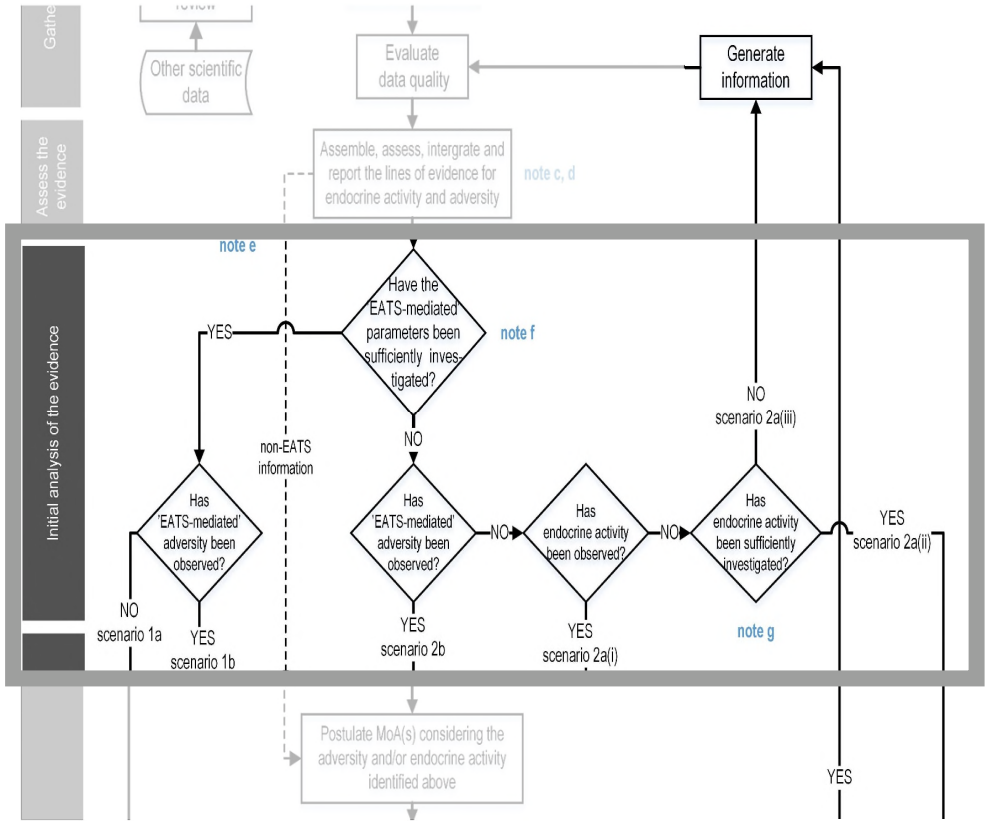
- 'EATS mediated' parameters **sufficiently investigated** and no EATS mediated adversity observed **OR**
- Endocrine activity sufficiently investigated and no endocrine activity observed (and also no EATS mediated adversity)

2)Move to MoA analysis if:

