State-of-the-Art Assessment of Endocrine Disrupters

An overview of the final report of the EU/DG Environment Project

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EFSA Stakeholder Meeting
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Marriott Renaissance Hotel, Brussels

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Terms of reference

Tasks

1. Scientific literature
2. Assessment of endocrine disrupting properties of substances
3. Policy relevant questions
   - ➢ Suitability and availability of tests
   - ➢ Comparative analyses of EU MS proposals

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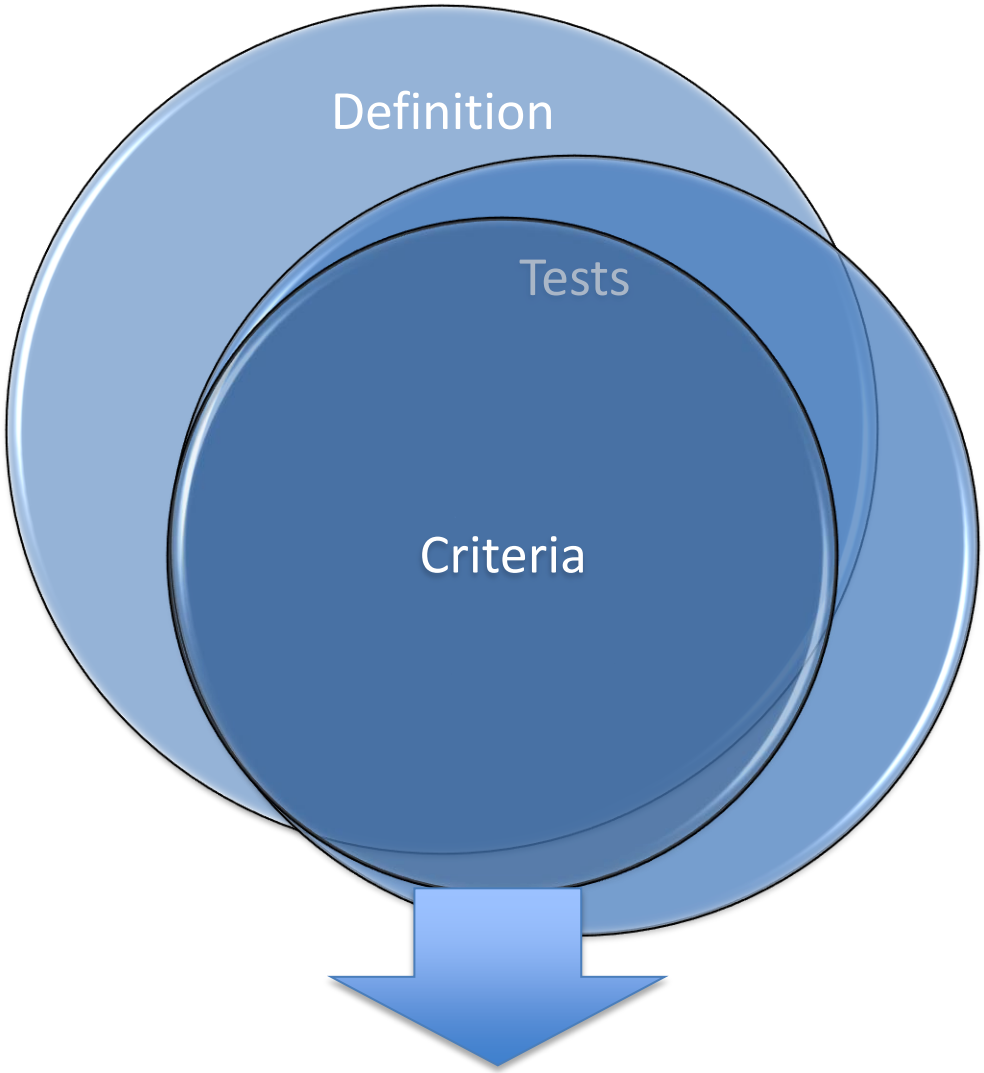

Regulatory Decision

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Definition(s)

"An endocrine disrupter 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)

- Adverse effect
- Endocrine disruption mode-of-action
- Proof of causality

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Definition(s)

Adversity

"*A change in morphology, physiology, growth,* reproduction*, 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*". (IPCS/WHO, 2004)

- Assay requirements
- Endocrine modulation
- Ecotoxicological effects

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Definition(s)

