



# Endocrine Disruptors: OECD work EU criteria and guidance

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# Development of Criteria for the Identification of EDCs

## Outline

- 1) WHO/IPCS Definition
- 2) OECD Conceptual Framework and Guidance Documents
- 3) EDs in the European Legislation
- 4) ED Criteria Development by the European Commission
- 5) EFSA/ECHA Guidance
- 6) BfR's Supporting Role
- 7) Summary & Conclusion



# WHO/IPCS definitions

## WHO / IPCS Definition of Endocrine Disruption

An ED 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 (WHO/IPCS 2002).

# WHO/IPCS definitions

## WHO / IPCS Definition of Adversity

A change in morphology, physiology, growth, development or lifespan of an organism which results in impairment of functional capacity or impairment of capacity to compensate for additional stress or increased susceptibility to the harmful effects of other environmental influences (WHO/IPCS 2004).

IPCS: International Programme on Chemical Safety of the WHO

# The OECD Conceptual Framework

**Level 1**  
Existing data  
non-testing methods

- Physical & chemical properties
- All available (eco)toxicological data.
- In silico predictions (Read across, categories, QSAR)

**Level 2**  
In vitro assays for selected  
endocrine pathways

- ER, AR, TR receptor binding
- Transcriptional Activation (TG 455, 457)
- Steroidogenesis assay (TG 456)
- MCF-7 proliferation assay

**Level 3**  
In vivo assays for selected  
endocrine pathways

- TG 440: Uterotrophic assay (estrogen-related)
- TG 441: Hershberger assay (androgen-related)
- Others (e.g. thyroid)

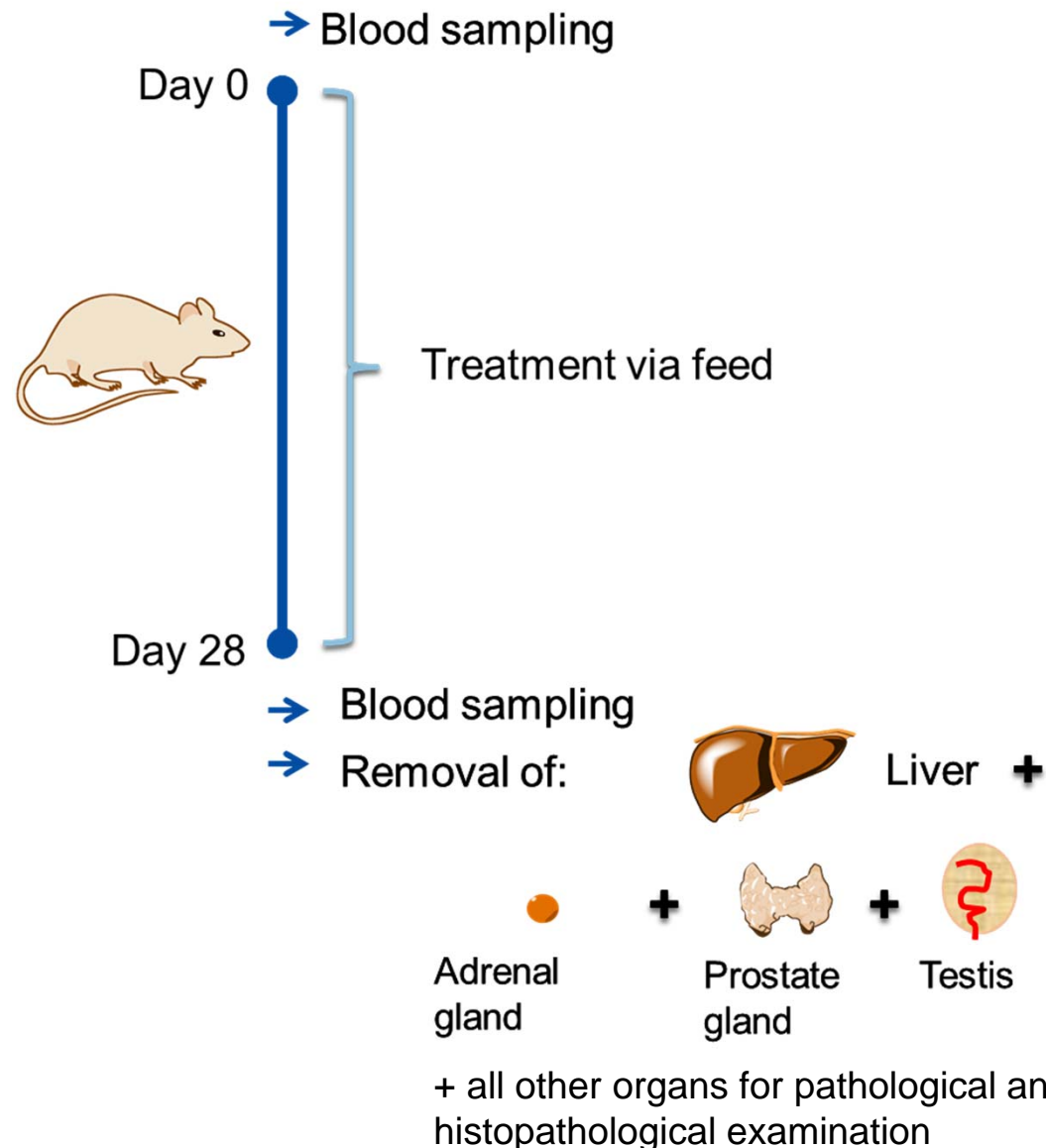
**Level 4**  
In vivo assays for adverse  
effects on endocrine  
relevant endpoints

