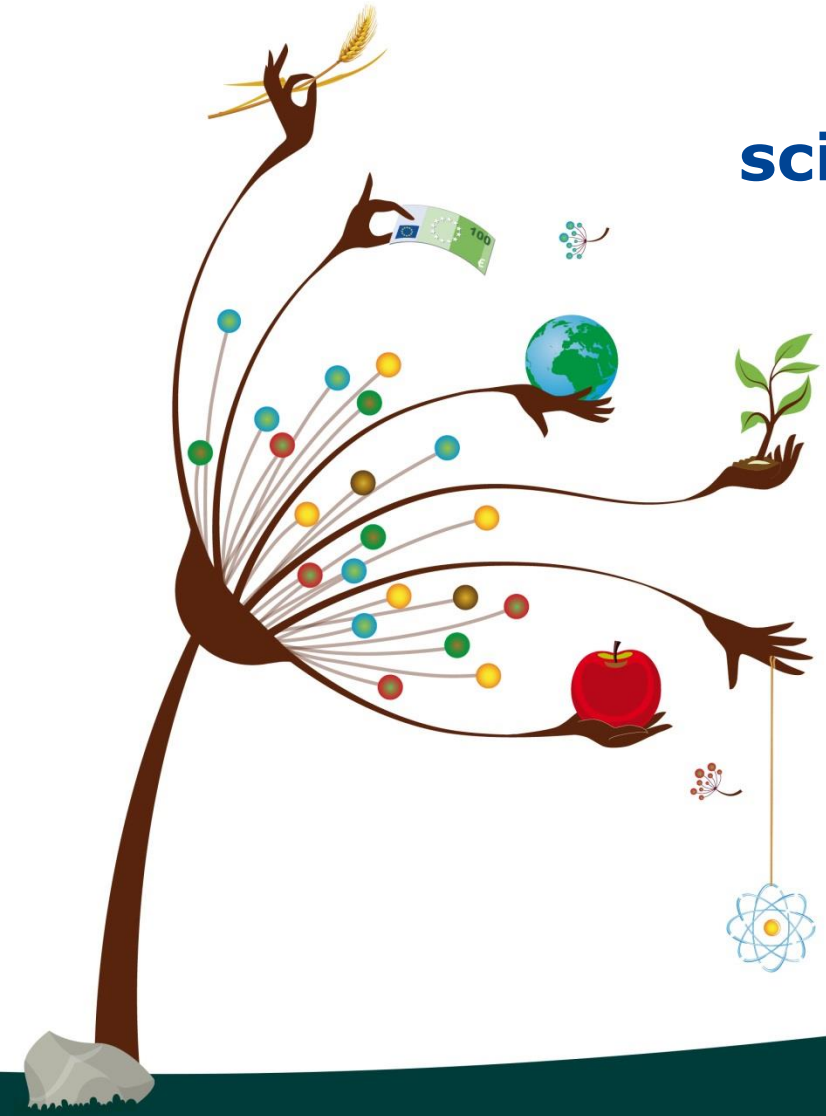
European Commission



The European Commission's science and knowledge service

Joint Research Centre

Endocrine disruptors: EURL ECVAM activities related to validation

Elise Grignard

Joint Research Centre

EU legislative background on endocrine disruptors

- 1996, "Weybridge report", potential impacts of endocrine disruption on the health of humans and wildlife
- 1999, Community Strategy for Endocrine Disruptors (COM(1999)706)
  - ✓To identify the problem of endocrine disruption, its causes and consequences
  - ✓ To identify appropriate policy action on the basis of the precautionary principle

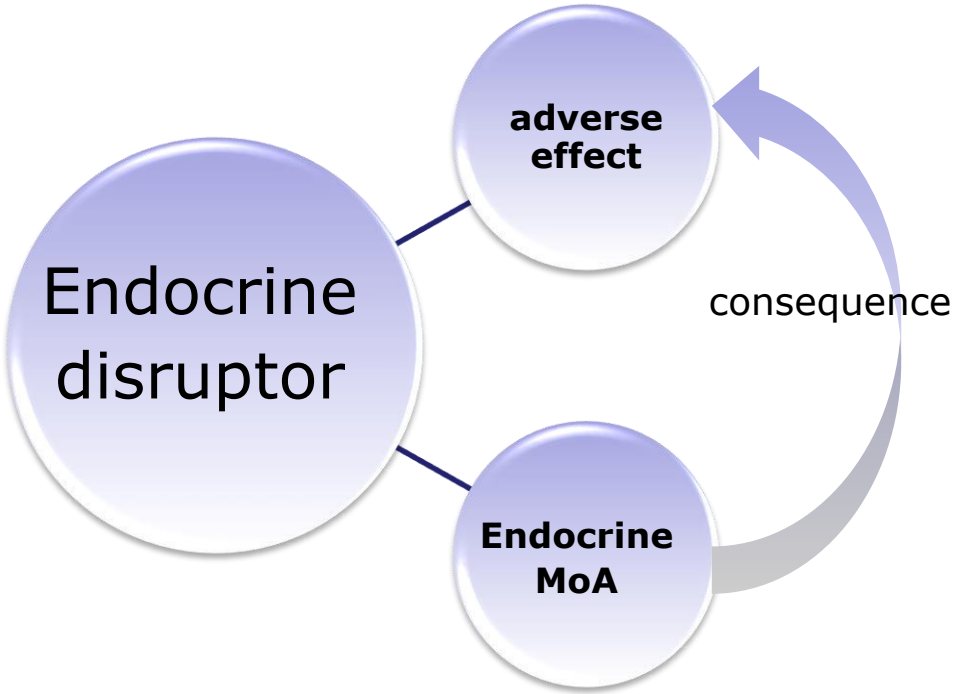
EU legislative background on endocrine disruptors

