GERMAN FEDERAL INSTITUTE FOR RISK ASSESSMENT

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Bundesinstitut für Risikobewertung

Regulatory aspects of developmental toxicology and endocrine effects

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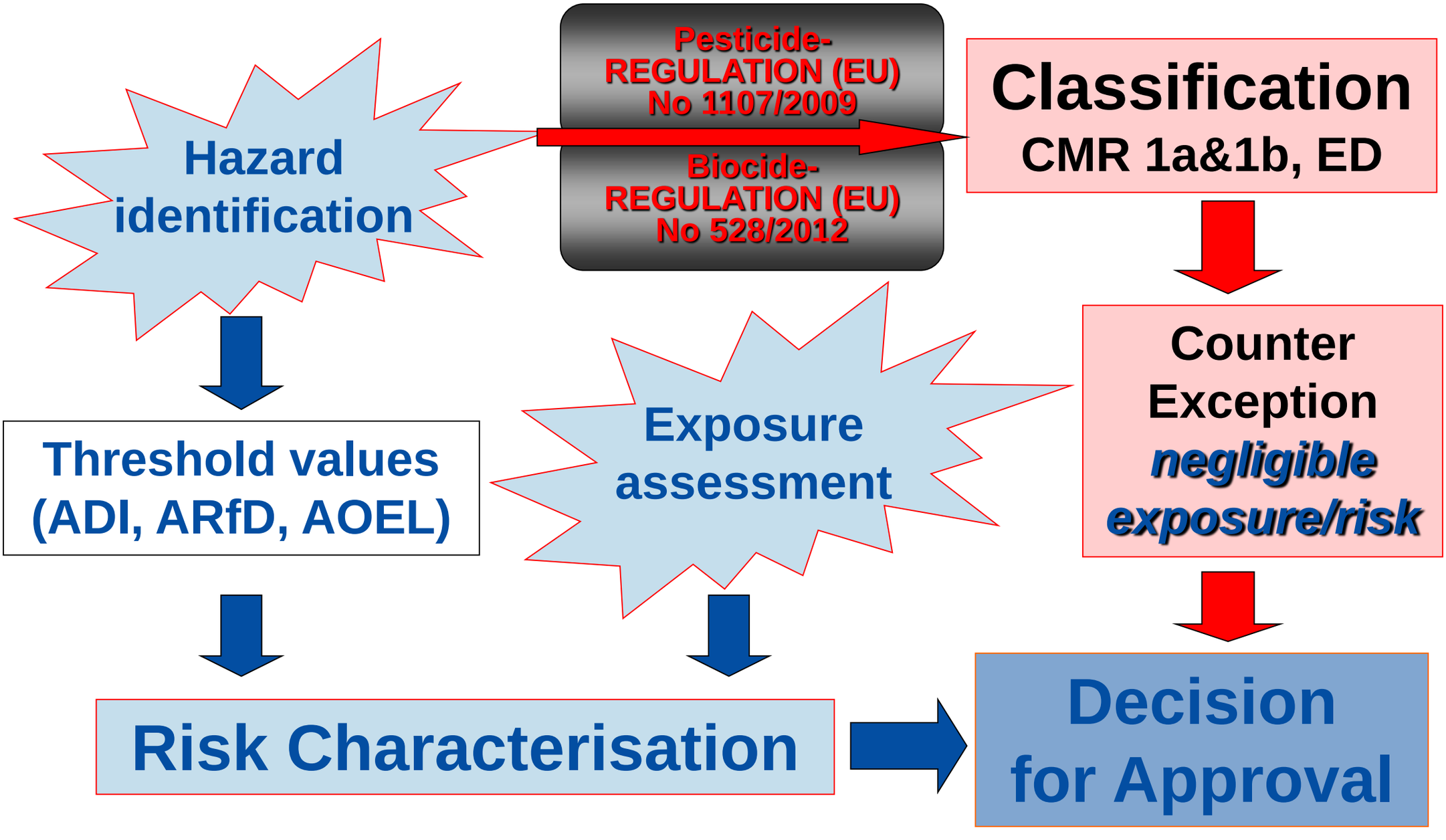
Principles of legal regulation in Europe



