Endocrine Disrupters

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- Legislative context (Biocides and REACH)
- Define the criteria
- Criteria development
- Guidance
- Endocrine Disrupters Expert Group

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The criteria for biocidal products are published and entered into force on 7 December 2017. They apply from 7 June 2018 to all new and on-going applications for biocides

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ED Substances and products considered under the following headings under the BPR

Article 5(d) Exclusion Criteria

This includes:
carcinogens, mutagens and reprotoxic substances categories 1A or 1B according to the CLP Regulation
endocrine disruptors
persistent, bioaccumulative and toxic (PBT) substances
very persistent and very bioaccumulative (vPvB) substances

Article 19
Conditions for granting an biocidal product authorisation
Section 4 (d) it has endocrine-disrupting properties

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BPR allows use of an active substance that is an ED *via:*

→Negligible risk of exposure

→Essentiality

→the socio-economic route

Derogation to BPR article 5 (exclusion criteria)

or a product:

→if it is scientifically demonstrated that under relevant field conditions there is no unacceptable effect.

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REACH

Article 57 abc (CMR)
Article 57 de (PBT and vPvB)
Article 57 f (ED)
ELOC

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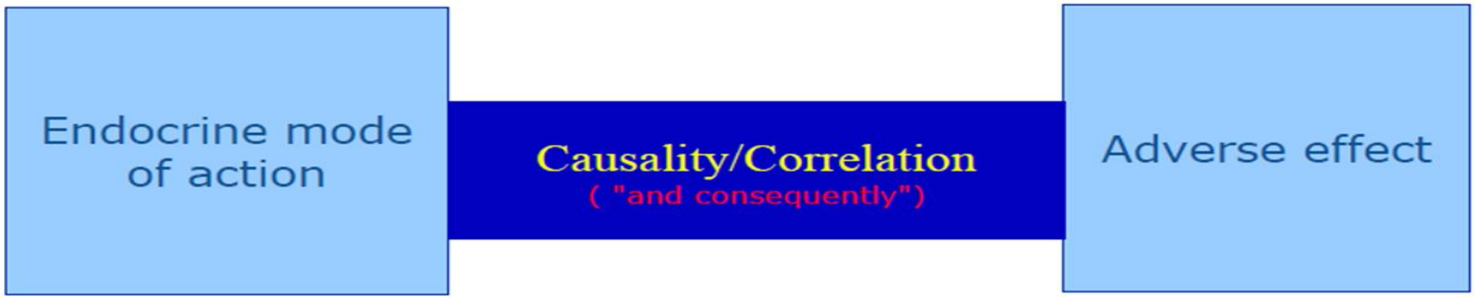
What is an endocrine disrupter?

Criteria put forward:

- → **Contain the 3 elements of the 2002 WHO/IPCS definition of an endocrine disruptor:**



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Definition is a combination of;

WHO/IPCS definition ED

An endocrine disruptor is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations

and

WHO/IPCS definition adversity:
Change in the morphology, physiology, growth, development, reproduction, or, life span of an organism, system, or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences

Section A — Endocrine-disrupting properties with respect to humans

A substance shall be considered as having endocrine-disrupting properties that may cause adverse effect in humans if it is a substance that meets all of the following criteria, unless there is evidence demonstrating that the adverse effects identified are not relevant to humans:

(a) it shows an adverse effect in an intact organism or its progeny, which is a change in the morphology, physiology, growth, development, reproduction or life span of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress or an increase in susceptibility to other influences;

(b) it has an endocrine mode of action, i.e. it alters the function(s) of the endocrine system;

(c) the adverse effect is a consequence of the endocrine mode of action

Section B — Endocrine-disrupting properties with respect to non-target organisms

A substance shall be considered as having endocrine-disrupting properties that may cause adverse effects on non-target organisms if, if it meets all of following criteria, unless there is evidence demonstrating that the adverse effects identified are not relevant at the (sub)population level for non-target organisms:

(a) it shows an adverse effect in non-target organisms, which is a change in the morphology, physiology, growth, development, reproduction or life span of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress or an increase in susceptibility to other influences;

(b) it has an endocrine mode of action, i.e. it alters the function(s) of the endocrine system;

