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How to consider the XETA in the assessment strategy of the ECHA/EFSA ED Guidance

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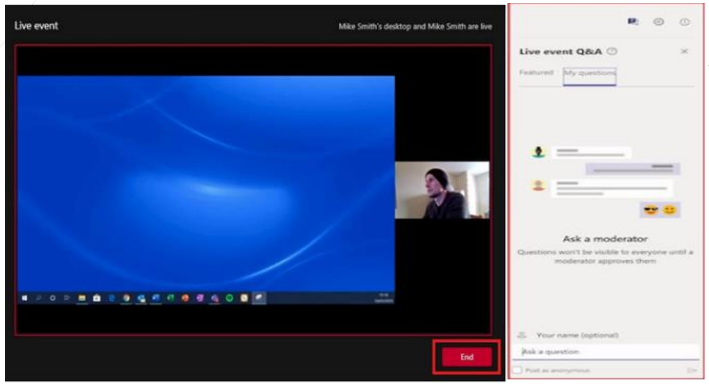

Q&A box: For any questions related to the topic or unexpected IT issues

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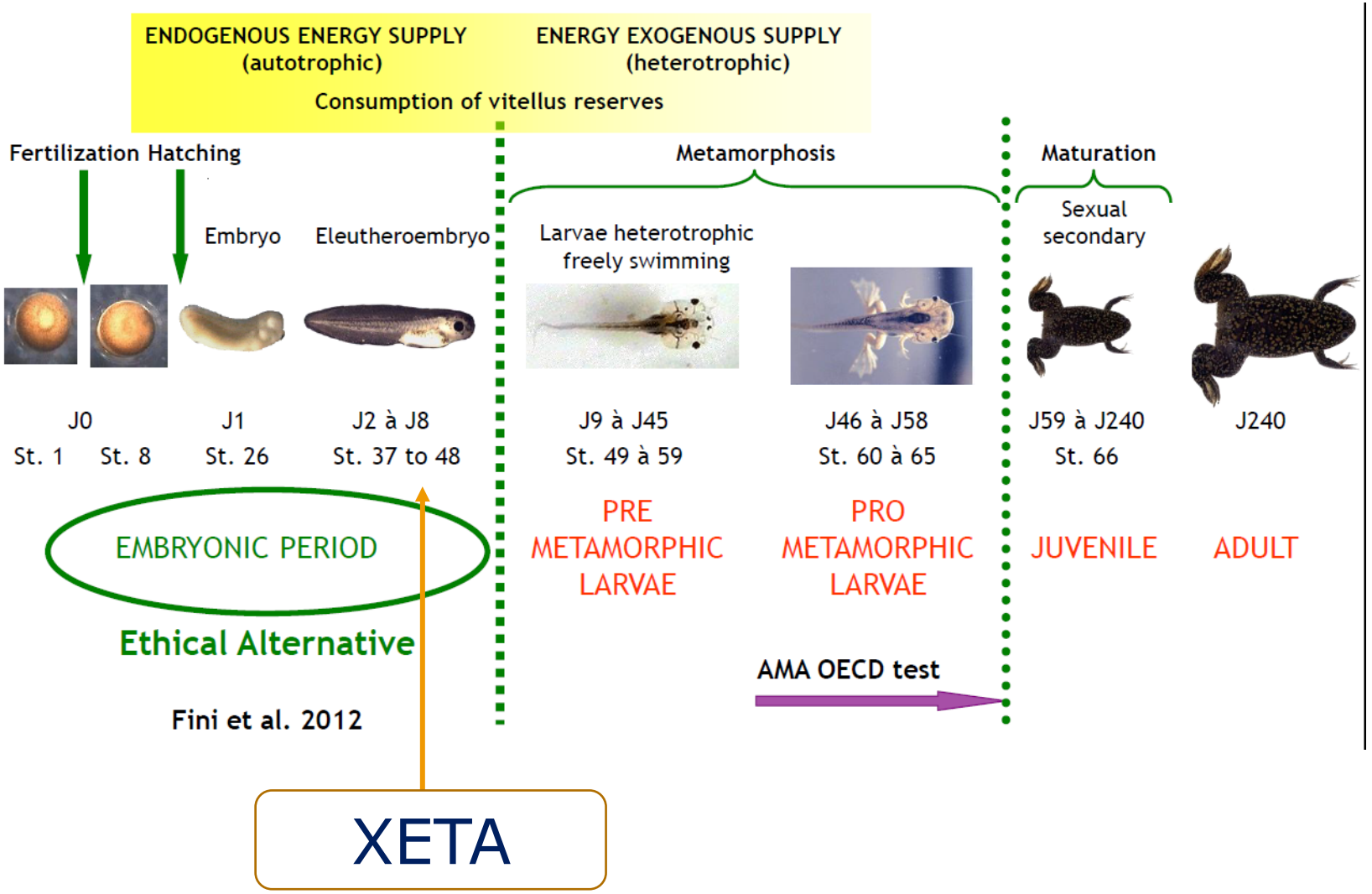
Agenda