Mode-of-action

- (anti)estrogenicity, (anti)androgenicity, steroidogenesis and thyroid disruption
- Specificity or lead toxicity
- Definition of the endocrine system

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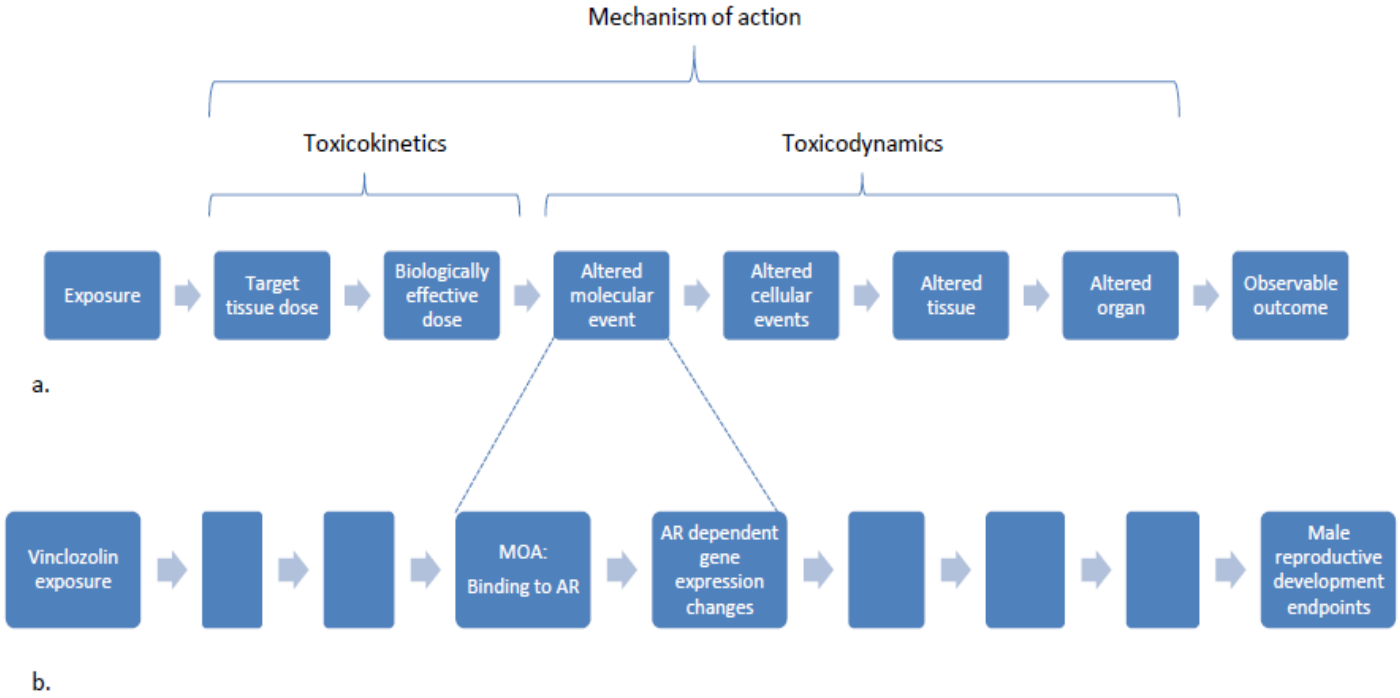
Definition(s)

Proof-of-causality



- **Scientific vs legal**
  - REACH: “probable serious effects”
  - PPPR: “may cause adverse effects…”

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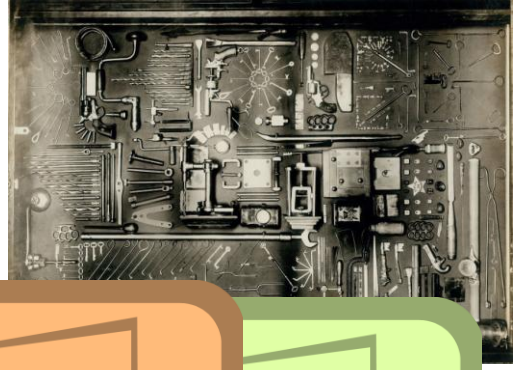
Tests