- Repeated dose 28-day study (OECD TG 407)
- Repeated dose 90-day study (OECD TG 408)
- 1-generation reproduction toxicity study (OECD TG 415)
- Male pubertal assay (see GD 150, Chapter C4.3)3
- Female pubertal assay (see GD 150, Chapter C4.4)3
- Intact adult male endocrine screening assay (see GD 150, Chapter Annex 2.5)
- Prenatal developmental toxicity study (OECD TG 414)
- Chronic toxicity and carcinogenicity studies (OECD TG 451-3)
- Reproductive screening test (OECD TG 421 if enhanced)
- Combined 28-day/reproductive screening assay (OECD TG 422 if enhanced)
- Developmental neurotoxicity (OECD TG 426)

**Level 5**  
In vivo assays detecting  
adverse effects over more  
extensive parts of the life  
cycle of the organism

- Extended one-Generation Reproductive Toxicity Study (OECD TG 443)
- 2-Generation Assay (TG416 enhanced)

# A way forward: update of existing OECD TG (e.g. TG407)



**Additional parameters:**  
T3, T4, TSH measurement  
mandatory, „specific  
hormones“ case-by-case  
Oestrus cycle  
Consideration of diurnal  
rhythms

Accordingly TG408 and TG414  
are under revision  
TG443 has been established

# OECD GD150: Overview on scope of individual TG

Test guideline or other test method	Endpoints for estrogen-mediated activity	Endpoints for androgen-mediated activity	Endpoints for thyroid-related activity	Endpoints for steroidogenesis-related activity
<b>OECD TG 407</b>	<p>Histopathologic changes in ovary, uterus/cervix, vagina.</p> <p>Decrease in weight of epididymides, prostate + seminal vesicles with coagulating glands.</p> <p>Histopathologic changes in testes, epididymides, prostate + seminal vesicles with coagulating glands.</p> <p>...</p>	<p>Histopathologic changes in ovary, uterus/cervix, vagina.</p> <p>Increase in weight of prostate + seminal vesicles with coagulating glands. Decrease in weight of testes.</p> <p>Histopathologic changes in testes, epididymides.</p> <p>...</p>	<p>Possible liver weight increase (in combination with other thyroid-related endpoints).</p> <p>Histopathologic changes in thyroid (follicular cell height increase &amp; colloid area decrease)</p> <p>...</p>	<p>Possible effects on: Histopathologic changes in ovary, uterus/cervix, vagina.</p> <p>Weight of, prostate + seminal vesicles with coagulating glands.</p> <p>...</p>

GD 150 provides similar sections also for all other relevant TG, e.g. TG408, 414, 416, 443...

# OECD GD150: How to interpret results of TG

Scenarios	Result of AR STTA)	Existing In vitro mech.	Results In vivo	Possible conclusions	Next step which could be taken to increase evidence if necessary	Other considerations
<b>A</b>	+	+	+	AR (ant)agonism combined with effects on ER/T/S and potential for adverse effects via multiple mechanisms.	Perform assay from upper levels e.g. HB assay (level 3) or male PP assay (level 4) or ext-1 or 2-gen assays (level 5)	A positive result indicates strong probability of interaction with ERs in other taxa. If existing data are from level 5 there may be sufficient information to conclude evidence of concern for endocrine disruption (the ext-1 gen assay provides the most information
...				...	...	...
<b>R</b>	-	Eq/0	Eq/0	No evidence for AR (ant)agonism. Unknown potential for adverse effects via other mechanism.	For the "0" scenario perform AR STTA with added metabolizing system or perform H assay if existing data indicate a need	Negative result indicates interaction with AR in other taxa is unlikely. Consider possible routes of exposure, implications of metabolism. Check data on chemical analogues. Further mechanistic studies would help determine MoA. Equivocal results may indicate chemical has multiple MOAs.