- Background
- General description and limitations of the XETA
- How to consider the XETA in the assessment strategy of the ECHA/EFSA Guidance: Case 1
- How to consider the XETA in the assessment strategy of the ECHA/EFSA Guidance: Case 2
- Q&A and Conclusion

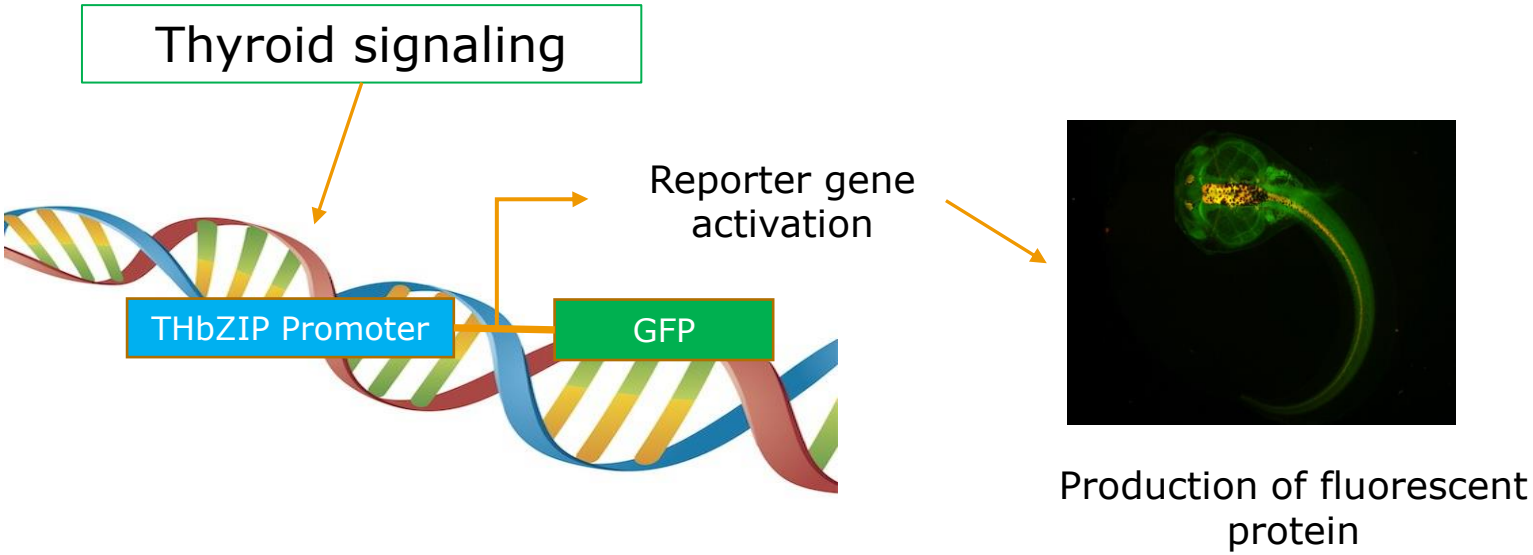
Background

- OECD TG published in 2019
- Annex to the Guidance drafted mid-2020
- Targeted consultation with EFSA MSs and ECHA EDEG and BPC Environment Working Group in Oct-Nov 2020
- Webinar with stakeholders today
- Finalisation of the Annex and publication