Scientific summary

OECD Conceptual Framework Guidance

Novel endpoints DRP

REACH

PPPR

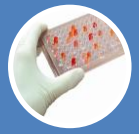
Disease

Taxon

Mode-of-action

Critical windows of exposure

Human or population relevance



Assay/endpoints

Testing requirements

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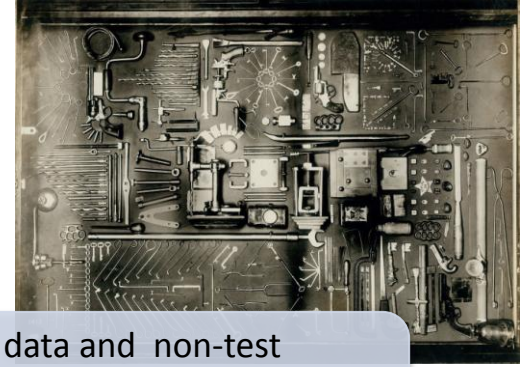
Tests - REACH



Human health

Level 1	• Existing data and non-test information • e.g. QSAR, Read-across
Level 2	
Level 3	
Level 4	• 28-day repeated toxicity study TG 407 (annex VII)
Level 5	• 2-generations reproductive toxicity TG 416 (Annex X)

Ecotoxicology

Level 1	• Existing data and non-test information • e.g. QSAR, Read-across
Level 2	
Level 3	
Level 4	
Level 5	

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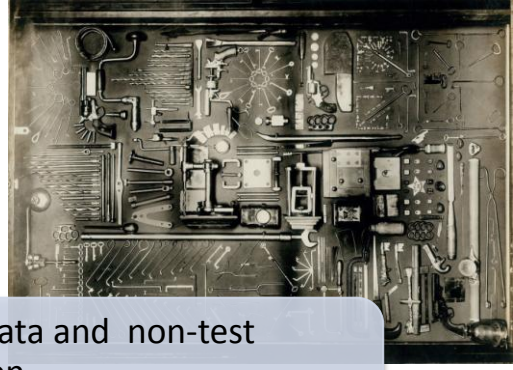
Tests - PPPR



Human health

Level 1	• Existing data and non-test information • e.g. QSAR, Read-across
Level 2	
Level 3	
Level 4	• 28-day repeated toxicity study (TG 407)
Level 5	• 2-generations reproductive toxicity (TG 416)

Ecotoxicology

Level 1	• Existing data and non-test information • e.g. QSAR, Read-across
Level 2	
Level 3	
Level 4	• Avian Reproduction (TG 206)
Level 5	

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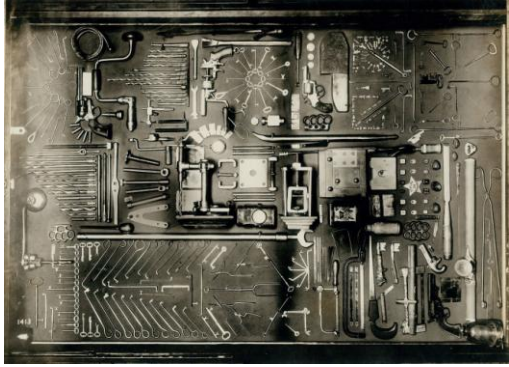
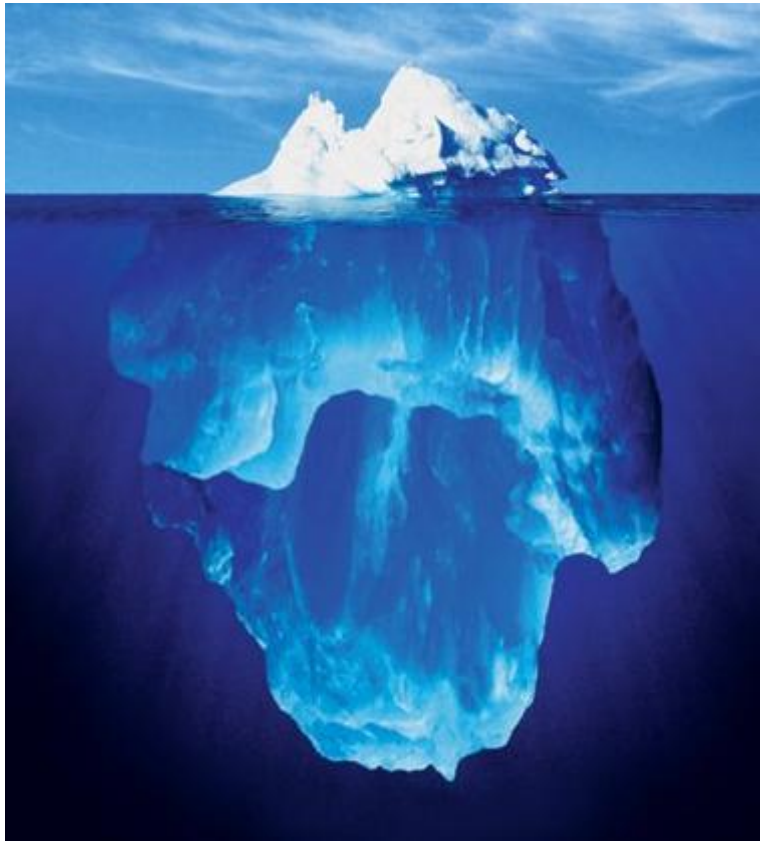
Tests