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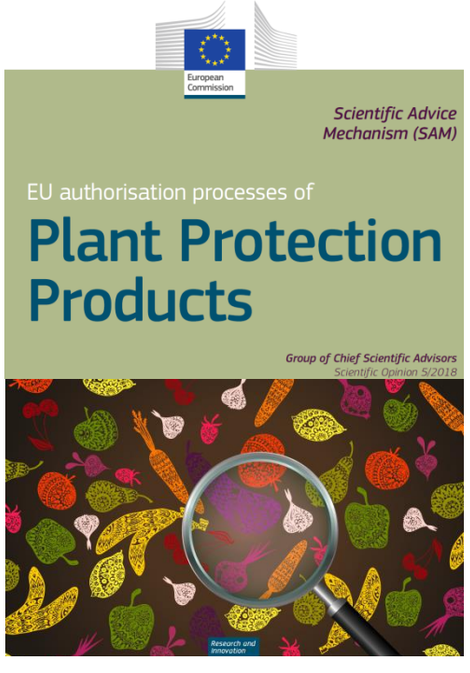
Principles of legal regulation in Europe



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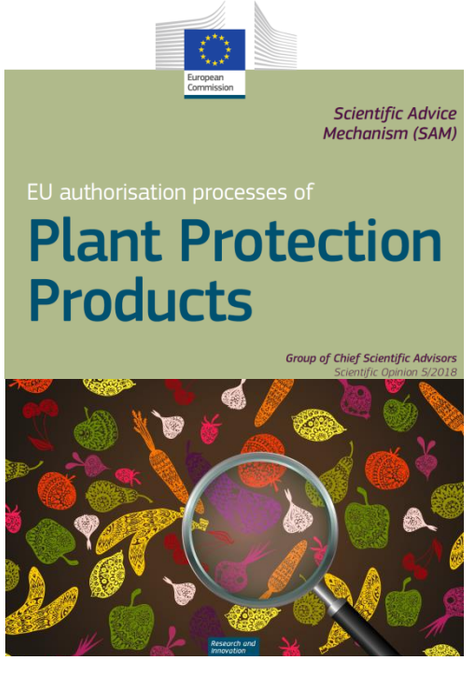
June 2018

- PPP Regulation states that an pesticidal active substance cannot be approved if it is …
  toxic for reproduction … endocrine disruptive…
- Hazard cut-off approach means that AS not approved in the EU if it has any of these hazardous properties, regardless likelihood of hazard causing actual harm…
- Outside EU, only 1 country employs hazard cut-off criteria, all other countries consider likelihood of hazard as part of a risk assessment, including risk mitigation measures.
- 2 other EU legislation also employ hazard cut off criteria, Biocides Regulation in similar manner to the PPP, and REACH, substances of very high concern for substitution.
- Other major regulatory frameworks, including the assessment of medicines, do not employ hazard-based cut-offs.

Principles of legal regulation in Europe



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Advantages of the hazard cut off criteria approach

- should be faster, less expensive and more protective.
- valuable to exclude AS with potential for most harm
- important - existing exposure models underestimate risks,
- allows regulators to send a clear message to the market
- intrinsically less hazardous substances will be favoured over ones that may be more hazardous.

Opponents argue that hazard cut-off criteria approach

- is fundamentally unscientific
- may needlessly exclude much needed PPPs from market
- unlikelihood that inherent hazard will translate into a ris
- hazard characterisation - first steps in risk assessments
- authorisation with risk assessment not less protective.

The debate would clearly benefit from a critical assessment of how well hazard cut-off criteria approach is working in practice, including evidence from post-market monitoring and from regions outside the EU.

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Principles of legal regulation in Europe

Definitions “Negligible exposure” as a counter exception

- Negligible exposure according to **Pesticide Regulation** 1107/2009
  - the **exposure** … **is negligible,**
  - the product is **used in closed systems** or **excluding contact with humans** & where **residues concerned on food and feed** do not exceed the default value**.**

- Negligible exposure according to the **Biocide Regulation** 528/2012
  - the **risk** … **from exposure** … **is negligible**,
  - the product is **used in closed systems** or aim at **excluding contact with humans** and release into the environment.