(c) the adverse effect is a consequence of the endocrine mode of action

Impact of criteria on biocides and pesticides

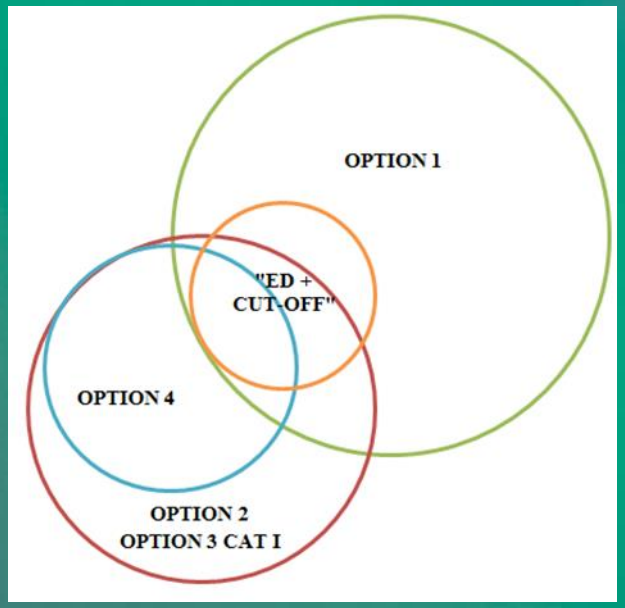
Impact assessment

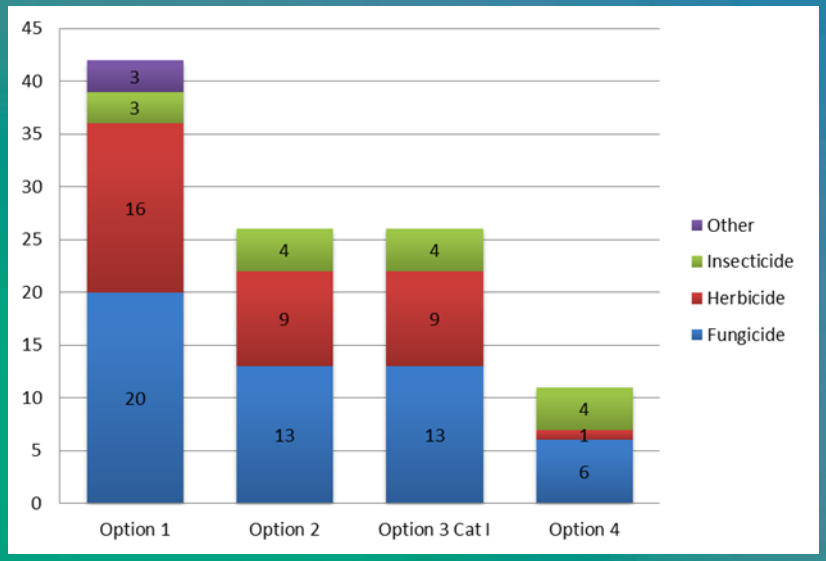
Draft EU criteria to identify ED

- **Option 1 (baseline); No policy change; Interim criteria in the BPR and the PPPR apply**
- **Option 2: WHO/IPCS definition to identify ED**
- **Option 3: WHO/IPCS definition to identify ED + additional categories based on the different strength of evidence**
- **Option 4: WHO/IPCS definition to identify ED + inclusion of potency**

This exercise gives good information on the likely regulatory effects of the ED criteria.

Impact on biocides and pesticides





PPP Option 1 (42) Option 2 and Option 3 Cat I (26) Option 4 (11) [324subs]

BP: Option 1 (16) Option 2 and Option 3 Cat I (5) Option 4 (2) [98]

Impact Assessment
Option 1

	PPP	BP
False positives (identified under Option 1 but not under Options 2 to 4)	37	13
False negatives (identified under Options 2 to 4 but not under Option 1)	21	2

New Criteria much better than the interim criteria (C2 and/or R2 according to Regulation (EC) No 1272/200841) for picking up Eds

ECHA Guidance

Objective of the guidance

Provide technical guidance for the implementation of the ED criteria in the context of the Biocidal Products and the Plant Protection Products Regulations

The guidance is for:

Applicants
Assessors of competent regulatory authorities

Scope of the ECHA/EFSA guidance

- Guidance covers endocrine disrupting modes of action caused by estrogen, androgen, thyroid and steroidogenic (EATS) modalities. Available information on potential non-EATS mediated ED modes of action must also be followed up.

- Guidance focuses on ED effects in vertebrates i.e. mammals (humans), fish and amphibians.