- Plant Protection Products Regulation (EC 1107/2009)
- Biocidal Products Regulation (EU 528/2012)
- Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH, EC 1907/2006)
- Cosmetic Products Regulation (EC 1223/2009)
- Water Framework Directive (2000/60/EC)

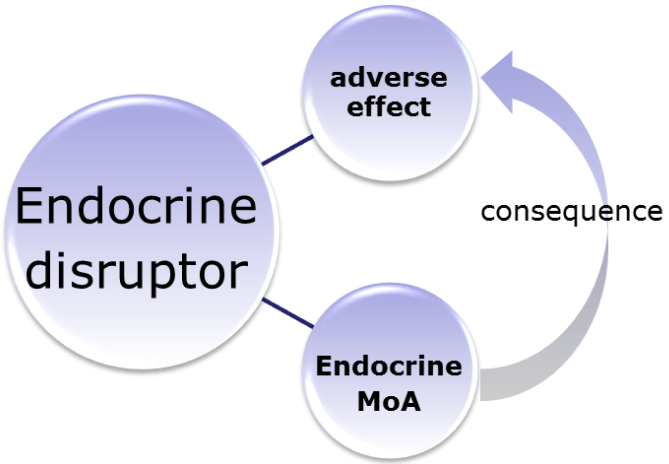
Draft criteria to identify endocrine disruptors

- published 15 June 2016

"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" (IPCS/WHO, 2002)

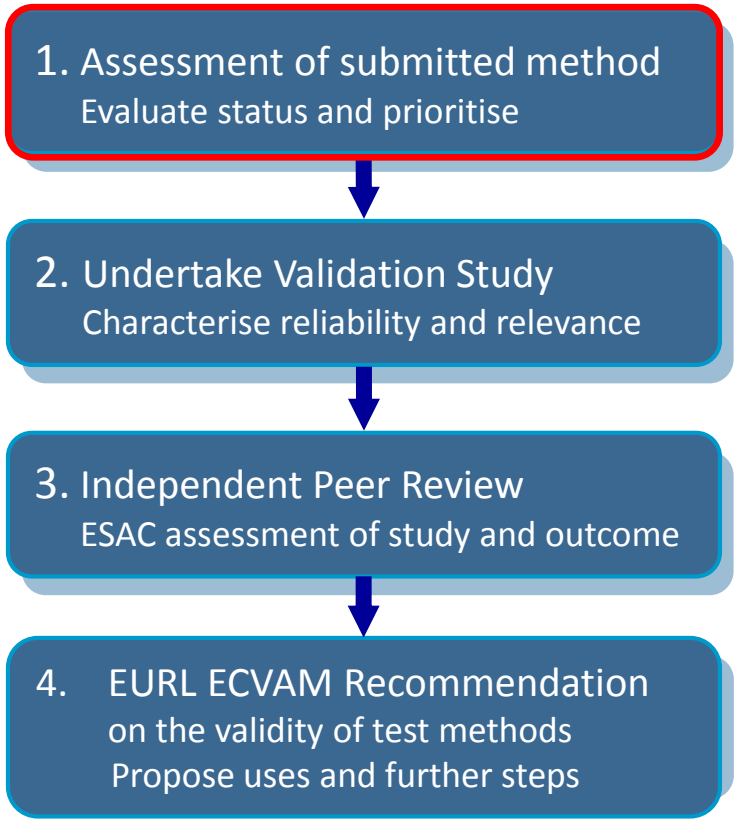


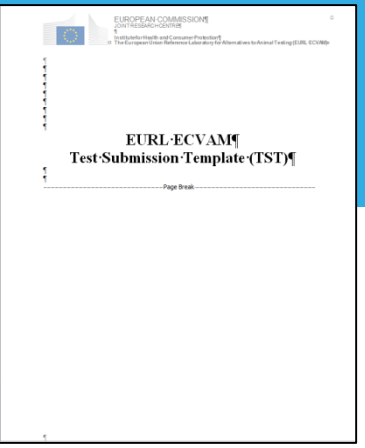
Draft criteria to identify endocrine disruptors