- Negligible exposure cannot be based on the precautionary principles
  - Closed systems do not exclude necessarily exposure of worker, bystander and residents of all applied uses during authorisation.
  - A MRL of 0.01 mg/kg food cannot exclude relevant exposure for substances with very low threshold values.

Guidance Documents

Guidance on the Application of the CLP Criteria

Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures

Version 5.0
July 2017

Guidance Documents

3.7. REPRODUCTIVE TOXICITY

3.7.1. Definitions and general considerations for reproductive toxicity

In this classification system, reproductive toxicity is subdivided under two main headings:

(a) Adverse effects on sexual function and fertility;

(b) Adverse effects on development of the offspring.

Annex I*: 3.7.1.4.* *Adverse effects on development of the offspring*

Developmental toxicity includes, in its widest sense, any effect which interferes with normal development of the conceptus, either before or after birth, and resulting from exposure of either parent prior to conception, or exposure of the developing offspring during prenatal development, or postnatally, to the time of sexual maturation. However, it is considered that classification under the heading of developmental toxicity is primarily intended to provide a hazard warning for pregnant women, and for men and women of reproductive capacity. Therefore, for pragmatic purposes of classification, developmental toxicity essentially means adverse effects induced during pregnancy, or as a result of parental exposure. These effects can be manifested at any point in the life span of the organism. The major manifestations of developmental toxicity include (1) death of the developing organism, (2) structural abnormality, (3) altered growth, and (4) functional deficiency.

…. the effects of a developmental toxicant can differ between dose levels from variations via malformations to death of the foetuses…