Assessment

- Hazard Criteria

Applicants and Assessors of competent regulatory authorities have been assessing the hazards associated with substances for many years. Carcinogenicity, reprotoxicity and mutagenicity have been assessed and concluded on for many years.

Assessment of the endocrine disrupting properties of substances will not be very different

Assessment tools

→ED criteria for Biocides and Plant Protection Products

→OECD conceptual framework for testing and assessment of ED

- OECD test guidelines/ standardised test methods→ which can be used to evaluate substances for ED
- Provides guidance on the use of the test methods, but is not a testing strategy

→OECD guidance document 150 on standardised test guidelines for evaluation of endocrine disruption

- Helps the interpretation of results for the parameters investigated in the assays available for ED testing

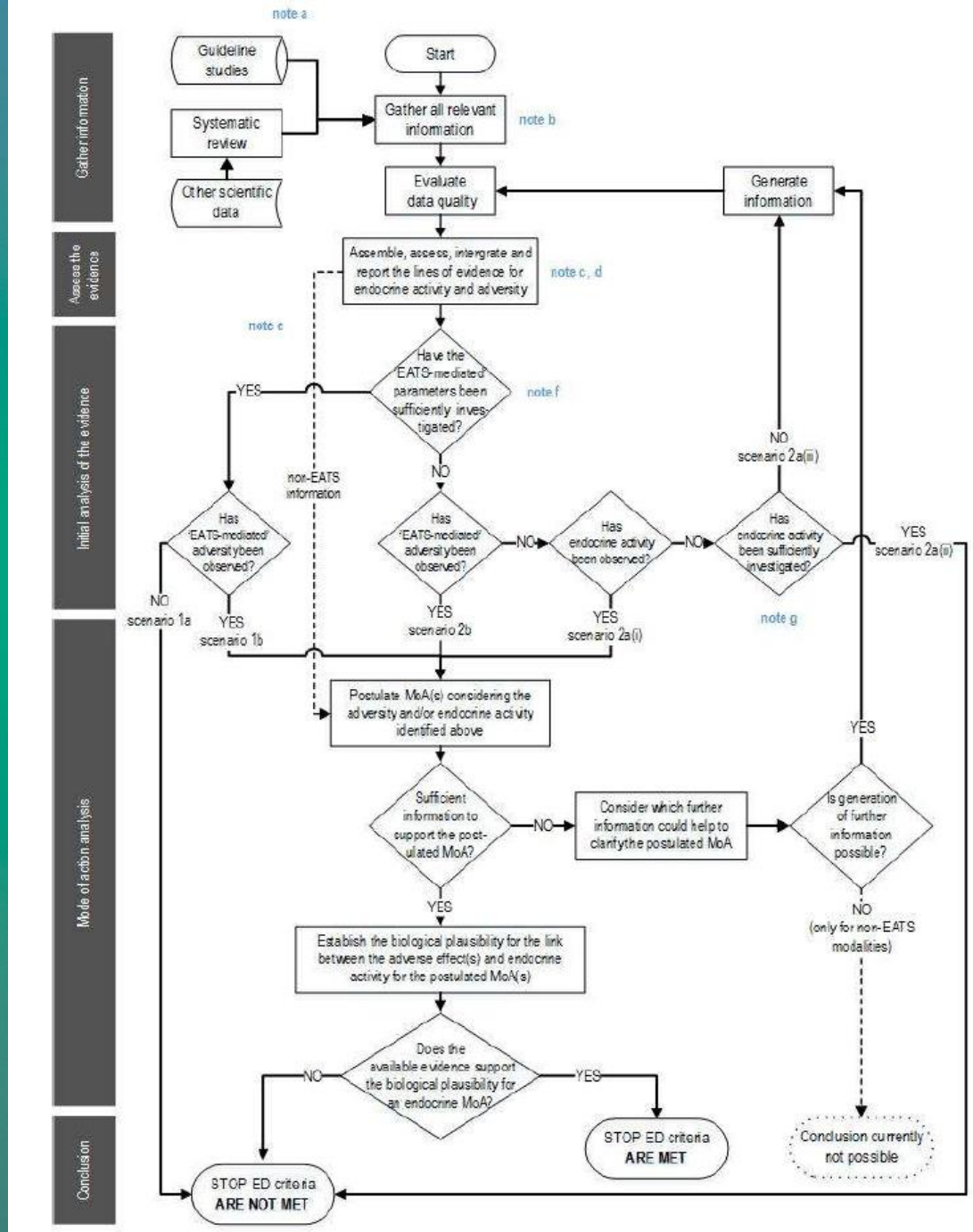
Assessment according to the guidance (5 stages)

I) Gather all relevant information
II) Assemble, assess and integrate the lines of evidence
III) Initial analysis of the evidence
IV) Mode of action analysis
V) Conclusion whether the substance meets the ED criteria

Assessment according to the guidance (5 stages)

Flow chart
Figure 1 of the guidance Document.