# EDs in European Legislation

## „One Substance – One Assessment”

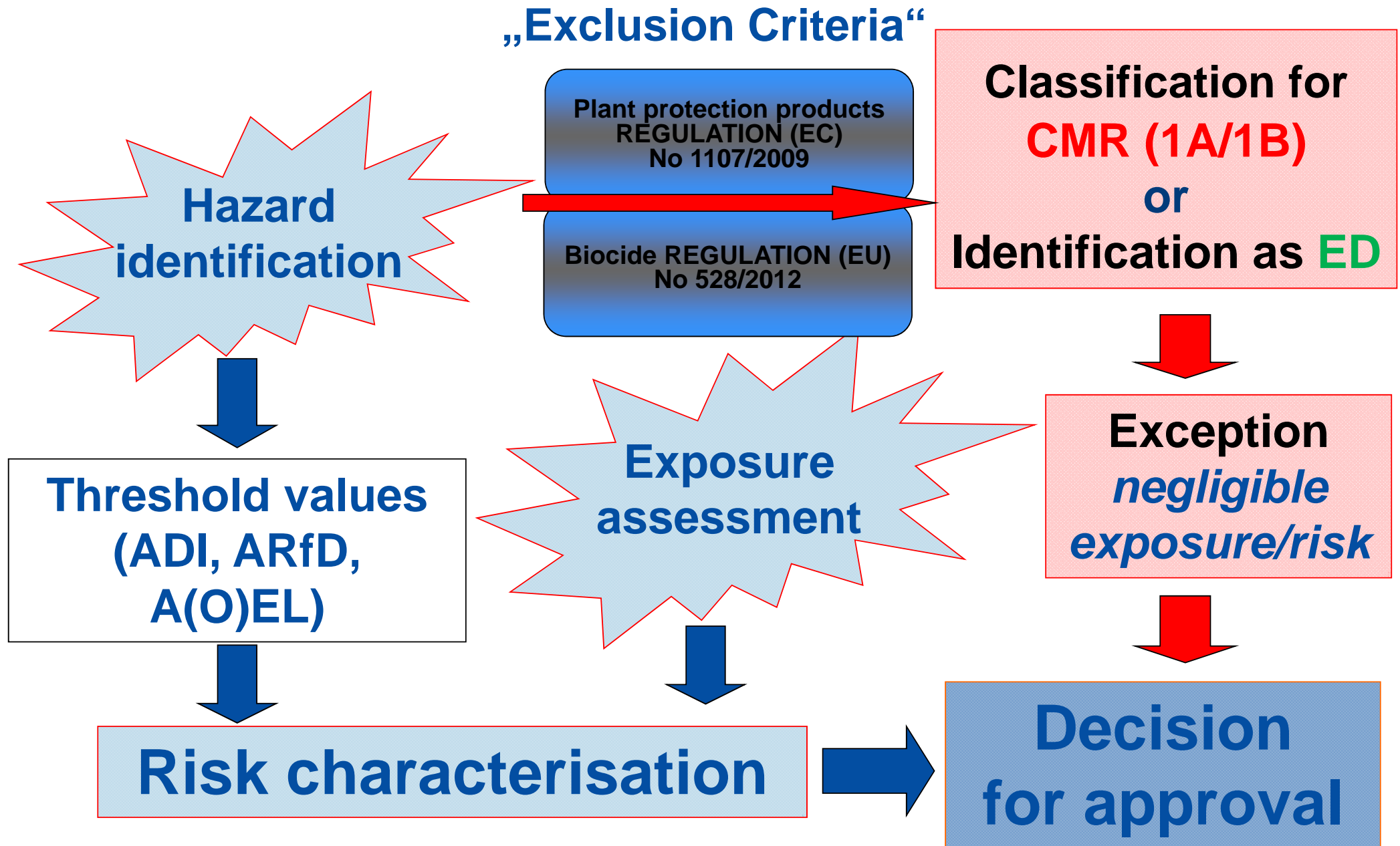
- But:
- different regulations
  - different data requirements
  - different regulatory outcomes

Plant Protection Products (EC1107/2009)	Pharmaceuticals	Food additives (EC 1333/2008)	REACH (EC 1907/2006)	Plastics with food contact (EU 10/2011)	Cosmetics (EC 1223/2009)	Food and others
Biocides (EU 528/2012)						
Are data requested under the regulation sufficient for identification?						
✓	✓	✓	(✓)	(✓)	(✓)	?

