Proposal for criteria for identification of endocrine disruptors‡

Human Health

Data from intact animals*:
Strong WoE**:

- Adverse effect[4] via relevant route and at relevant doses, and
- Causal relationship between primary ED MoA and the adverse effect[5], and
- Relevance to humans cannot be excluded

Environment

Data from intact animals*:
Strong WoE**:

- Adverse population-relevant effect[4] via relevant route, and
- Causal relationship between primary ED MoA and the adverse effect[5]

High concern in terms of:

- Potency[6]
- Severity of effects[7]
- Lead toxic effect/decisive for the overall (eco)toxicological profile[7]

UNLESS (FOR ENVIRONMENTAL HEALTH)

- *Unless* it is scientifically demonstrated that under relevant field conditions there is no unacceptable effect[8]

*** When there are data from humans or animal species living in the environment they should be taken into account**

Strong WoE**:

- Adverse effect (population relevant for environmental health), and
- Demonstrated primary ED Mode of Action[1], and
- Relevant (eco)epidemiological data[2] providing evidence of causality for a specific substance

****WoE = Weight of evidence:**
'the process of considering the strengths and weaknesses of various pieces of information in reaching and supporting a conclusion concerning a property of the substance'[3]

[1] EFSA Scientific Opinion March 2013 (p. 17) http://www.efsa.europa.eu/en/efsajournal/pub/3132.htm,
[2] per STROBE Guidelines
[3] Scientific Committee on Emerging and Newly Identified Health Risks 2012 http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_s_001.pdf, ECHA Practical Guide 2, 2010 (p. 2) http://echa.europa.eu/documents/10162/13655/pg_report_weight_of_evidence_en.pdf
[4] WHO/IPCS 2002 http://who.int/ipcs/publications/en/ch1.pdf , OECD CF level IV & V http://www.oecd.org/env/ehs/testing/OECD%20Conceptual%20Framework%20for%20Testing%20and%20Assessment%20of%20Endocrine%20Disrupters%20for%20the%20public%20website.pdf
[5] Bradford Hill Criteria: Hill, Austin Bradford (1965). "The Environment and Disease: Association or Causation?". *Proceedings of the Royal Society of Medicine* 58 (5): 295-300 and OECD CF level IV & V
[6] Based on Specific Target Organ Toxicity Repeated Exposure (STOT-RE) as seen in DE/UK position paper 2011 (p. 6)
[7] EFSA Scientific Opinion March 2013 (p. 42)
[8] Biocides Regulation (EU) No. 528/2012, Annex VI, also relevant to industrial chemicals and pesticides

‡ *This proposal is for criteria for the purposes of hazard assessment; substances should be subject to comprehensive risk assessment, considering both hazard and exposure.*

Explanatory note on the proposal for criteria for identification of endocrine disruptors

The above proposed criteria to identify substances of regulatory concern take into account both human health and environmental concerns. They are protective, clear, and based on the views expressed in EFSA's Scientific Opinion[1] and the report of the ED Expert Advisory Group (hosted by JRC)[2]. The criteria apply a weight of evidence approach – using all available data – to ensure a balanced, transparent and scientifically robust approach. The main goal is to identify Endocrine Disruptors (EDs) of concern such that appropriate regulatory action can be taken continuing to ensure a high level of human and environmental health.

The concept includes a single set of criteria to identify ED substances. This is consistent with the legislative mandate under Regulation 1107/2009 (PPPs) and Regulation 528/2012 (Biocides) which requires the Commission to develop *"…scientific criteria for the determination of endocrine disrupting properties…"*. There is no legal requirement to establish a categorisation scheme for ED which appears to be the preferred approach of DG Environment. A categorisation scheme also has no scientific foundation: using the CMR[3] classification scheme for ED is inappropriate as CMR represent well-defined adverse effects (suitable for categorisation). Endocrine disruption, however, is a very general descriptor that encompasses many different modes of action with the potential to lead to many different adverse effects also of variable severity and concern.

The attached concept for the ED criteria is based on the **WHO/IPCS definition**[4] for an ED. The key elements of this definition are the occurrence of an adverse effect via an endocrine mode of action; i.e. in order for a substance to be considered as an endocrine disruptor it must be demonstrated that the adverse effect(s) are caused via an interaction with the endocrine system. This must also occur in an intact animal (as opposed to animals that have been modified, i.e. surgically).