I
II
III
IV
V



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I) Gather all relevant information

All relevant information.

Evaluation of data quality → Biocidal Products Regulation
Parameters relevant for ED assessment include;

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

II) Assemble, assess and integrate the lines of evidence

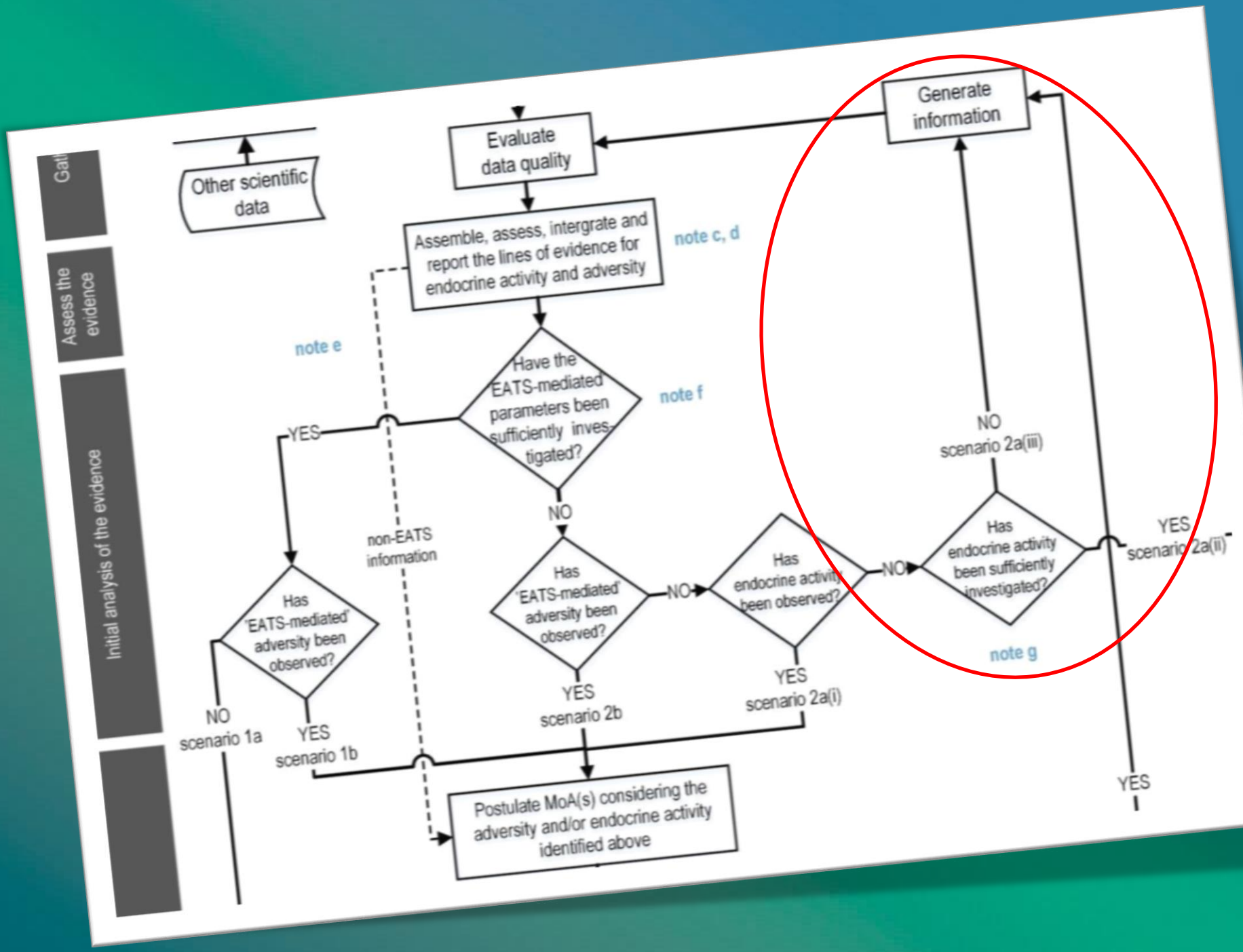
Evidence for adversity
Evidence for endocrine activity

