Case study

efsa
European Food Safety Authority

BACKGROUND INFORMATION

- The active substance is a systemic herbicide, mainly absorbed by the leaves.
- It exerts its main effect by inhibiting the process of cell division in the meristematic organs of the plant.
- The chemical structure of the active substance contains an arylamide and a sulphonamide group and a major rat metabolite contains a sulphanilamide group

T-modality

T-modality

- **Is the dataset complete for the ED assessment in line with the ED GD?**

T-mediated adversity

Available evidence:

- **Rat, 90-days** (doses: 128.5/157.9; 387/479.4; 1327.3/1651.5 mkd M/F)
  - Describe relevant effects

T-mediated adversity

Available evidence:

- **Rat, 2-years** (doses: 36/47, 180/243, 953/1280 mkd M/F)
  - Describe relevant effects

T-mediated adversity

Available evidence:

- **Rat, prenatal developmental toxicity** (doses: 30, 45, 67.5 mkd in F)
  - Describe relevant effects

T-mediated adversity

Available evidence:

- **Rat, 21-days dermal study** (doses: 50, 125, 250 mkd in M/F)
  - Describe relevant effects

T-mediated adversity

Available evidence:

- **Mouse, 2-years** (doses: 74/95, 730/938, 8040/10353 mkd in M/F)

  ➢ Describe relevant effects

T-mediated adversity

Available evidence:

- **Dog, 26-weeks** (doses: 60, 300, 1500 mkd in M/F)
  - Describe relevant effects

T-mediated adversity

Available evidence:

- **Dog, 1-year** (doses: 100, 300, 600 mkd in M/F)
  - ➢ Describe relevant effects

T-mediated endocrine activity

- Describe relevant effects

T mediated adversity: DISCUSSION

Overall discussion:

Selection of relevant scenario

Adversity based on T-mediated parameters	Positive mechanistic OECD CF level 2/3 Test	Scenario	Next step of the assessment	Scenario selected (indicate with an "x" the scenario selected based on the assessed lines of evidence)
No (sufficiently investigated)	Yes/No	1a	Conclude: ED criteria not met because there is no "T-mediated" adversity	
Yes (sufficiently investigated)	Yes/No	1b	Perform MoA analysis	
No (not sufficiently investigated)	Yes	2a (i)	Perform MoA analysis (additional information may be needed for the analysis)	
No (not sufficiently investigated)	No (sufficiently investigated)	2a (ii)	Conclude: ED criteria not met because no T-mediated endocrine activity observed	
No (not sufficiently investigated)	No (not sufficiently investigated)	2a (iii)	Generate missing level 2 and 3 information. Alternatively, generate missing "EATS-mediated" parameters. Depending on the outcome move to corresponding scenario	
Yes (not sufficiently investigated)	Yes/No	2b	Perform MoA analysis	

EAS-modalities

EAS-modalities

- **Is the dataset complete for the ED assessment in line with the ED GD?**

EAS-mediated adversity

Available evidence:

- **Rat:**
  - Describe effects
- **Mouse:**
  - Describe effects
- **Dog:**
  - Describe effects

EAS-mediated endocrine activity

Available evidence:

