ED Developments in Europe and their relevance to GreenScreen

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The Struggle in the EU to resolve ED Criteria

- The European Commission established an ED Strategy Group as early as 2002 which sought to build on the science based on EAT modes of action once thyroid was included
- Member State experts were involved in periodic meetings to help develop a common understanding of the criteria resulting in several EC Communications
- These contained elements such as potency and irreversibility, but the discussions did not lead to an absolutely water-tight definition of an ED
- Ahead of its Entry into Force in 2007, REACH needed to address the ED endpoint, but with no legally defendable definition, they needed to leave it to Member States to take legal responsibility for ED identification through Article 57(f)

Article 57(f) of REACH reads as follows:

Article 57

Substances to be included in Annex XIV

The following substances may be included in Annex XIV in accordance with the procedure laid down in Article 58:

(f) substances — such as those having endocrine disrupting properties or those having persistent, bioaccumulative and toxic properties or very persistent and very bioaccumulative properties, which do not fulfil the criteria of points (d) or (e) — for which there is scientific evidence of probable serious effects to human health or the environment which give rise to an equivalent level of concern to those of other substances listed in points (a) to (e) and which are identified on a case-by-case basis in accordance with the procedure set out in Article 59.

The Struggle in the EU to resolve ED Criteria

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- These contained elements such as potency and irreversibility, but the discussions did not lead to an absolutely water-tight definition of an ED
- Ahead of its Entry into Force in 2007, REACH needed to address the ED endpoint, but with no legally defendable definition, they needed to leave it to Member States to take legal responsibility for ED identification through Article 57(f)
- However, this also left Member States with the freedom to develop their own criteria and ranking schemes

Absence of EU-wide criteria has made room for schemes at Member State level

Denmark

Category 1 – Endocrine Disruptor

- Adverse in vivo effects where an ED mode of action is highly plausible
- An ED mode of action in vivo that is clearly linked to adverse in vivo effects (e.g. by read across)

Category 2a – Suspected Endocrine Disruptor

- Adverse effects in vivo where an ED mode of action is suspected
- ED mode of action in vivo that is suspected to be linked to adverse effects in vivo
- ED mode of action in vitro combined with toxico-kinetic in vivo data (and relevant non test information such as read across, chemical categorisation and QSAR predictions)

Category 2b – indicated Endocrine Disruptor

- Substances are placed in category 2b when there is in vitro/in silico evidence indicating potential for endocrine disruption in intact organisms. Additional evidence could also be observed, potentially ED-mediated in vivo effects.

Comparisons with the GreenScreen approach

- Category 1 would align well with ‘High’ under the current GreenScreen method
- Category 1 stresses ‘in vivo’ evidence of adversity with plausible link
- GreenScreen takes more account of ‘in vitro’ and ‘in silica’ as part of weight-of-evidence for decision-making
- GreenScreen looks at the quality of the data whereas the Danish process makes no explicit reference to quality
- ‘Moderate’ under GreenScreen would seem to cover both Categories 2a and 2b, hence the reason why there might be so many ‘moderate’ allocations
- There is no equivalent for ‘Low’ under the Danish system (evidence of no effect)
- In summary, there is no pressure to account for all chemicals under the Danish system so non-listed chemicals are assumed to have no ED activity

Emergence of EU ED Guidance Document

- Seeking to have a single definition horizontally across all relevant regulations (biocides, pesticides and industrial chemicals)
- EU ED Guidance Document published on 7th June 2018 in 'pre-publication' format
- Focused primarily on identifying EDs in relation to the Biocide and Pesticide Regulations where licensing depends on not being ED
- Guidance Document based on the WHO/IPCS definition
- Does not provide guidance on assessing hazard potential or risk
- Provides a systematic approach to ED identification which all EU stakeholders (especially Member States) are encouraged to follow to provide transparency in assessments

Steps in the ED Guidance Document

There are five defined steps which can be summarised as:

1. Gather all relevant information, including an evaluation of data quality;
2. Assemble, assess and integrate lines of evidence;
3. Initial analysis, e.g. have EATS (Estrogen, Androgen, Thyroid, Steroidogenic) parameters been sufficiently investigated?
4. Mode of Action Analysis;
5. Conclusion – does the substance meet the ED criteria on previous slide?

Individual Member States will now be required to follow this approach

Steps in the ED Guidance Document

Scientific criteria for EDs are agreed:

- Adverse effect in an intact organism…results in impairment of functional capacity
- Endocrine mode of action
- Adverse effect is a consequence of the ED mode of action
- "…impairment of functional capacity" – isolated organ weight changes are not necessarily indicative of functional impairment – although sometimes used for NOAEL setting
- "the adverse effect is a consequence of the endocrine mode of action" – no guidance on how plausible the link should be

Still not totally clear how this will align with *'probable serious effects'* threshold within REACH

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Steps in the ED Guidance Document

Reference to specific terms

Reversibility

- Technical description relating to Key Events in an Adverse Outcome Pathway
- A Key Event is blocked or diminished in reversibility studies

Potency

- One of the factors used to identify a category of substances – where there is a constant pattern in potency properties across the group

Threshold

- NMDR is referenced, not threshold specifically
- More likely to be detected in in vitro studies (more doses) than in vivo
- Standard tox tests are designed to identify adverse effects so chances are that any NMDR will be detected

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