State-of-the-Art Assessment of Endocrine Disrupters
An overview of the final report of the EU/DG Environment Project

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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
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
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
Definition(s)

Mode-of-action

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

Definition(s)

Scientific vs legal

- REACH: “probable serious effects”
- PPPR: “may cause adverse effects...”
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
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**
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**
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
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
Criteria

Potency-based cut-offs

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