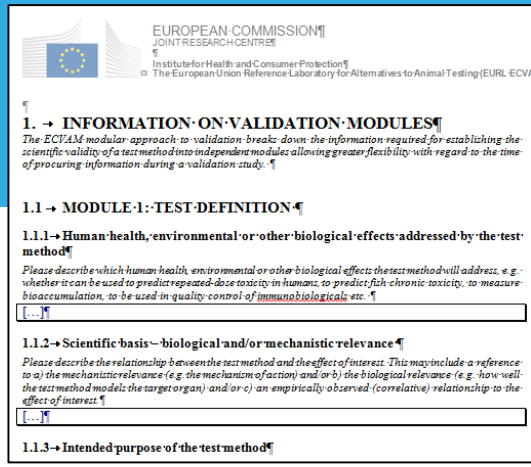


- Need to develop mechanistic assays in order to identify the mode of action
- Expand beyond EATS

EURL ECVAM Validation Workflow




EURL·ECVAM¶
Test·Submission·Template·(TST)¶


EUROPEAN·COMMISSION¶
JOINT·RESEARCH·CENTRE¶
Institute·for·Health·and·Consumer·Protection¶
The·European·Union·Reference·Laboratory·for·Alternatives·to·Animal·Testing·(EURL·ECVA

1. → INFORMATION·ON·VALIDATION·MODULES¶

The·ECVAM·modular·approach·to·validation·breaks·down·the·information·required·for·establishing·the·scientific·validity·of·a·test·method·into·independent·modules·allowing·greater·flexibility·with·regard·to·the·time·of·procuring·information·during·a·validation·study.·¶

1.1 → MODULE·1:·TEST·DEFINITION·¶

1.1.1→ Human·health,·environmental·or·other·biological·effects·addressed·by·the·test·method¶

Please·describe·which·human·health,·environmental·or·other·biological·effects·the·test·method·will·address,·e.g.·whether·it·can·be·used·to·predict·repeated-dose·toxicity·in·humans,·to·predict·fish·chronic·toxicity,·to·measure·bioaccumulation,·to·be·used·in·quality·control·of·immunobiologicals·etc.·¶

[…]¶

1.1.2→ Scientific·basis·–·biological·and/or·mechanistic·relevance¶

Please·describe·the·relationship·between·the·test·method·and·the·effect·of·interest.·This·may·include·a·reference·to·a)·the·mechanistic·relevance·(e.g.·the·mechanism·of·action)·and/or·b)·the·biological·relevance·(e.g.·how·well·the·test·method·models·the·target·organ)·and/or·c)·an·empirically·observed·(correlative)·relationship·to·the·effect·of·interest.·¶

[…]¶

1.1.3→ Intended·purpose·of·the·test·method¶

Assessment of test submissions

- Scientific plausibility
- Possible contribution of the test method to the 3Rs principles
- Regulatory relevance

Assessment of test validity

Test definition	• Scientific purpose • Mechanistic basis • Standard Operating Procedure
Within-laboratory variability	• Variability over time, and for different operators
Transferability	• Demonstrates robustness of test • Evaluate the practicability of the test
Between-laboratory variability	• To be evaluated using chemicals covering the full range of toxic effects, relevant chemical classes and physicochemical properties
Predictive capacity	• Accuracy of prediction of results
Applicability domain	• Toxicological endpoints, chemical classes, test materials, physicochemical properties and/or products for which the test can be used
Performance standards	• Definition of reference chemicals that can be used to demonstrate the equivalence in performance between a new test and a previously validated test

Reliability

Relevance

Recent submissions and current validations

- Submission of an androgen receptor transactivation assay, using yeast
  - ✓ For peer review

- Androgen receptor transactivation assay, using U2OS cells stably transfected with the full-length human androgen receptor and a luciferase reporter gene (AR CALUX)