### What are regulatory consequences for substances identified as endocrine disruptors?

Approval procedure	Approval procedure	Approval	Registration, authorisation	Risk assessment	Risk assessment	Risk assessments
Ban	Restriction Labelling	Restriction	Authorisation required	Restriction	Restriction Ban	Restriction

# EDs in European Legislation





- Twenty-three international scientists from different disciplines discussed principles and open questions on ED identification.
  - Observers from ECHA, EFSA, European Commission, US, JP.
  - Two-day meeting in April 2016 to discuss controversies and to identify ways of resolving the differences of opinion that exist.
  - Participants reached a consensus regarding scientific principles for the identification of EDs and research needs.
- 
- Published in Archives of Toxicology, 2017, Solecki et al. Scientific principles for the identification of endocrine disrupting chemicals: a consensus statement

# Proposal of the European Commission, July 2017

- WHO definition for EDs and adverse effects fully applies
- Weight of evidence approach as main approach
- Taking into account all relevant scientific information
- Potency considerations not included in identification of EDs
- Separate parts for human health and environment
- Points out necessity for further research
- Different legal procedures for plant protection products and biocides have to be followed for implementation
- Criteria for biocides will enter into force in December 2017

# EFSA/ECHA Guidance Document



APPROVED: 16 December 2016



PUBLISHED: 20 December 2016

In December 2016 EFSA and ECHA published an Outline for a Draft Guidance Document.

[https://www.efsa.europa.eu/sites/default/files/documents/161220\\_ed\\_guidance\\_outline.pdf](https://www.efsa.europa.eu/sites/default/files/documents/161220_ed_guidance_outline.pdf)

## **Outline of Draft Guidance Document for the Implementation of the Hazard-based Criteria to Identify Endocrine Disruptors**

# EFSA/ECHA Guidance Document

## 2. Scope of the Guidance Document

The Guidance Document will provide guidance for the implementation of the scientific criteria concerning the hazard-based identification of EDs in the context of Regulations (EC) No 1107/2009 and (EU) No 528/2012. The Guidance is intended to be suitable for both applicants and regulatory authorities.

Although the (identical) criteria for EDs will formally apply only in the context of the Biocidal Products and Plant Protection Products legislation, the scientific approach(es) to be described in the joint Guidance could be relevant for other chemical substances, since the ED identification step will be based exclusively on the evaluation of the relevant hazardous properties of a substance.

The Guidance will focus on the data and information needed for ED hazard identification. It will also provide an indication on which information may be considered sufficient to conclude on the ED properties of a substance in accordance with the criteria. The evaluation approach will take toxicological and eco-toxicological information into account in an integrated manner and provide guidance for identifying data gaps that would trigger the need for additional data across the human health and environment domains.