The concept considers both the **weight of evidence**[5] in evaluating potential endocrine-mediated effects, and the **relevance (e.g., lead toxicity, severity, potency) of the adverse effect** resulting from an endocrine mode of action. The concept can be used to identify a level of concern and subsequent regulatory action.

Specific regulatory action as stipulated under the PPP and biocides regulations or consideration for inclusion in the list of SVHCs under REACH should be restricted to those substances that meet all the criteria outlined below. Risk assessment and risk management methodologies are suitable for

[1] EFSA Scientific Committee; Scientific Opinion on the hazard assessment of endocrine disruptors: scientific criteria for identification of endocrine disruptors and appropriateness of existing test methods for assessing effects mediated by these substances on human health and the environment. EFSA Journal 2013;11(3):3132, http://www.efsa.europa.eu/en/efsajournal/pub/3132.htm

[2] Key scientific issues relevant to the identification and characterisation of endocrine disrupting substances - Report of the Endocrine Disrupters Expert Advisory Group, 2013

[3] Carcinogenic, mutagenic or toxic for reproduction as defined in the CLP Regulation.

[4] The WHO/ICPS definition defines an ED as an "*exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse effects in an intact organism, or its progeny, or (sub) populations"*. The WHO/IPCS further defines an adverse effect as 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"*.

[5] Following the internationally recognised principals for weight of evidence assessment: SCENIHR (Scientific Committee on Emerging and Newly Identified Health Risks), Memorandum on the use of the scientific literature for human health risk assessment purposes – weighing of evidence and expression of uncertainty, 19 March 2012. http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_s_001.pdf

ED as for any other chemical substance. All other substances where endocrine activity causes effects of low relevance or for which the available strength and weight of evidence does not lead to a concern should be managed through the standard procedures in line with the respective EU Regulation and guidance. These regulations already provide a high level of protection for human health and environment.

Proposed ED criteria:

Data from intact animals (human health and environment)

- ***Strong weight of evidence, including:***

  - ***Adverse effect in intact organism via relevant route of exposure and at relevant doses/ Adverse population relevant effect via relevant route of exposure and at relevant doses and demonstrated primary ED mode of action***
    - Primary test methods for detecting adverse effects on endocrine relevant endpoints in intact animals are levels 4-5 studies of the OECD conceptual framework for the testing and assessment of endocrine disrupting chemicals e.g. the rodent two-generation reproductive toxicity study (TG 416), the extended one-generation reproductive toxicity study (TG 443), the rodent chronic toxicity and carcinogenicity studies (TG 451, TG 452, TG 453), the enhanced 28 day toxicity study (TG 407) and fish sexual development test (TG 234).
    - Evidence for the endocrine mode of action includes an appropriate and consistent set of mode of action data providing scientifically valid support that the adverse effects seen in studies in intact animals are due to a demonstrated primary endocrine mode of action (i.e. the temporal association of the biochemical and cellular events and the adverse effect should be described and understood). This evidence can be provided by validated *in vitro* and *in vivo* screening studies providing data about selected endocrine mechanisms or pathways such as levels 2–3 studies of the OECD conceptual framework for the testing and assessment of endocrine disrupting chemicals e.g. the estrogenic receptor transcriptional activation test (TG 455), the steroid genesis in vitro test (TG 456), the MCF-7 cell proliferation assay, the uterotrophic assay (TG 440), and the Hershberger assay (TG 441).
    - Furthermore an assessment of whether the endocrine mode of action is relevant to humans should be made. The assumption for substances requiring specific regulatory action for ED is that the relevance to humans cannot be excluded.
    - Results from *in vivo* studies should be using physiological (i.e. relevant) routes of exposure (i.e., oral (preferably), dermal or inhalation).

  - ***Causal relationship between primary ED Mode of Action and the adverse effect***[6]
    - The adverse effect must be demonstrated to be mediated via an endocrine mode of action.

