EU Conference on Endocrine Disruptors

Session 1: Scientific debate on criteria to identify EDs. The view of science

EFSA SC Opinion on the hazard assessment of endocrine disruptors

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MANDATE

Terms of Reference (Commission 2012, published March 2013):

1. What scientific criteria should be used to identify 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?

The EFSA opinion should take stock of already existing information.

Other scientific advisory bodies, incl. EMA, ECHA, EEA and the EC Scientific Committees should be involved during the preparation of the opinion.

METHODOLOGY (1/2)

Expertise needed to address the question:

- Endocrinology (general, human, environmental)
- Risk assessment
- Toxicology (general, human, environmental)
- Up-to-date knowledge of OECD test methods for EAS

Working Group composition:

- Experts with the above areas of expertise from EFSA SC and Panels
- EFSA Expert Database
- Observers from EC (SANCO + JRC), EMA, ECHA, EEA
- Link with related work from international organisations:
  - OECD
  - WHO

METHODOLOGY (2/2)

Sources of information:

- Limited timeframe → no systematic review of the literature
- National (FR, UK/DE, DK, SE position papers, input from the focal points)
- European (Kortenkamp SAAED, Weybridge and Weybridge+15 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 SC Guidance on transparency (2009)

DEFINITION

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

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).
- No generic criteria available for differentiating adverse effect from endocrine modulation
- EAS = ED if biologically plausible link between the induced endocrine perturbation and the adverse effect.

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.
- 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 an ED.
- Need for a testing strategy to generate appropriate data (currently lacking)

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**: Consideration of epidemiological data (for humans), field data (for wildlife), computational toxicology and non-test methods at this level. Their strengths and weaknesses are discussed in the opinion.
- **Level 2**: In vitro tests cover sufficiently well the detection of endocrine activity through the Oestrogen & Androgen receptor and Steroidogenesis modalities for mammalians. Tests for Thyroid receptor are in the pipeline and non-mammalian tests are under discussion.
- **Levels 3 to 5**: In vivo tests cover sufficiently well the detection of endocrine activity through the Oestrogen & Androgen & Thyroid receptor and Steroidogenesis modalities for mammalians and fish (and lesser extent amphibians). For birds, validation is ongoing and for invertebrates tests are under discussion.

APPROPRIATENESS OF CURRENT ASSESSMENT METHODS

Not specific to EAS

- **Critical windows of susceptibility:**

Some OECD 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 will be addressed by EFSA in a separate activity.

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

No consensus as to their 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 some elements 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 be evaluated in relation to degree and duration of exposure, as well as timing of exposure.

In conclusion: to inform on risk and level of concern for the purpose of RM decisions, RA (taking into account hazard and exposure data/prediction)makes best use of available information. EDs can be subject to RA and not only to hazard assessment.

RELATED ACTIVITIES SINCE 2010

EFSA

- Systematic Review methodology (guidance 2010)
- Expert Knowledge Elicitation (guidance 2014)

Scientific Committee (work ongoing)

- Uncertainty in RA
- Weight of Evidence
- Biological Relevance

- Review of non-monotonic dose-response of substances for human RA (ongoing)

TIMELINES FOR SC GUIDANCES

- ✓ **Uncertainty in RA**: public consultation in summer 2015, finalisation draft guidance end 2015, testing phase until summer 2016, finalisation guidance end 2016
- ✓ **Weight of Evidence**: public consultation probably in 2016, finalisation Sept 2017
- ✓ **Biological Relevance**: probably a public consultation in early 2016, finalisation end 2016

REVIEW OF NON-MONOTONIC DOSE-RESPONSE OF SUBSTANCES FOR HUMAN RISK ASSESSMENT

- Overall objective: critically review literature to evaluate the evidence for NMDR hypothesis in the last decade (from 2002 onward) for substances (other than essential nutrients) in the food safety area

- Reference: GP/EFSA/SCER/2014/01
- Grant procedure awarded to Consortium ANSES (leader)+ AGES +Karolinska Institute + RIVM
- Duration: 18 months
- Completion of report: end 2015
- To be published: probably January 2016

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ANY QUESTIONS?