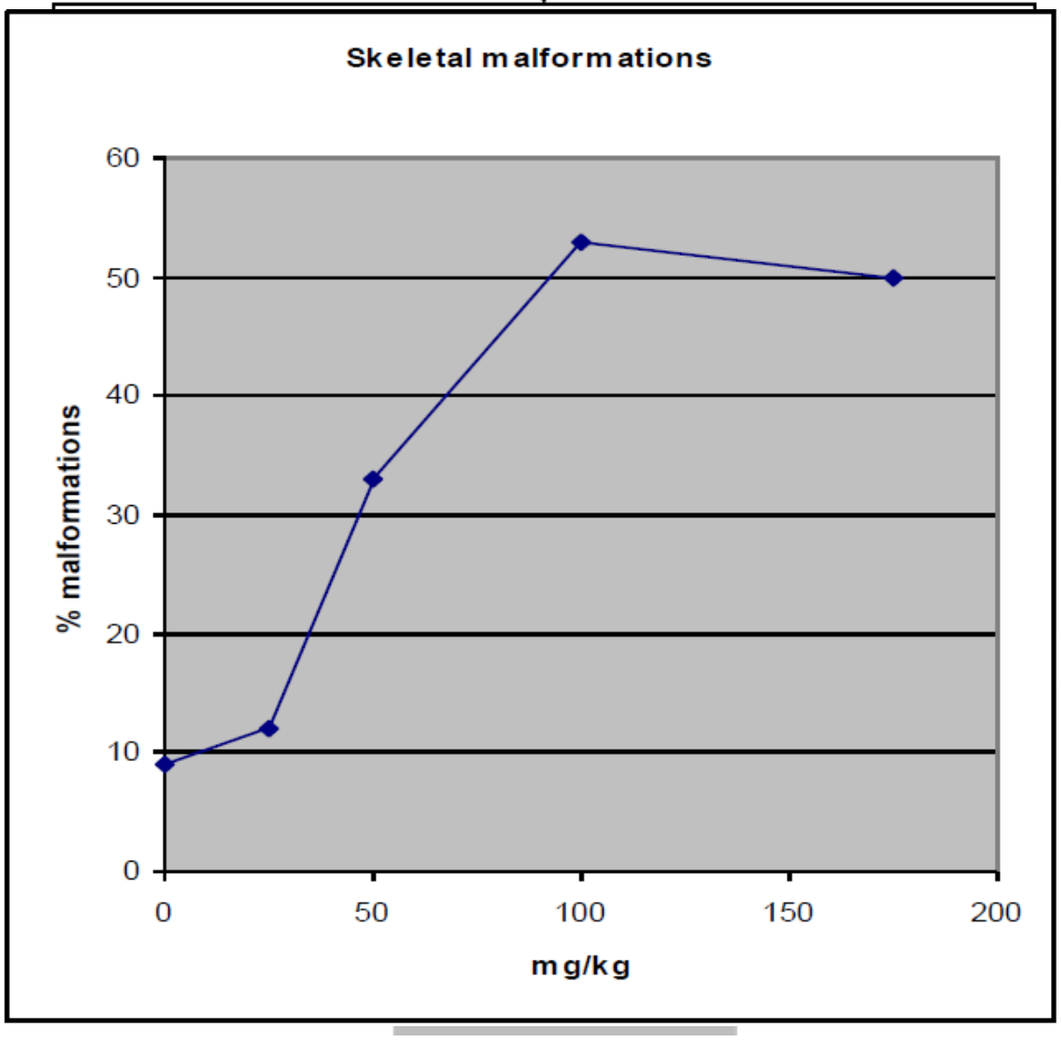
Guidance Documents

Classification of substances for fertility or developmental effects

Does the substance have data on reproductive toxicity?

No → Classification not possible

Yes



Yes → Category 1

Danger

Yes → Category 2

Warning

Counter Exception *negligible exposure/risk*

Decision for Approval

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Guidance Documents

ECHA
EUROPEAN CHEMICALS AGENCY

GUIDANCE

efsa
European Food Safety Authority

ADOPTED (ECHA): 5 June 2018
ADOPTED (EFSA): 5 June 2018

doi: 10.2903/j.efsa.2018.5311

Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009

European Chemical Agency (ECHA) and European Food Safety Authority (EFSA) with the technical support of the Joint Research Centre (JRC)

Guidance Documents

ECHA
EUROPEAN CHEMICALS AGENCY

GUIDANCE

efsa
European Food Safety Authority

First Draft (Jan – Apr 2017)

First Consulting Group Commenting (Apr – May 2017)

Second Consulting Group Commenting (July – Aug 2017)

Public Consultation (Dec 2017 – Jan 2018)

Revision of Second Draft (Feb – Apr 2018)

Consultation ECHA & EFSA Scientific Bodies (Apr 2018)

Consultation with risk managers (May 2018)

Publication (June 2018)

Applicability: Biocides – Sep 2018, PPP – Nov 2018)