Xenopus Eleutheroembryonic Thyroid Assay



Xenopus Eleutheroembryonic Thyroid Assay

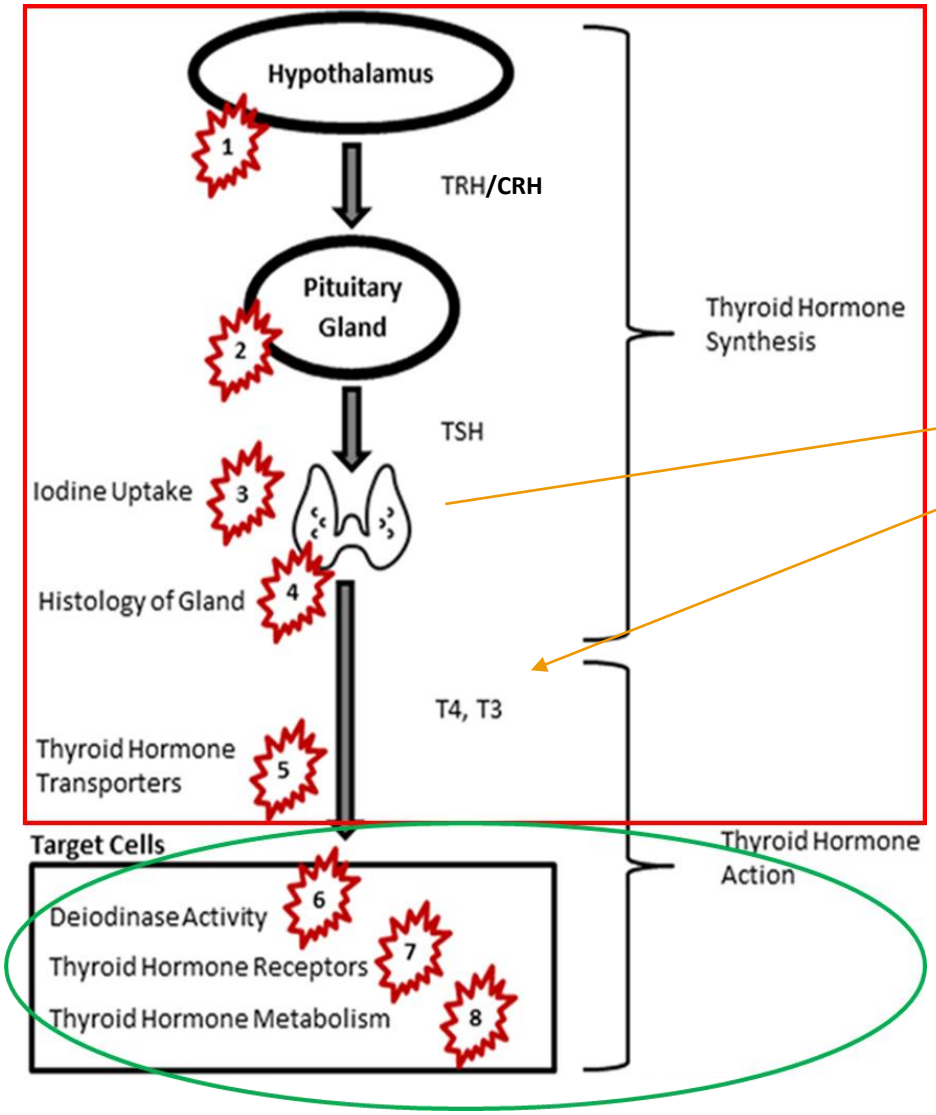


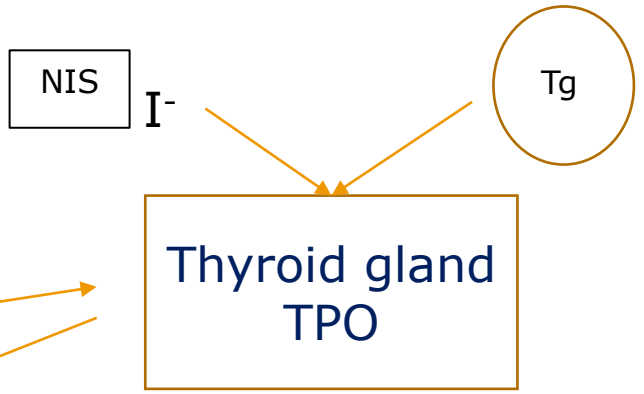
The TH/bZIP gene codes for a transcription factor associated with amphibian metamorphosis, a process controlled by THs