Lines of evidence

Lines of evidence for endocrine activity and adversity

Study (oral exposure)	Reliab.	Adverse Effect(s)	Mechanism?	Relevance?	NOAEL (mg/kg/d)	LOAEL (mg/kg/d)	Result and remarks
Rat 28 and 90 day repeat dose	1-2	↓T4, ↑ TSH ↑ thyroid wt & hypertrophy / hyperplasia;	Thyroid disruption	Yes	7	15	T4 / TSH; LOEL for wt / h'plasia 60
Mouse 90 day	1-2	↑ thyroid wt & hypertrophy / hyperplasia	Thyroid disruption	Yes	18	180	
Dog							ter 6 day
Dog							
Rat							a 2nd rat ce
Rat 2 generation reproduction	1-2	Thyroid toxicity (inc tumours!)	Thyroid disruption	Yes	12	80	No effects on reproduction
Rat developmental neurotox	1-2	No developmental effects	NA	NA	30	>30	
Rat mechanistic with relevant metabolite	1-2	Thyroid peroxidase inhibition		Yes			Used high doses
Monkey 6 month with relevant metabolite	1-2	↑ thyroid wt & hypertrophy / hyperplasia; ↓T4, ↑ TSH; ↑Iodine uptake	Thyroid peroxidase inhibition	Yes	0.5	2.5	

Mouse 90 day	1-2	↑ thyroid wt & hypertrophy / hyperplasia	Thyroid disruption	Yes	18	180


Gat
Assess the evidence
Initial analysis of the evidence
Other scientific data
Evaluate data quality
Generate information
Assemble, assess, intergrate and report the lines of evidence for endocrine activity and adversity
note c, d
note e
Have the EATS-mediated parameters been sufficiently inves-tigated?
note f
YES
non-EATS information
NO
scenario 2a(iii)
Has endocrine activity been sufficiently investigated?
YES
scenario 2a(ii)
note g
Has "EATS-mediated" adversity been observed?
Has "EATS-mediated" adversity been observed?
NO
Has endocrine activity been observed?
NO
NO
scenario 1a
YES
scenario 1b
YES
scenario 2b
YES
scenario 2a(i)
YES
Postulate MoA(s) considering the adversity and/or endocrine activity identified above