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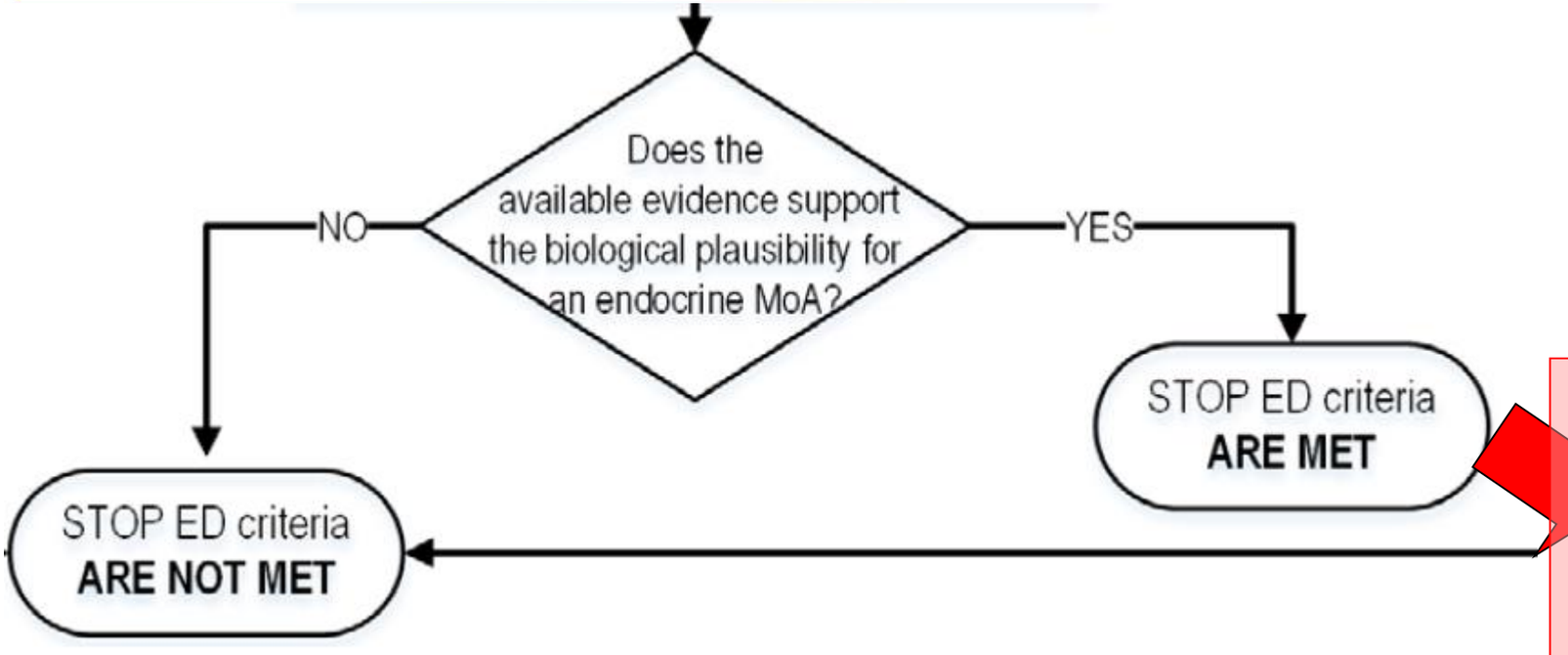
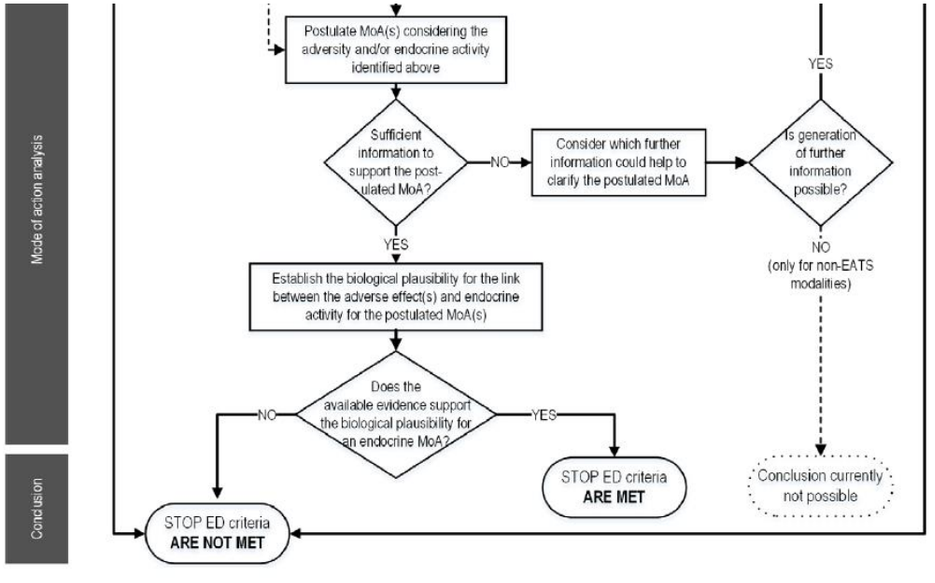
Guidance Documents

ECHA EUROPEAN CHEMICALS AGENCY Guidance for the identification of endocrine disruptors in biocides and pesticides efsa European Food Safety Authority



Counter Exception *negligible exposure/risk*



Decision for Approval

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Guidance Documents

Do the ED-Guidance address the complexity of the endocrine system?