Xenopus Eleutheroembryonic Thyroid Assay

Thyroidal MoA covered by XETA		
T-MoA	**Substances tested for validation**	
Modulators of TH clearance including UDP-glucuronosyltransferase modulators	Phenobarbital	✓
Modulators of TH metabolism, including deiodinase inhibitors	Iopanoic acid	✓
Thyroid receptor agonist	T4, TRIAC	✓
Thyroid receptor antagonist	NH3	✓
Interference with THs synthesis	-	✗
Interference with TH transport via interaction with TH plasma binding proteins or Inhibition of TH transmembrane transporters	-	✗

MoA covered by XETA

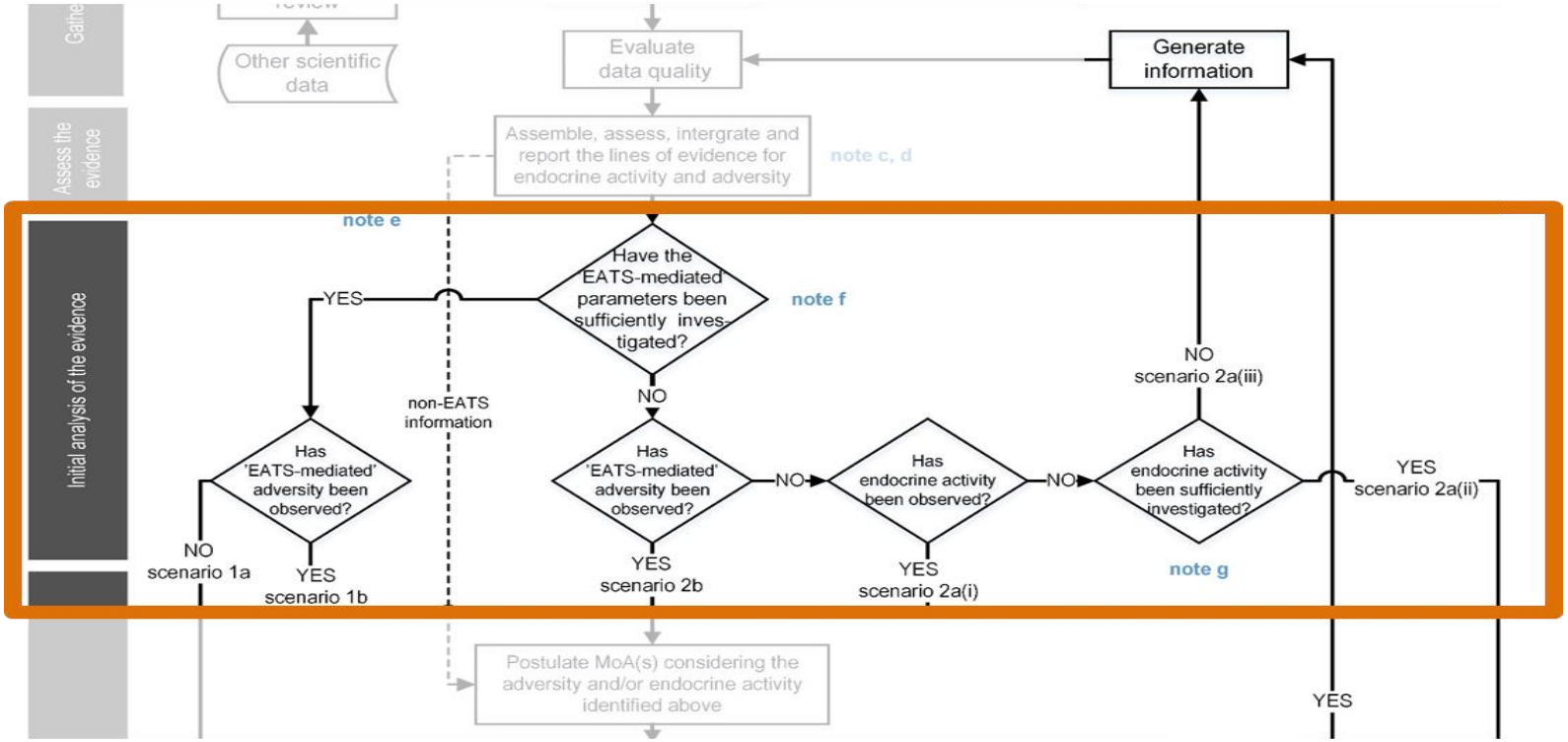




Ghassabian and Trasande, 2018

XETA in the assessment strategy

The ECHA/EFSA Guidance (2018) recommends to first conclude on the ED properties with regard to humans and in parallel, using the same data package, on mammals as non-target organisms. Only if the criteria are not met for mammals as non-target organisms, the assessment should proceed considering other taxonomic groups and in particular fish and amphibians.