Possible outcomes of initial analysis

1. ED criteria not met.

'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

EATS mediated adversity observed
Or
Endocrine activity observed

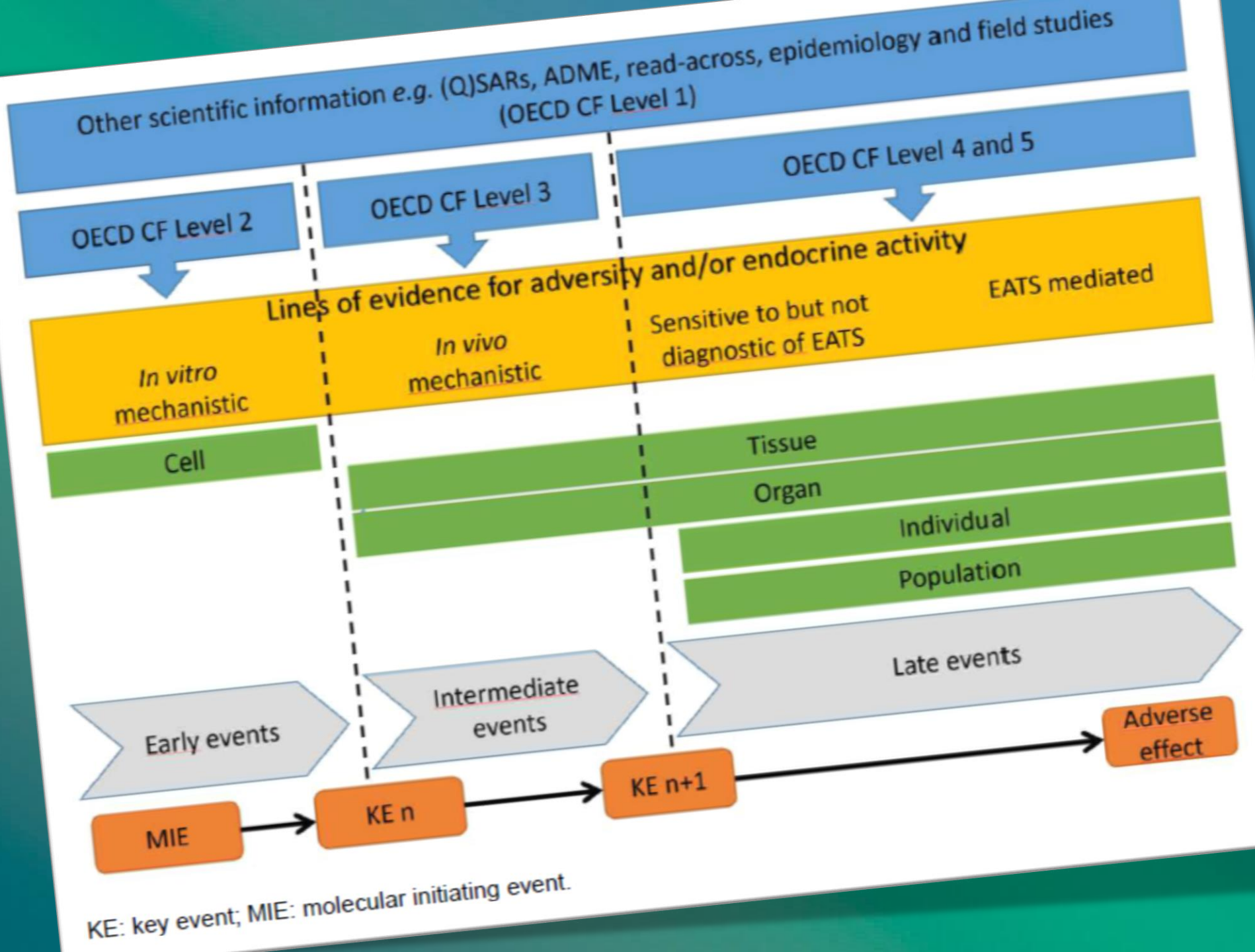
3. Generate information

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

IV) Mode of action analysis

Biologically plausible link→ endocrine activity and adverse effect(s) → relevant for humans?

Biologically plausible link → endocrine activity and adverse effect(s) → relevant for non-target organisms at population level?


Other scientific information e.g. (Q)SARs, ADME, read-across, epidemiology and field studies (OECD CF Level 1)
OECD CF Level 2
OECD CF Level 3
OECD CF Level 4 and 5
Lines of evidence for adversity and/or endocrine activity
In vitro mechanistic
In vivo mechanistic
Sensitive to but not diagnostic of EATS
EATS mediated
Cell
Tissue
Organ
Individual
Population
Early events
Intermediate events
Late events
MIE
KE n
KE n+1
Adverse effect
KE: key event; MIE: molecular initiating event.

Conclusion of the ED assessment

A conclusion must be reached as a definitive outcome is required

Data → EATS mediated parameters to be sufficiently investigated in mammals

- EAS → 2 gen repro [OECD TG 416 (2001)] or EOGRTS [OECD TG 443]
- E-modality → ToxCast ER Bioactivity Model or Uterotrophic bioassay [OECD TG 440 (2007d)].
- A-modality → Hershberger bioassay [OECD TG 441 (2009d)].

  Example: Thyroid effects → investigated → repeated dose toxicity, reproductive toxicity and carcinogenicity.

- S-modality → level 2 in vitro assays → H295R steroidogenesis assay [OECD TG 456 (2011c)] and aromatase assay [OPPTS 890.1200 (US EPA, 2009b)] / [OECD TG 441] → E and A modalities → absence of endocrine activity for the S modality ?.

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Data → EATS mediated parameters → sufficiently investigated in non-target organisms

- Fish short term repro assay [FSTRA; OECD TG 229] / or 21-day fish assay [OECD TG 230 (OECD, 2009b)]
- Preferred/alternative: Mechanistic data from OECD TG 229 or OECD TG 230 (e.g. OECD TG 234).
- T-modality sufficiently investigated → Amphibian metamorphosis assay [AMA; OECD TG 231 (2009c)] conducted

ED expert group

- Experts from MS → non-binding advice on substances regarding ED.
- MS are encouraged to engage the EDEG when they suspect their substance is ED.

Take home messages

- The ED criteria now apply to biocides
- Good guidance → evaluate ED potential of substances
- Core data set for biocidal active substances → sufficient → ED assessment.
    - Generation of further data only when necessary
- ECHA ED expert committee available to MSs and eCAs for non-binding advice