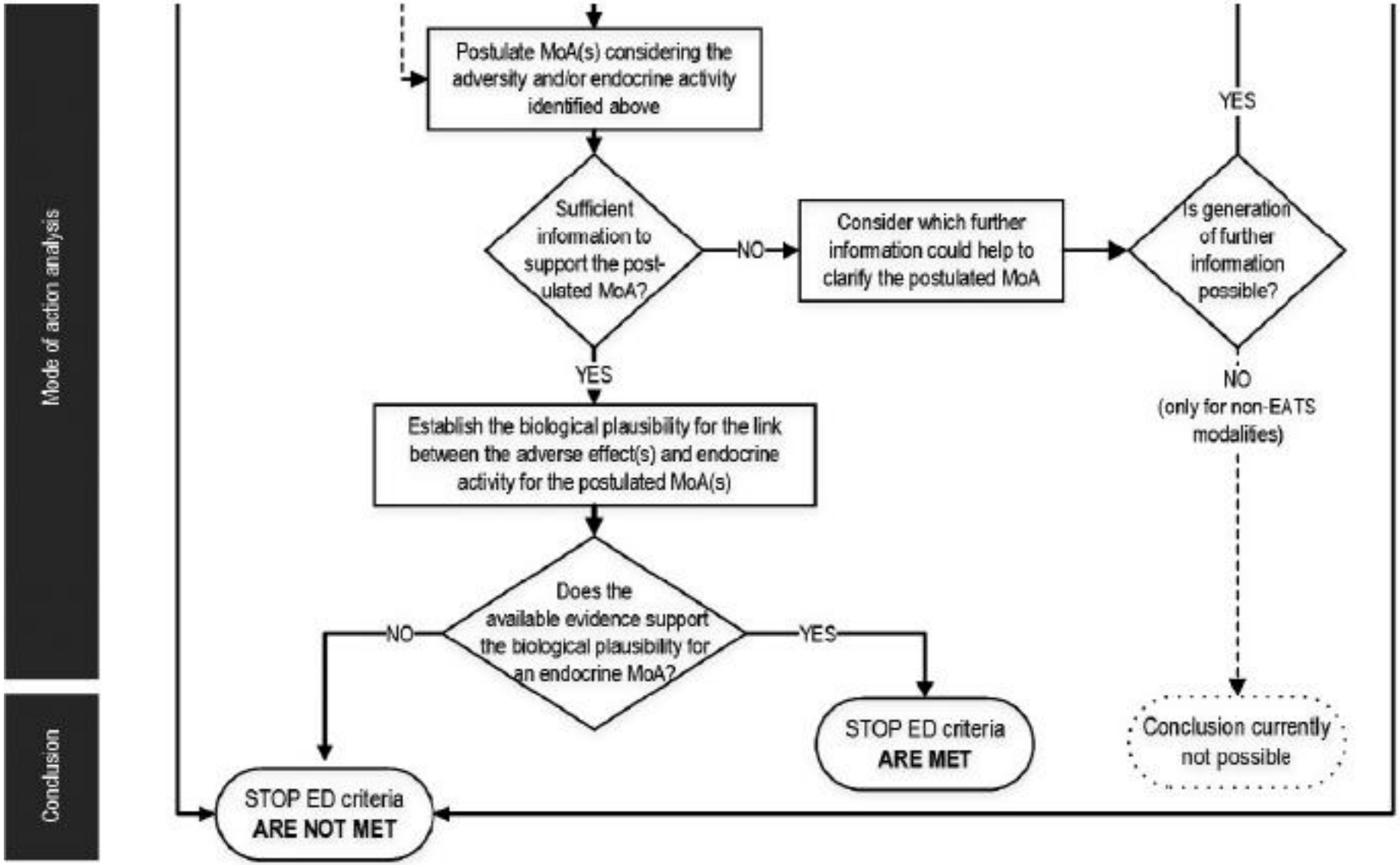
- Describe effects

Selection of relevant scenario

Adversity based on T-mediated parameters	Positive mechanistic OECD CF level 2/3 Test	Scenario	Next step of the assessment	Scenario selected (indicate with an "x" the scenario selected based on the assessed lines of evidence)
No (sufficiently investigated)	Yes/No	1a	Conclude: ED criteria not met because there is no "T-mediated" adversity	
Yes (sufficiently investigated)	Yes/No	1b	Perform MoA analysis	
No (not sufficiently investigated)	Yes	2a (i)	Perform MoA analysis (additional information may be needed for the analysis)	
No (not sufficiently investigated)	No (sufficiently investigated)	2a (ii)	Conclude: ED criteria not met because no T-mediated endocrine activity observed	
No (not sufficiently investigated)	No (not sufficiently investigated)	2a (iii)	Generate missing level 2 and 3 information. Alternatively, generate missing "EATS-mediated" parameters. Depending on the outcome move to corresponding scenario	
Yes (not sufficiently investigated)	Yes/No	2b	Perform MoA analysis	