Limited to EATS Pathways

Dermis

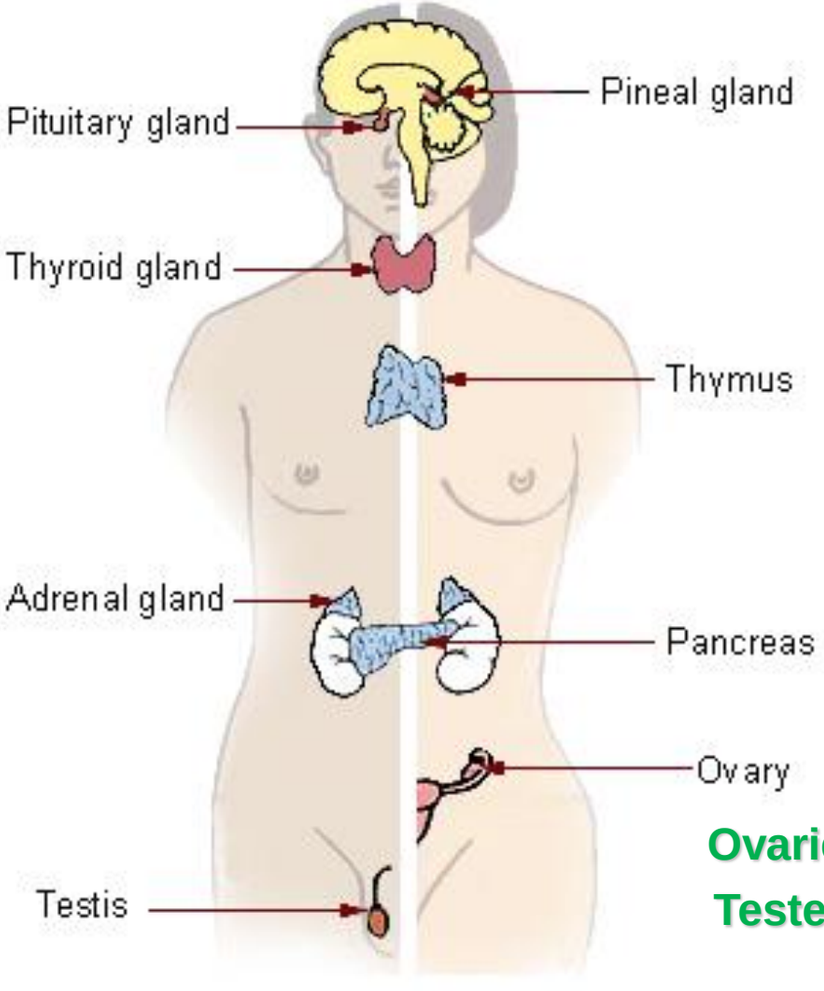
Thymus

Adipose tissue

Stomach

Kidney

Pancreas



Hypothalamus/Pituitary

Thyroid gland

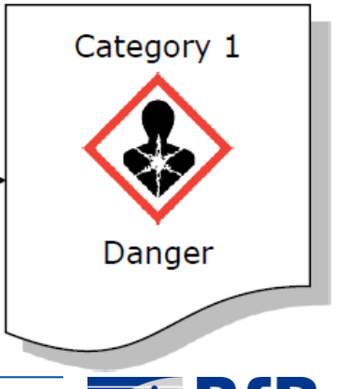
Parathyroid

Adrenal gland

Ovaries (Females)

Testes (Males)