Current activities:
Androgen Receptor Transactivation Assay

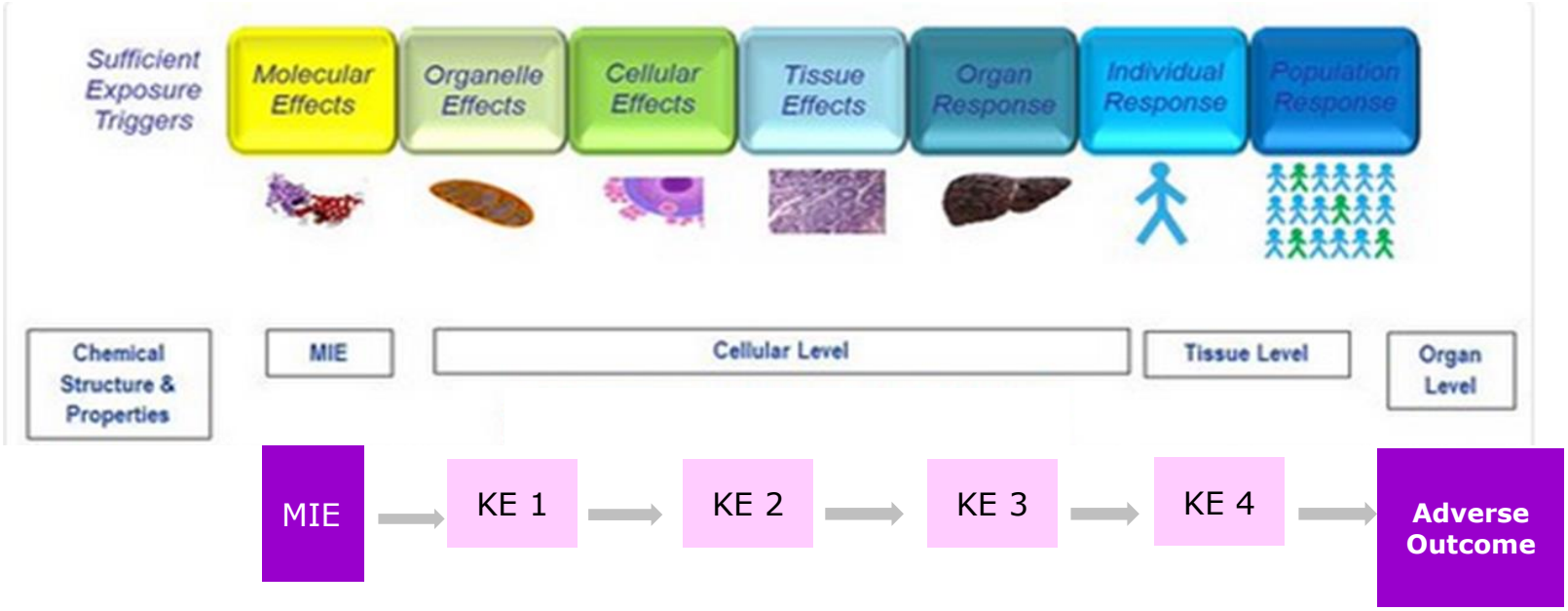
- Validation of the method AR CALUX
  - ✓ Assessment of submission
  - ✓ Implementation in EURL ECVAM, and optimisation of SOPs
  - ✓ Validation exercise
    - managed by EURL ECVAM, and a validation management group
    - 3 laboratories
    - Transfer phase finalised (6 chemicals)
    - Next phase: 10 chemicals, blind-coded

Current activities:
Androgen Receptor Transactivation Assay

- Development of Performance Standards
  - ✓ Work in the framework of OECD VMG-NA
  - ✓ Taking into account other ARTA methods (validated and undergoing validation)
    - Essential test method components
    - A minimum list of reference substances
    - Test method performance and reliability values

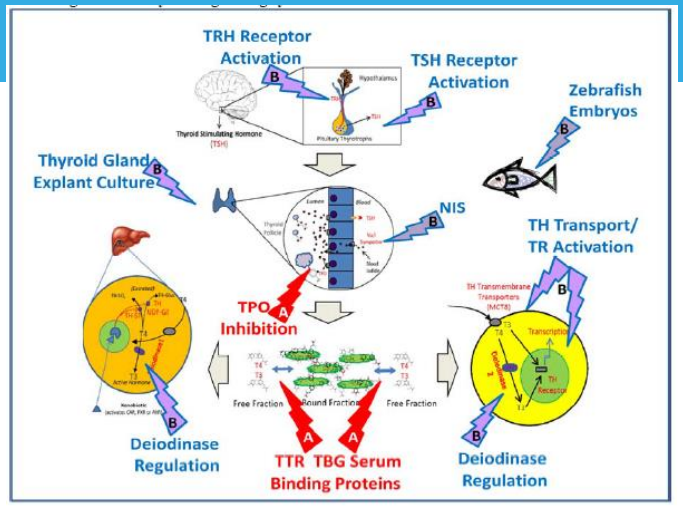
Current activities

- In support to
  - ✓ Need of mechanistic (mode of action) information for the development of Adverse Outcome Pathways



  - ✓ Expand knowledge on, and beyond EATS pathways

Current activities



- Thyroid
  - ✓ Multiple aspects of the regulation of the thyroid
  - ✓ Sensitive endpoints
  - ✓ Cross species extrapolation

- Retinoic acid Pathway
  - ✓ Importance: fertility, development, vision, cardio-vascular function …

OECD, 2014

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