Current testing requirements

OECD Conceptual Framework

Endpoints and assays not yet validated, for which detailed guidance is not yet drafted or those included in the Detailed Review Paper

Other receptors /pathways

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Criteria

ECETOC

UK CRD

German BfR, BAuA, UBA

Joint DE-UK

French ANSES

Danish EPA

CHEM Trust

PAN

Adversity	Mode-of-action	Causality	Relevance	Specificity	Potency

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Criteria

Controversial issues

- Strength of evidence
  - GLP standardised, validated studies vs peer-review
  - CLP definitions consistent with IARC
- Lead toxic effect
- Potency-based cut-offs

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Criteria

Potency-based cut-offs

- Equivalent concern with CMRs or PBT, vPvBs
- Across legislations (different data requirements)
- STOT-RE cut-off values are arbitrary

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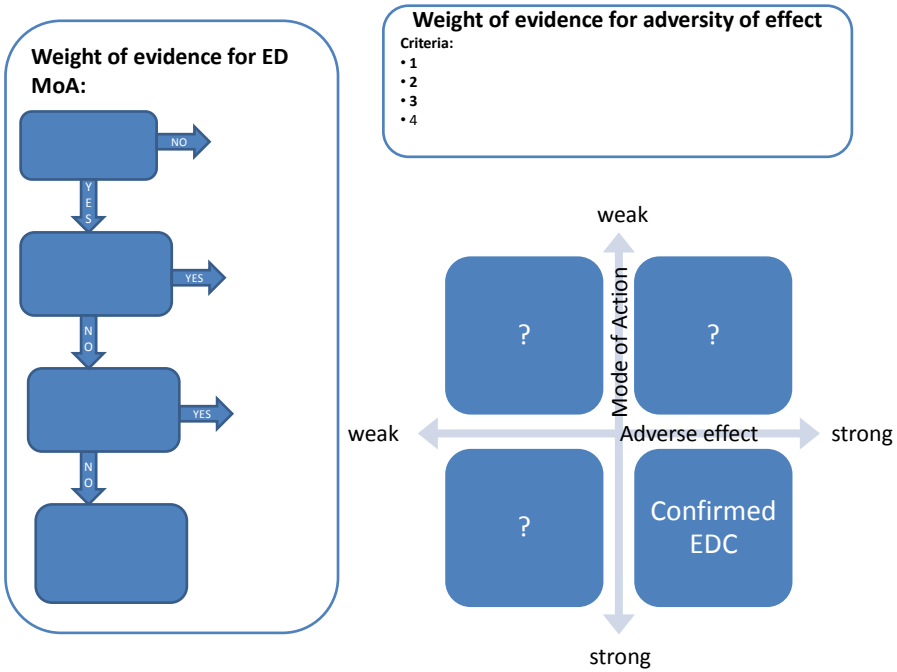
Recommendations

Decision tree



1. Evidence for adversity and mode-of-action should be considered in parallel rather than in sequence.
2. Human or ecological relevance
3. Toxicological evaluation
   - Potency
   - Lead toxicity
   - Specificity
   - Severity
   - Irreversibility
4. Classification and categorisation

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Recommendations

- Implementation of **test methods** as part of information requirements
- Further development of **guidance documents** for the interpretation of test data
- Develop **weight of evidence procedures** for criteria “adversity” and “mode of action” in an inclusive, but not mutually exclusive, way
- Create regulatory categories that **stimulate the provision of data**

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