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EFSA Scientific Committee Opinion on the hazard assessment of endocrine disruptors

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Mandate

Terms of Reference

1. What scientific criteria should be used to identify Endocrine Disruptor (EDs)

2. What is an adverse effect and how can it be distinguished from physiological modulation?

3. Are existing toxicity testing methods appropriately covering the effects of endocrine active substances

Methodology to develop the opinion

Sources of information

- No systematic review of the literature
- National (FR, UK/DE, DK, SE position papers
- European (Kortenkamp SAAED, Weybridge (1997) and Weybridge+15 (2012) reports)
- International (OECD GD and test guidelines, WHO assessment of the state of the science of EDs 2002 and 2012)
- Stakeholders (PAN Europe, CHEM Trust and ECETOC position papers)

Application of the general risk assessment principles for the evaluation of collected information, see Scientific Committee Guidance on Transparency (2009)

Definitions

Endocrine Active Substance (EAS)

Substance with the ability to interact directly or indirectly with the endocrine system, and subsequently result in an effect on the endocrine system, target organs and tissues; there is however uncertainty as to whether it is likely to produce adverse effects measured on apical endpoints *in vivo*. *(EFSA, 2010)*

Endocrine Disruptor (ED)

"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)

Adversity

"Change in the morphology, physiology, growth, development, reproduction, or, life span of an organism, system, or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences." (WHO/IPCS EHC 240, 2009)

Criteria for identifying EDs (ToR I)

Endocrine activity with adverse effect → ED

Endocrine activity is a mode of action and not an (eco) toxicological endpoint in itself

Adversity to be demonstrated *in vivo* (human health) or at a population level (environment)

EAS = ED if biologically plausible link between the induced endocrine perturbation and the adverse effect

Scientific criteria for assessment of adversity have not been generally defined. It is therefore difficult to propose ED-specific criteria for adversity (ToR II)

ED identification: additional considerations

- Data for endocrine activity / adverse effect with demonstrated robustness are acceptable - No need for the test method to be internationally validated

- No difference in the level of evidence needed to demonstrate the endocrine activity / adverse effect

- By default, any adverse effect seen in toxicity studies is relevant to humans, unless non-relevance is demonstrated

- It will never be possible to demonstrate that a substance is not endocrine active

Availability and appropriateness of test methods

OECD Conceptual Framework is used as starting point

It comprises *in vitro* and *in vivo* test methods that are (or soon will be) validated in **5 Levels**

Level 1 – Existing data and non-test information

- Physical & chemical properties, e.g., Molecular Weight reactivity; volatility, biodegradability.
- All available information including:
  - ✓ Epidemiological data
  - ✓ Field data
  - ✓ (Eco)toxicological data from standardised or non-standardised tests
  - ✓ Read across, chemical categories, (Quantitative) Structure Activity Relationship ((Q)SARs) and other in silico predictions, and Absorption, Distribution, Metabolism and Excretion (ADME) model predictions

Their strengths and weaknesses are discussed in the opinion

Availability and appropriateness of test methods

Levels 2 to 5 - *In vitro* and *in vivo* assays providing data about selected endocrine mechanism(s)/pathways and on adverse effects on endocrine-relevant endpoints

EATS (oestrogen/androgen/thyroid/steroidogenic) endocrine modalities

- *In vitro* tests based on mammalian systems: only applicable for detecting oestrogen/androgen/steroidogenic activity
- *In vitro* tests based on other vertebrate systems: will be potentially covered in the future when additional test guidelines become available
- *In vivo* tests with vertebrates: most of the EATS modalities and their apical effects are detectable for mammals, fish and (to a lesser extent) amphibians. No standardised assays for reptiles, and only apical assays in birds
- *In vivo* tests with invertebrates: no standardised mechanistic assays available; some apical (reproduction) assays are under development

Availability and appropriateness of test methods

Non-EATS endocrine modalities

- *In vitro* and *in vivo* tests for mammals: no validated mechanistic screens developed yet, although work is ongoing; some apical tests validated for EATS modalities may also be sensitive for non-EATS modalities.
- *In vitro* and *in vivo* tests for the environment: no mechanistic assays; some apical tests validated for EATS modalities may also be sensitive for non-EATS modalities
  - ✓ Aquatic vertebrates: non-validated *in vitro* mechanistic assays for some modalities already exist; the major gap concerns in vivo mechanistic assays
  - ✓ Aquatic invertebrates: absence of in vivo mechanistic assays for all modalities in invertebrates due to poor knowledge of endocrinology in many invertebrate phyla

General considerations on appropriateness of test methods

- Whole life-cycle analysis for mammalians and tests for non-EATS modalities need further development
- Apply a weight-of-evidence approach: in principle, no single test can identify an ED, since MoA from mechanistic information + adversity from apical information is required
- Limitations of animal tests exist with respect to certain human endocrine disorders (e.g. endometriosis) in which EDs have been suggested to play a role
- Guidance for interpretation of the different tests is also available from OECD but need for further development of testing strategies to generate adequate data for the identification and assessment of endocrine disrupting properties

Appropriateness of current assessment methods

Not unique to EAS

- **Critical windows of susceptibility**

  Some OECD Level 4&5 tests cover critical windows of development *in utero*, however, current mammalian tests do not cover certain effects that might be induced during foetal or pubertal development which may emerge during later life stages

- **Multiple chemical exposures**

  Exposure to multiple EAS could occur in such a way that combined toxicity could arise. The issue of combined exposure to multiple chemicals is being addressed by EFSA in separate activities

- **Low-dose effects and Non-Monotonic Dose Response Curves**

  No consensus as to their existence/significance in connection to endocrine activity, ED or other endpoints/modes of actions. If triggered by unusual findings, an extended dose/concentration-response analysis could be performed

Hazard characterisation

Not needed to identify an ED but the following may be considered when discussing levels of concern

- **Critical effect**

  Hazard characterisation should be based on the effect leading to the lowest health/ecotoxicology-based guidance value

- **Severity / Irreversibility / Potency**

  These aspects should not be used alone, but be evaluated in relation to degree and duration of exposure, as well as timing of exposure

Whether or not a specified level of concern is reached, can only be determined by risk assessment

Conclusions

- A lot of similarities between the EFSA opinion and the JRC Report: same definitions, same criteria for identifying EDs

- Complementarity of the documents:

  - JRC more descriptive on the level of evidence needed to characterise endocrine activity, adverse effect and the plausible link between the two, with consideration of case studies

  - EFSA more descriptive on the tools and test methods available, discussing their suitability and gaps

"To inform on risk and level of concern, it is the opinion of EFSA Scientific Committee that risk assessment makes best use of available information"

Recommendations

Specific to EAS

- Invest on further development of test/screen methods
- Further research needed on whether exposures to chemical substances, which could affect non-EATS modalities, are associated with adverse effects in humans or in the environment
- Need for further development of testing strategies to generate adequate data for the identification and assessment of endocrine disrupting properties

General

- Clarify in a broader context the issues of biological thresholds and criteria for adversity, combined exposure to multiple substances and non-monotonic dose response curves