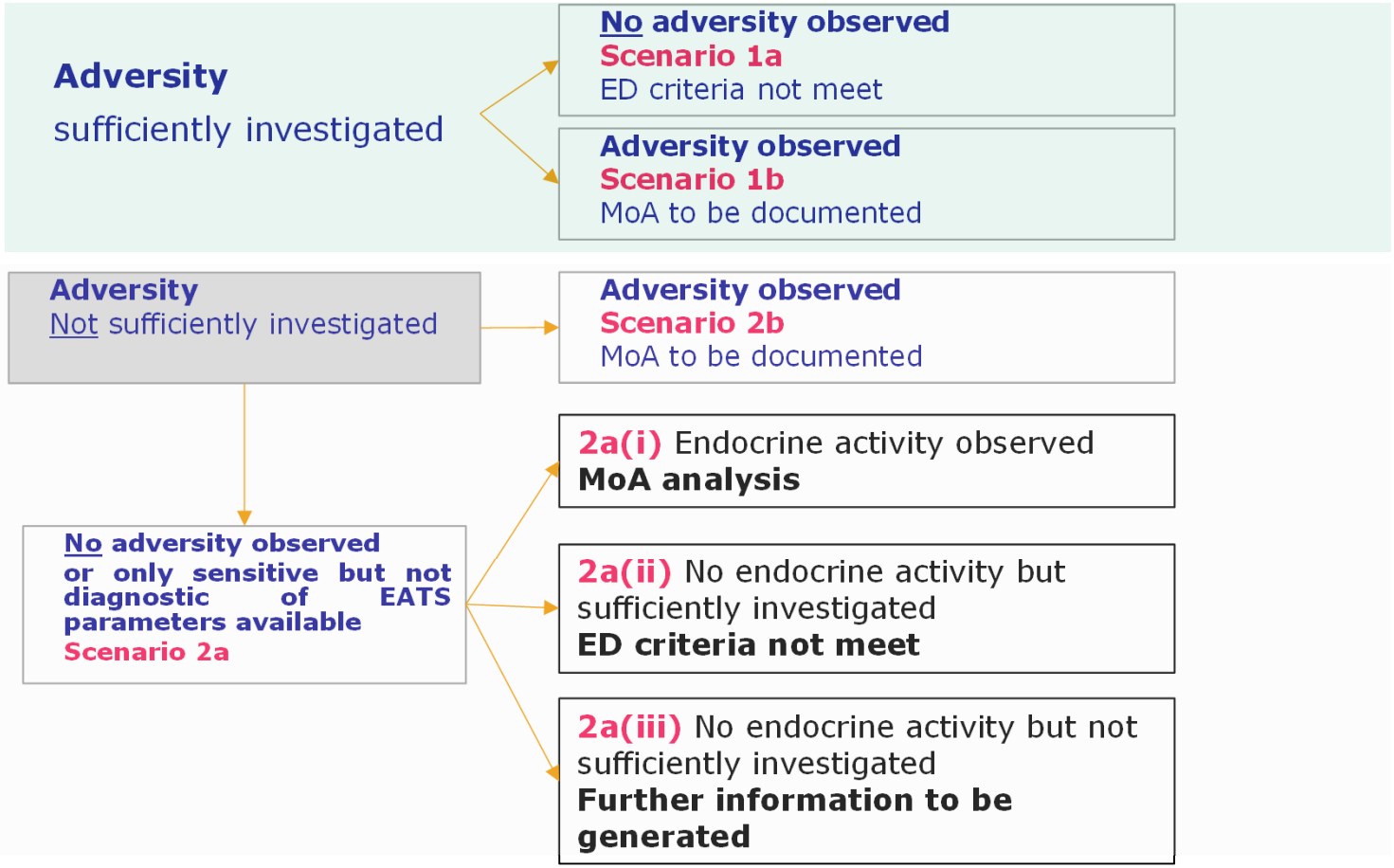
- EATS mediated adversity observed **OR**
- Endocrine activity observed

3)Generate information if:

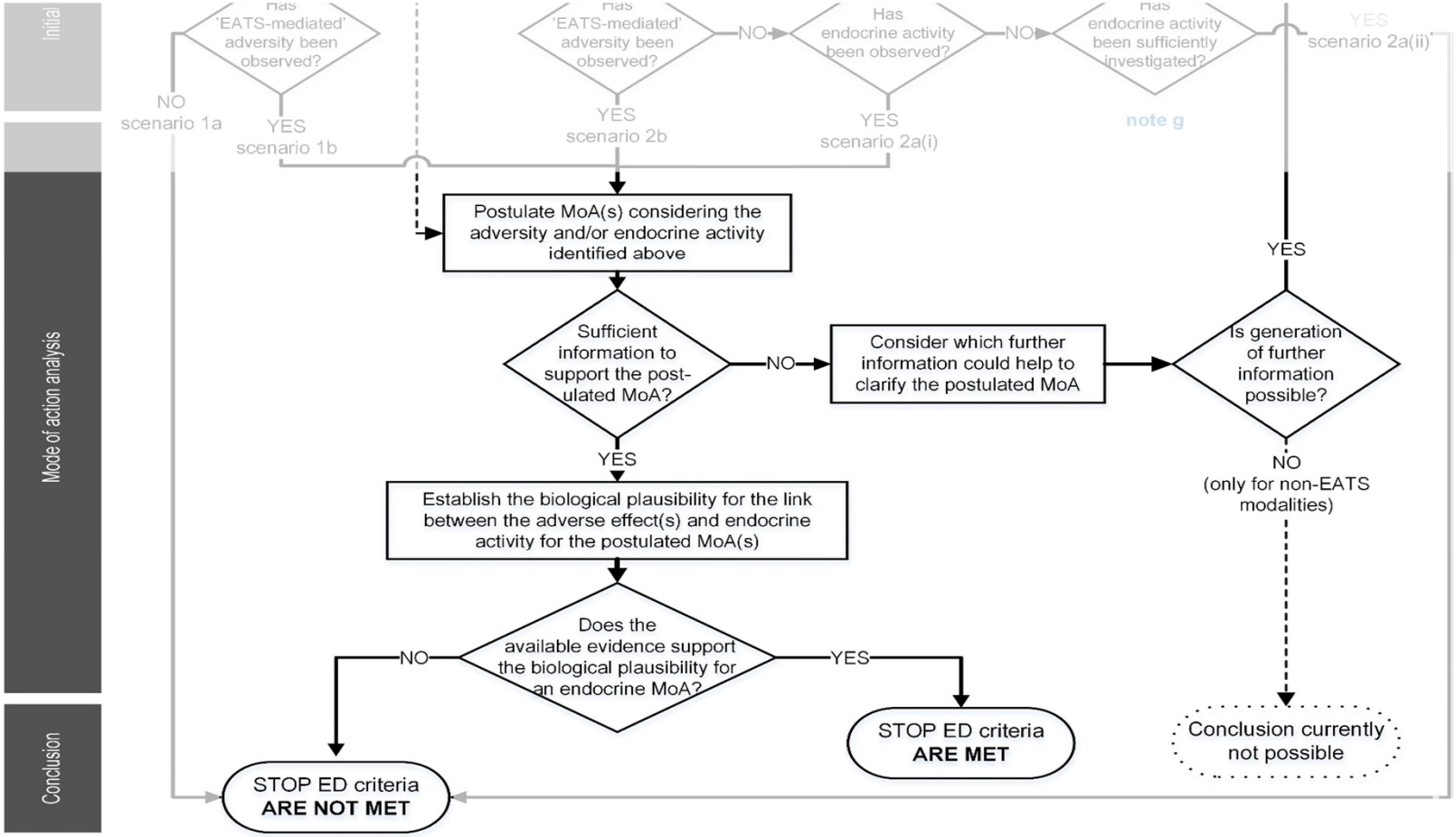
- No EATS mediated adversity and no endocrine activity observed but endocrine activity not sufficiently investigated



SCENARIOS


Adversity
sufficiently investigated
No adversity observed
Scenario 1a
ED criteria not meet
Adversity observed
Scenario 1b
MoA to be documented
Adversity
Not sufficiently investigated
Adversity observed
Scenario 2b
MoA to be documented
No adversity observed or only sensitive but not diagnostic of EATS parameters available
Scenario 2a
2a(i) Endocrine activity observed
MoA analysis
2a(ii) No endocrine activity but sufficiently investigated
ED criteria not meet
2a(iii) No endocrine activity but not sufficiently investigated
Further information to be generated

Mode of action analysis/Conclusion



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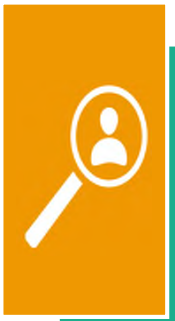

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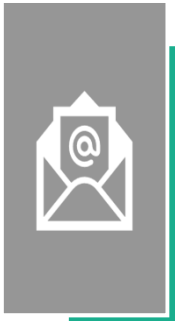

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