Public Consultation Planned December 2017-January 2018

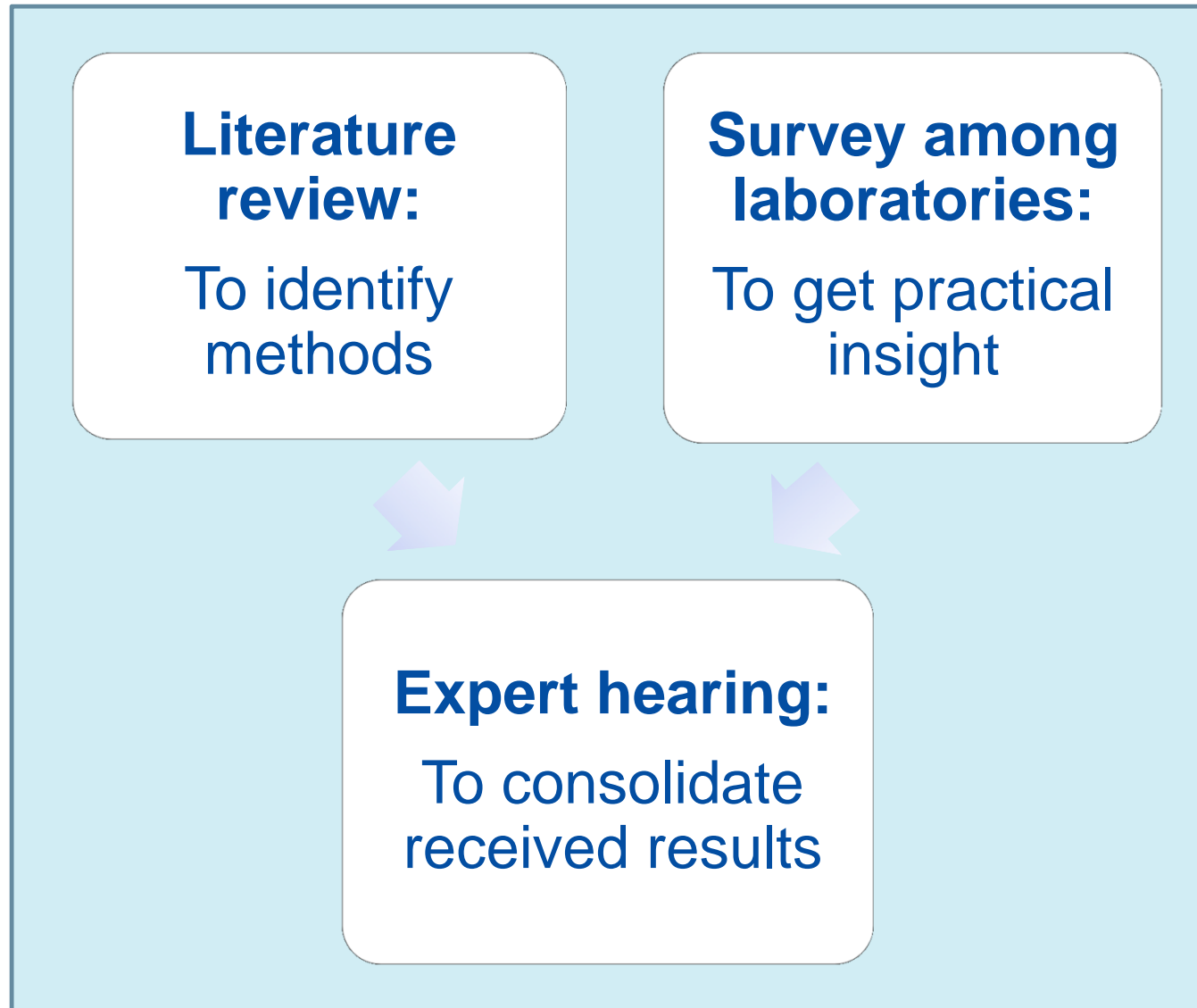
# Supporting Project of the BfR

## The Idea:

- To develop recommendations concerning the practicability of hormone measurement methods
- These recommendations were given to the EFSA Guidance Document drafting team and potentially included in the annex of this document.
- This information will also be published as a report in a scientific journal
- Ultimately: Addition of ED endpoints to existing OECD TGs if/where feasible

# Supporting Project of the BfR

## The Approach:





# Supporting Project of the BfR

## Laboratory Survey:

- 50 contract, industry and academic laboratories contacted, ~25 responded
- Four hormonal axes:
  - Hypothalamus-Pituitary-Gonad (HPG)
  - Hypothalamus-Pituitary-Thyroid (HPT)
  - Hypothalamus-Pituitary-Adrenocortical (HPA)
  - Non-EATS

# Supporting Project of the BfR

## Expert Hearing

- Survey participants have been invited to an expert hearing
- Hosted by the BfR in Berlin, 18-19th October
- Breakout groups discussed and elaborated on practical recommendations for hormonal measurements, esp. in regulatory studies

### Outcomes:

- Practical recommendations to complement guidance ✓
- Workshop Report for EFSA/ECHA
- Publication on further steps and recommendations to OECD

# Supporting Project of the BfR

## Recommendations on:

- Age of Animals and Maturation Status
- Reproductive Cycle
- Circadian Rhythms/Pulsatility
- Stress Avoidance
- Use of Anesthetics
- Method of Blood Collection
- Storage of Samples
- Method of Hormone Measurement
- Assay Validation
- Results, Evaluation and Interpretation of Data

# Summary and Conclusions

- EU legislation: need for ED identification
- Harmonised criteria for biocides adopted in the EU
- Guidance is now needed and being developed on OECD and EU level
- Currently limited to EATS pathways but activities on OECD and EU level will help to overcome this deficiency
- BfR is supporting this with recommendations based on published literature, a laboratory survey and an expert hearing
- More research, esp. on non-EATS pathways is urgently needed



Thank you very much

**Dr. Philip Marx-Stölting & Dr. Vera Ritz**

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