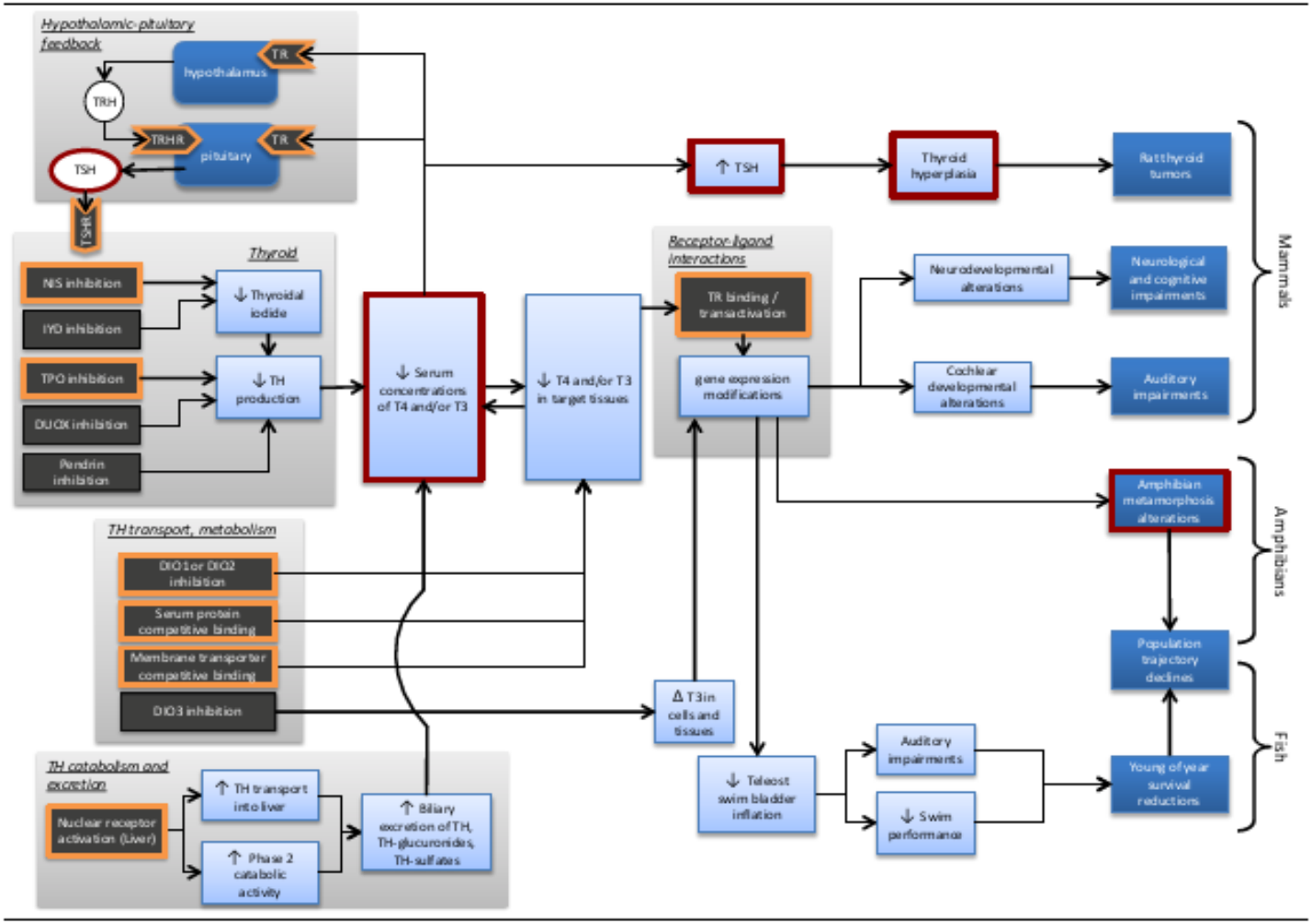
End of day 1

MoA analysis

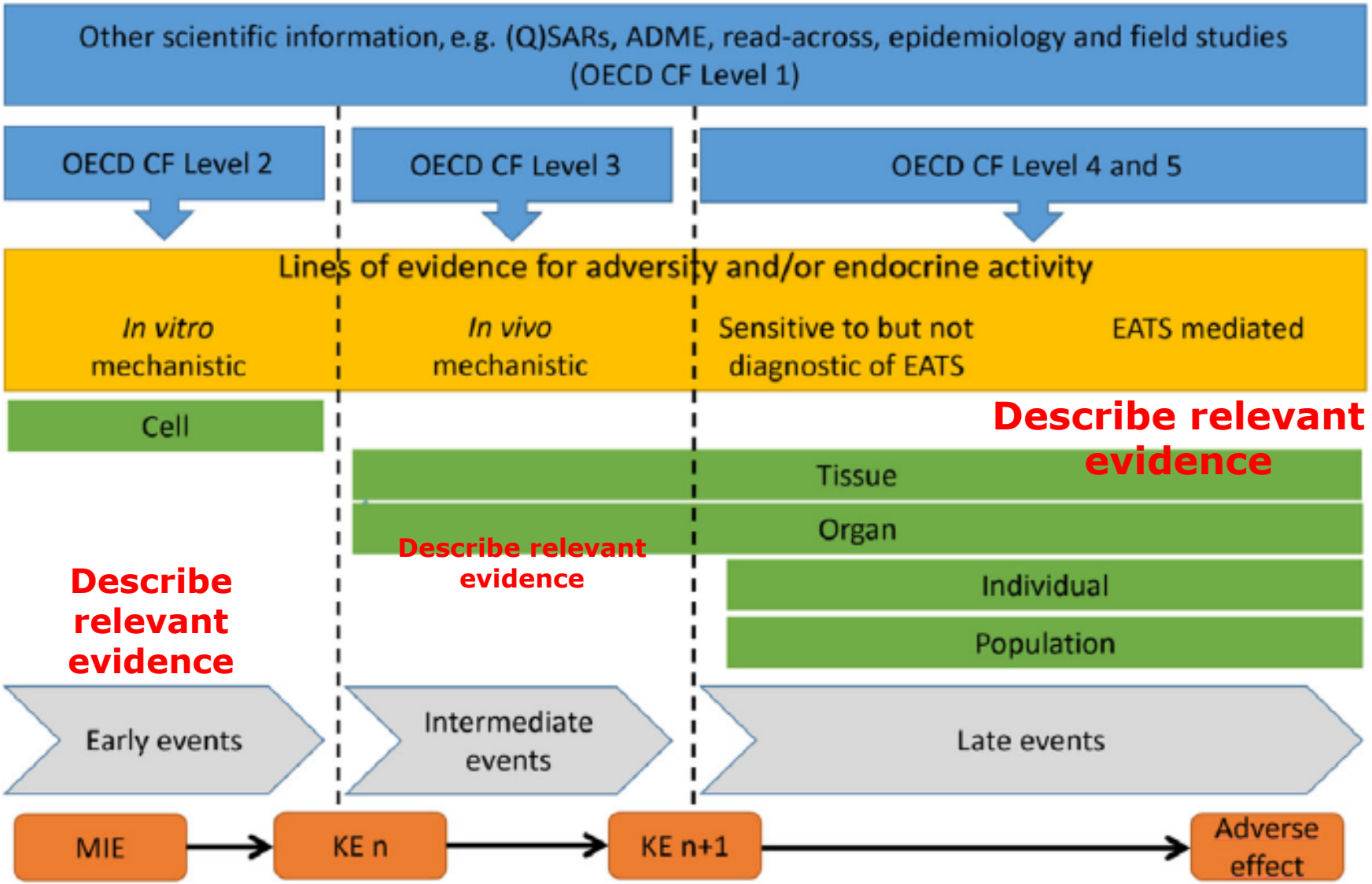


POSTULATE MoA CONSIDERING ADVERSITY AND/OR ENDOCRINE ACTIVITY

Proposed AOP network for chemically-induced thyroid bioactivity showing the integration of multiple individual AOPs



Use all available evidence to support your MoA analysis



KE: key event; MIE: molecular initiating event.

Postulate MoA

Important considerations

From the ECHA-EFSA ED Guidance:

For example in the scenarios 1b and 2b, ***where adversity is based on 'EATS-mediated' parameters the underlying knowledge of the likely endocrine nature of the effects may be such that judgement can be reached on the biological plausibility of a link without recourse to a detailed MoA analysis.***

In such cases, the MoA analysis could be very simple; when an adverse effect is 'EATS-mediated', the biologically plausible link is already pre-established in the absence of information proving the contrary (i.e. a fully developed non-ED MoA). This is because, in the case of 'EATS-mediated' parameters, where the pattern of effects is deemed adverse, the biological plausibility that the adverse effects are caused via an EATS-mediated MoA is high, based on existing knowledge and theory (i.e.coherence analysis), and as such, it may not be necessary to generate further empirical data on the substance under evaluation to substantiate the link between the observed adverse effect(s) and an endocrine-mediated MoA.

Selected lines of evidence for MoA analysis

	Description	Supporting evidence
MIE		
KE1		
KE2		
AO		

Dose- and temporal-concordance between key events

	MIE	KE1	KE2	AO

Conclusion on MoA analysis

	MIE to KE1	KE1 to KE2	KE2 to AO
Biological plausibility for the KER			
Empirical support for the KER			
Essentiality of the KE			
Consistency			
Analogy			
Specificity			

Uncertainties analysis

Conclusion on T-modality

EAS-modalities

Conclusion on EAS-modalities

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