  - ***Relevant epidemiological data or relevance to humans cannot be excluded/Relevance to animal species living in the environment cannot be excluded***
    - In relation to establishing that an endocrine-disrupting process applies to a particular effect and is of human relevance, a structured framework such as the IPCS mode of action framework[11] should be used to carry out a weight of evidence evaluation of the available information to reach a transparent and robust conclusion. Where a definitive

[6] Bradford Hill Criteria, see Reference No 15.

conclusion cannot be reached, then the evaluation should highlight what additional data may help to provide the necessary clarification.[7]

- ***Potency***
  - Potency should be considered as part of the weight of evidence assessment to decide whether a substance requires specific regulatory action for ED. The endocrine mediated lead adverse effects should have been observed in intact animals at doses equal or below the dose thresholds, such as have been specified under the European CLP Regulation (EC) No 1272/2008 for classification of a substance as a Category 1 'Specific Target Organ Toxicity' following repeated exposures ("STOT-RE").[8]

- ***Severity of effects***
  - As mentioned above, severity may be defined as the degree of difference from the untreated population either at the individual or population level.[9]

- ***Lead toxic effect/decisive for the overall (eco)toxicological profile***[10]
  - Endocrine-mediated adverse effects should only be considered if they are the most sensitive/lead toxic effect of the substance; i.e. there is a clear and significant endocrine-mediated toxic effect that occurs at a dose/exposure level lower than those producing other manifestations of toxicity and therefore drives the risk assessment. For substances where an ED mediated effect is not the lead toxic effect, the effect occurring at the lowest dose will require risk management measures which will also protect against any potential ED mediated effect. Furthermore an assessment of whether the endocrine mode of action is relevant to the environment should be made including an evaluation of the population relevance in regard to environmental protection goals.

- ***Unless for environmental health (field conditions)***
  - Unless it is scientifically demonstrated that under relevant ***field conditions*** there is no unacceptable effect. This unless clause is cited from Regulation 528/2012 (biocides), Annex VI, but is also relevant to industrial chemicals and pesticides.

- ***Strong evidence***
  Strong evidence includes also that the endocrine mediated adverse effect must be the **lead toxic effect** and is not considered to be a secondary non-specific consequence of other toxic effects. The lead toxic effect is considered as the effect occurring at the lowest dose/concentration and describes the most sensitive (eco)toxicological response within the totality of the toxicity database. When assessing the lead effect consideration should also be given to its **irreversibility and severity**. Severity may be defined as the degree of difference from the untreated population either at the individual or population level[11] and may describe the magnitude of an adverse effect and/or the qualitative nature of the effect.[12]

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[7] Boobis et al. (2006) IPCS framework for analysing the relevance of a cancer mode of action for humans. Crit. Rev. Toxicol. 36, 781-792.
[8] See also DE/UK position paper, May 2011 (p. 6)
[9] EFSA Scientific Opinion, March 2013 (see 1 above for the full reference)
[10] EFSA Scientific Opinion, March 2013 (p. 42) (see 1 above for the full reference)
[11] Risk assessment of endocrine active chemicals: identifying chemicals of regulatory concern. Bars R et al. Regul Toxicol Pharmacol, 2012 Oct; 64(1):143-54
[12] EFSA Scientific Opinion, March 2013 (p. 42) (see 1 above for the full reference)

In case that data from humans or animal species living in the environment are available:

- ***Strong weight of evidence, including:***
    - An adverse effect (population relevant for environmental health) demonstrated to be mediated through an endocrine mode of action[13]
    - Evidence from human data shall be from well-conducted epidemiological studies reported in line with e.g. STROBE guidelines[14] and based on a balanced assessment using e.g. the Bradford-Hill criteria[15].
    - Strong evidence can be determined following a weighing of the available evidence such as described by SCENIHR, 2012.[16]
    - Causality - the adverse effect demonstrated to be mediated via an endocrine mode of action.

Finally, validated testing methods and criteria have been developed on the basis of the scientific understanding of endocrine-mediated effects. Data generated in line with the OECD conceptual framework for the testing and assessment of endocrine disrupting chemicals should be used to assess substances against the criteria. Relevant scientific peer-review literature may also be considered, however a review of the quality of such literature (as with all evidence) should be made (e.g. using the Klimisch criteria).

Data and information on the above mentioned factors should be carefully assessed using a structured weight of evidence approach, considering quality and consistency of data.

[13] EFSA Scientific Opinion, March 2013, p. 17 (see 1 above for the full reference)
[14] STROBE stands for an international, collaborative initiative of epidemiologists, methodologists, statisticians, researchers and journal editors involved in the conduct and dissemination of observational studies, with the common aim of Strengthening the Reporting of Observational studies in Epidemiology. http://www.strobe-statement.org/index.php?id=available-checklists ; The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Von Elm E et al., Epidemiology. 2007, Nov; 18 (6): 800-4.
[15] Austin Bradford Hill, "The Environment and Disease: Association or Causation?" *Proceedings of the Royal Society of Medicine*, 58 (1965): 295-300.
[16] See Reference No 5.