Overlapping with CLP Classification Reprotox



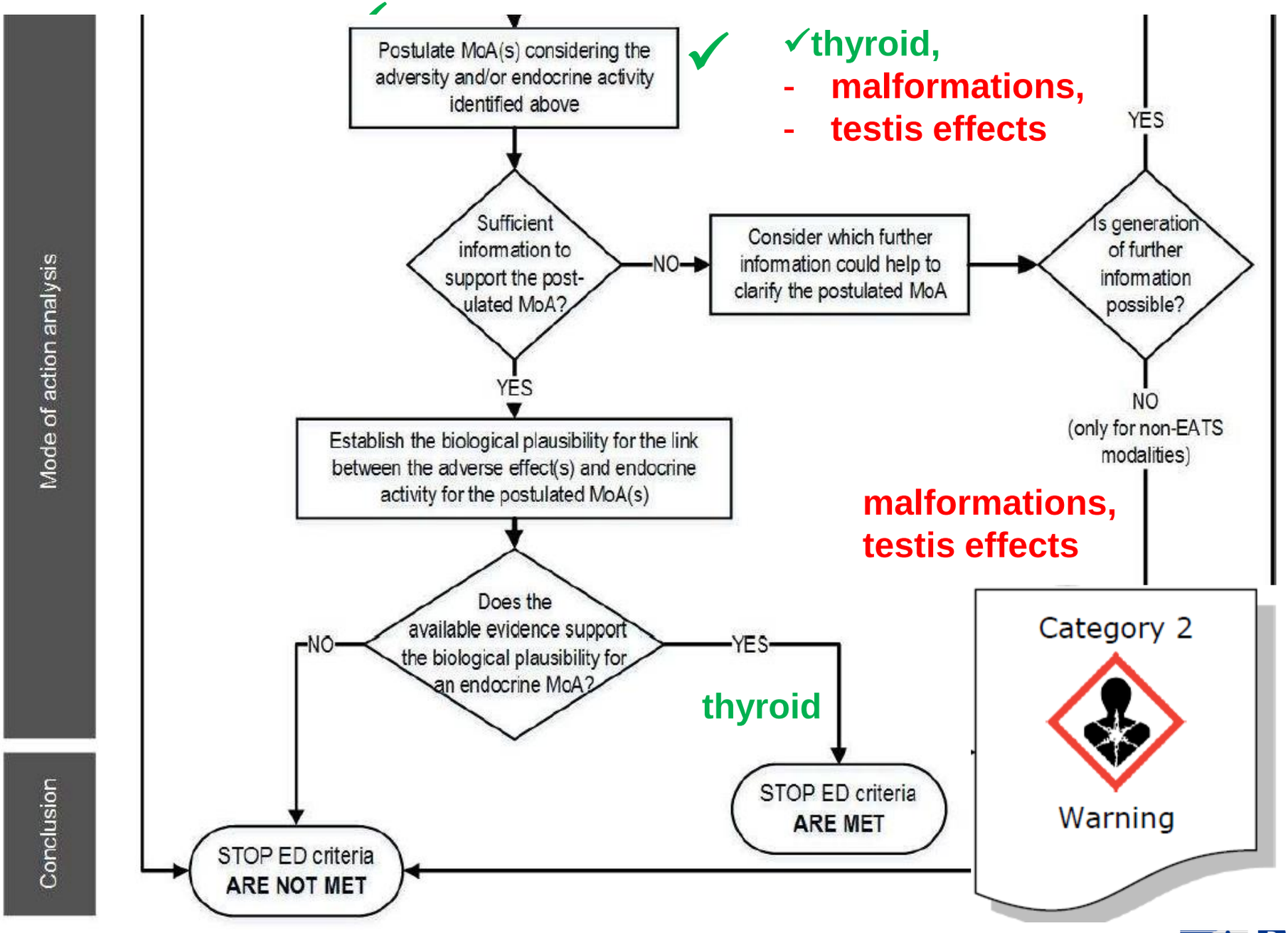
E: Estrogen
A: Androgen
T: Thyroid
S: Steroidogenesis

https://en.wikipedia.org/wiki/Endocrine_system

Case Study CYD:

	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y	
6											In vivo mechanistic	In vivo mechanistic	EATS-mediated	EATS-mediated	EATS-mediated	EATS-mediated	EATS-mediated	EATS-mediated	EATS-mediated	EATS-mediated	Sensitive to, but not diagnostic of, EATS	
7	Species	Doses tested	Dose unit	Route of administration	Exposure	Exposure unit	Generation /Life stage	Additional remarks	Relevance	Reliability	T3 and T4 level	Thyroid stimulating hormone (TSH) level	Colloid area	Epididymis histopathology	Epididymis weight	Ovary histopathology	Testis histopathology	Testis weight	Thyroid histopathology	Thyroid weight	Fertility	
8	Dog	0; 0.6; 2; 6	mg/kg bw/day	Oral	90	Days	Adult	Young dogs, 16-20 weeks; 6600 IU vitamin A per kg feed			Decrease 2.0 (<50% decrease T4 dose-dependent,			Increase 0.6 (Reduced number of sperms, Incidences,			Decrease 0.6 (Spermatogenesis, slight to	Decrease 6.0 (1 -small testes, 3 - unilateral cryptorchis				
9	Dog	0; 0.6; 6	mg/kg bw/day	Oral	90	Days	Adult	Supplementary study; Adult dogs, 52-58 weeks; 8100 IU vitamin A per kg feed						Increase 6.0 (Reduced number of sperms, Incidences)								
10	Dog	0; 0.2; 1.0; 5 (0;0,1;0,5; 2.5 w1-2)	mg/kg bw/day	Oral	1	Years	Adult	Vitamin A content in food is not known		No GLP	Decrease 5.0 (45% T4 decrease W52, stat sign)			Increase 1.0 (Immature sperms, Incidences, 1/1)			Increase 5.0 (Bilateral aspermatogenesis, Incidences, 1/4)			Increase 5.0 (55% Thyroid/parathyroid increase, stat sign,		
11	Mice	M:0; 4.2; 12.1; 25.5; F:0, 6, 13.4, 39.0	mg/kg bw/day	Oral	104	Weeks	Adult	Hydrogen cyanamide								Increase 39.0 (Granulosa-theca tumour,						
12	Rat	0; 5; 10; 20; 40	mg/kg bw/day	Oral	28	Days	Adult				Decrease 40 (28% decrease)	Increase 40 (100% increase)	Decrease 5 (Dose-response)					Decrease 20 (15% decrease, Absolute, sign)	Increase 5 (Small and closely packed follicles)	Increase 40 (Thyroid/parathyroid, 49% increase, Relative		
	Rat	0; 0.5; 1.5; 4.5	mg/kg bw/day	Oral	90	Days	Adult			Pre-GLP			Decrease 1.5 (Thyroid colloid									

Case Study CYD:



Summary and Discussion

Current approaches for classification of developmental toxicity and labelling of EDs may be overlapping.

Hazard classification of developmental or reproductive hazards should also consider if these hazards may be induced by disruption of endocrine pathways.

There are no harmonised WoE approaches to assess hazard for developmental/reproductive toxicants in relation to the disruption of endocrine pathways.

A consideration of both categories if used in classification/labelling could adjust the confidence for appropriate hazard analysis and support the options for risk management decisions.

Summary and Discussion

Hazard classification is a process involving identification of hazards, should be followed by assessment of the degree/potency of hazard.

Current approaches for classification of developmental toxicity and labelling of EDs only consider hazard identification.

There are no harmonised agreements to assess the degree of hazard based on potency (factors) for developmental toxicants and for EDs.

A grading of hazard categories if used in classification/labelling could adjust the confidence for appropriate hazard assessments and support the options for risk management decisions.

Summary and Discussion

- Transition from risk-based regulatory decisions
  - to hazard-based regulatory decisions for DevTox and ED
- Opinions vary whether this is **good or bad**
  - Advantages: high degree of safety, precautionary decisions….
  - Disadvantages**:** loss of compounds, not applied outside of Europe…
- Hazard estimation **not equal** to proper risk assessment
  - Proper risk assessment requires good exposure data
- Choosing **hazard** or **risk** based regulation is a **political decision**
  - Has to be applied by the European regulatory agencies
- Further **complicating factors**:
  - Harmonisation of approval and CLP processes necessary
  - Need for good practical definitions of negligible exposure/risk
  - **Overlapping effects for developmental toxicity and EDs**

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Thank you for your kind attention!

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