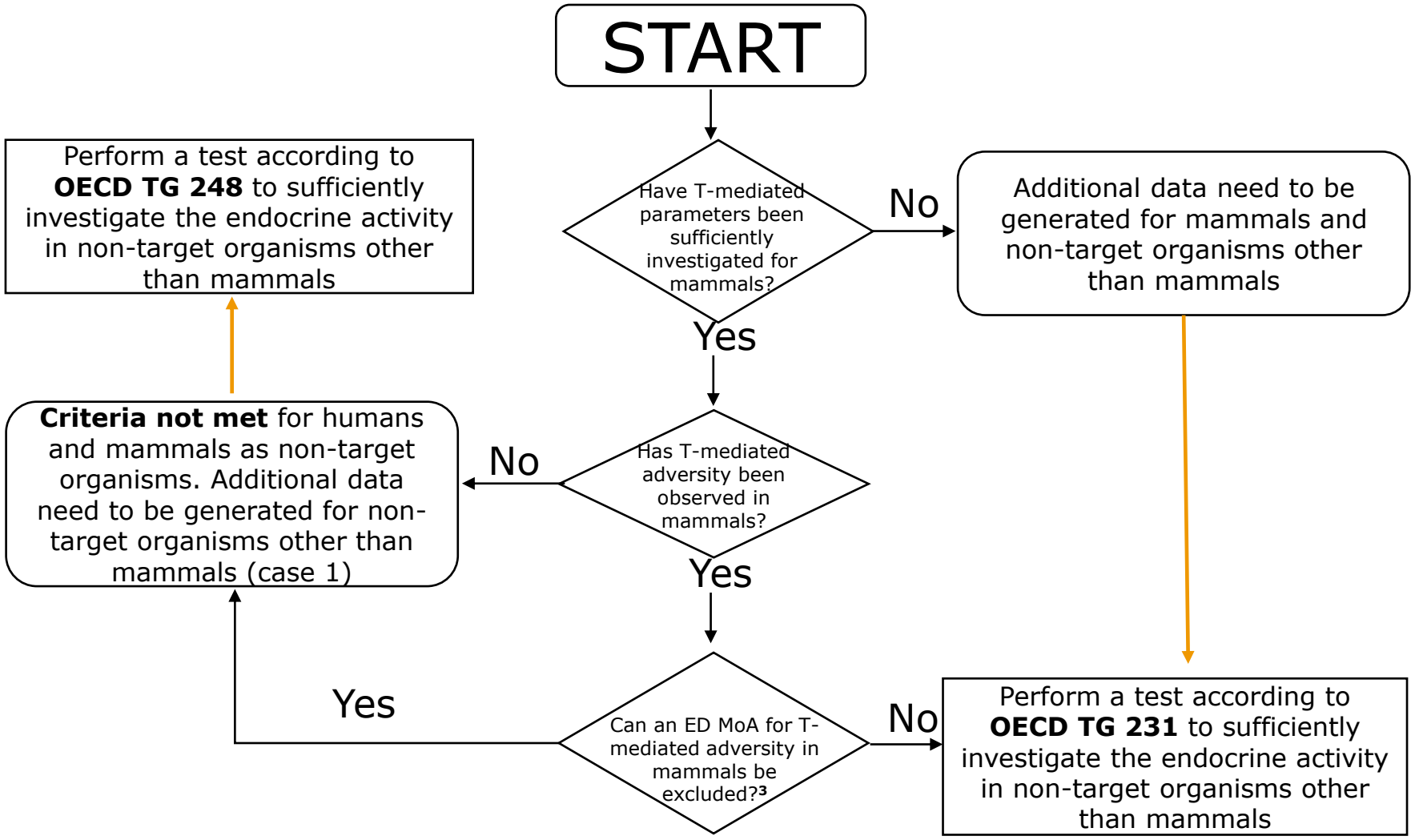
XETA in the assessment strategy

XETA is considered suitable for:

Case 1: ED criteria not met for humans and wild mammals

Case 2: ED criteria met for humans but not for mammals as NTOs

Case 1


START
Have T-mediated parameters been sufficiently investigated for mammals?
No
Additional data need to be generated for mammals and non-target organisms other than mammals
Yes
Has T-mediated adversity been observed in mammals?
No
Criteria not met for humans and mammals as non-target organisms. Additional data need to be generated for non-target organisms other than mammals (case 1)
Perform a test according to OECD TG 248 to sufficiently investigate the endocrine activity in non-target organisms other than mammals
Yes
Can an ED MoA for T-mediated adversity in mammals be excluded?[3]
Yes
No
Perform a test according to OECD TG 231 to sufficiently investigate the endocrine activity in non-target organisms other than mammals

Case 1

A XETA is considered a suitable test when:

- ✓ No adversity was observed in mammals based on a complete dataset
- ✓ Although some effects in T-mediated parameters were observed, a T-mediated MoA was excluded

It is important when deciding on a XETA *vs* an AMA that all the available information, including Level 1, are considered.

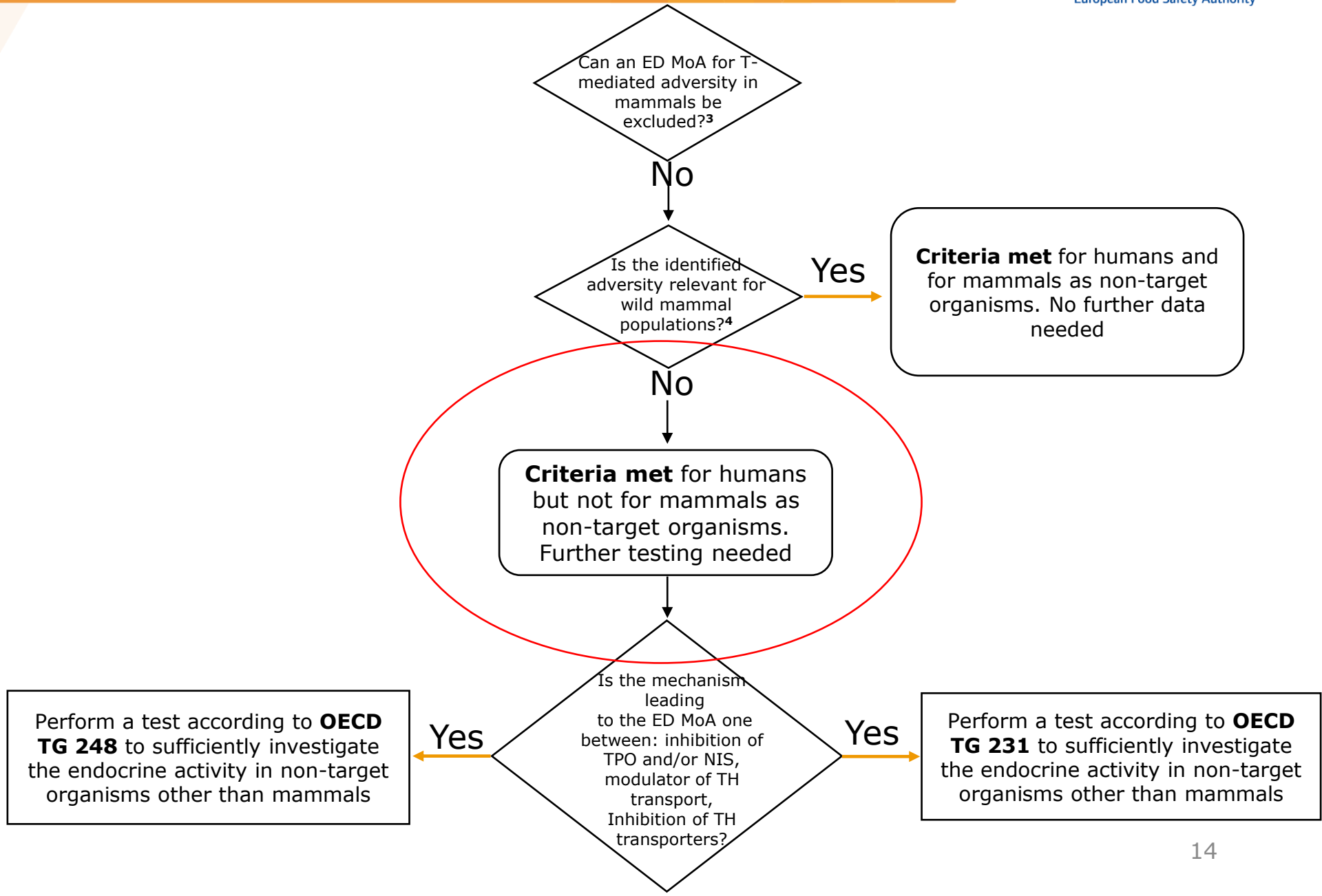
XETA in the assessment strategy

XETA is considered suitable for:

Case 1: ED criteria not met for humans and wild mammals

Case 2: ED criteria met for humans but not for mammals as NTOs

Case 2


Can an ED MoA for T-mediated adversity in mammals be excluded?[3]
No
Is the identified adversity relevant for wild mammal populations?[4]
Yes
Criteria met for humans and for mammals as non-target organisms. No further data needed
No
Criteria met for humans but not for mammals as non-target organisms. Further testing needed
Is the mechanism leading to the ED MoA one between: inhibition of TPO and/or NIS, modulator of TH transport, Inhibition of TH transporters?
Yes
Perform a test according to OECD TG 248 to sufficiently investigate the endocrine activity in non-target organisms other than mammals
Yes
Perform a test according to OECD TG 231 to sufficiently investigate the endocrine activity in non-target organisms other than mammals

Case 2

T-mediated adversity identified in mammals:

- It is considered to be caused by a T-mediated MoA

AND

- It is not relevant for wild mammal populations

Further data are needed on NTOs other than mammals

Case 2

A XETA might be suitable when the identified MoA is not:

- TPO inhibition
- NIS inhibition
- Modulators of TH transport via interaction with TH plasma binding proteins
- Inhibition of TH transmembrane transporters

Note: if the XETA is positive a MoA analysis should be performed and further data needed on adversity. Therefore, performance of a level 4 study, instead of a level 3, would address both endocrine activity and adversity.

Conclusion

1. In both cases 1 and 2, if the XETA is negative, the endocrine activity for the T-modality for non-target organisms other than mammals is considered sufficiently investigated and the ED criteria are not met.

2. A negative XETA alone may not be sufficient to conclude on the ED properties of a substance. The conclusion has always to be reached based on WoE

3. If the XETA is positive , according to Figure 1 of the ECHA/EFSA Guidance (ECHA/EFSA, 2018), a Mode of Action Analysis should be performed and further testing might be needed, i.e. a test according to OECD TG 241.

1. Do you agree with the proposal?

2. Any question?

Acknowledgement:

- Francesco Amoretti
- Anna Campanini
- Carla Dall'Aglio
- Alberto Goldoni

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