German Environment Agency

Umwelt Bundesamt

ECHA workshop on applications for authorisation for environmental endocrine disrupters

Report of EU COM ED expert advisory group on thresholds for Endocrine Disrupters and related uncertainties

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Outline

1. Scope of the group
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3. Main results
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Scope of the group

- Established November 2011 as a sub-group of the ad hoc group of Commission Services, EU Agencies and Member States for the Community Strategy on Endocrine Disrupters

- Composition: toxicologists and ecotoxicologists with regulatory and/or endocrinology backgrounds from member states, Industry and NGOs

- Main role: to provide detailed reflections on scientific issues relevant to identifying and assessing endocrine disrupting substances, not specific to any regulatory framework

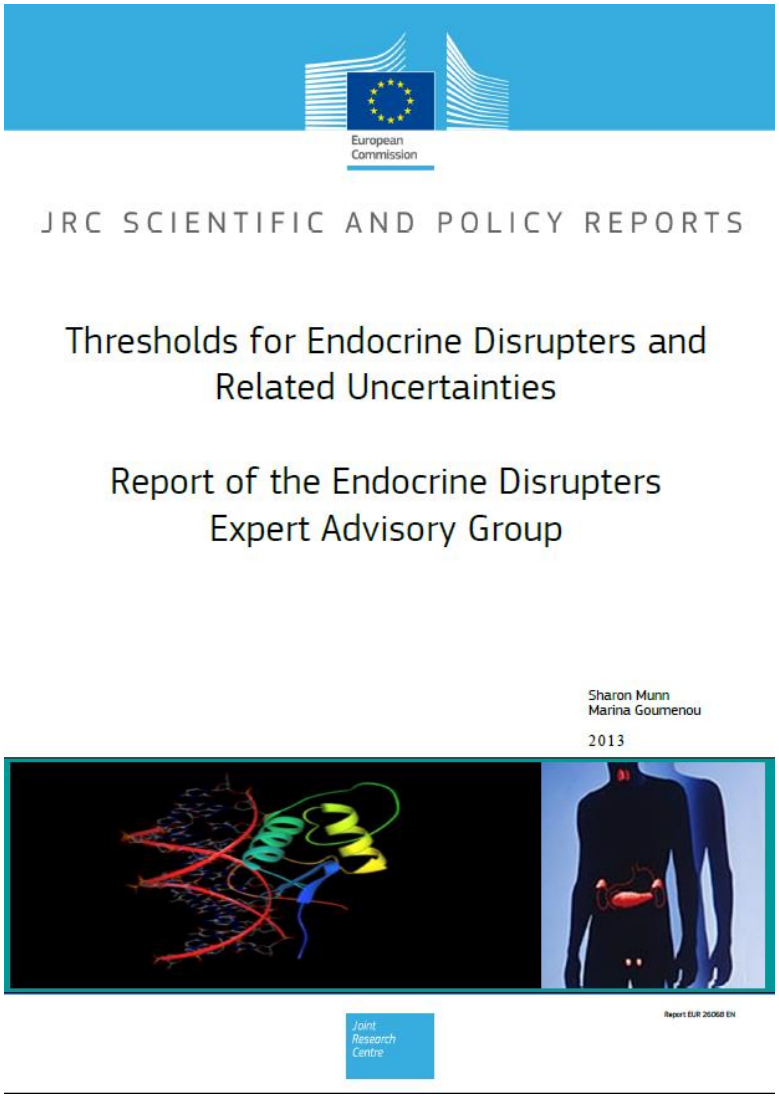
-> 2 day session at the 5th meeting of the
ED EAG on the 4 & 5th February 2013 on the topic

Topics

- Presence of absence of thresholds on the basis of mechanism of action
  - Critical windows of exposure
  - Low dose effects
  - Non-monotonic dose responses
  - Limitations of experimental approaches

- Characterising uncertainties

- Impact of mixtures on application of threshold or non-threshold approach



Expert views – mechanistic basis of threshold/non-threshold

Agreement:

- Theoretically one molecule could activate a receptor when adding to a background level of endogenous hormone and so it could be considered that there is no threshold on this level.

Majority positions:

- Most experts of the ED EAG considered that thresholds of adversity are likely to exist for EDs but may be very low for individual EDs. Some experts considered it uncertain whether there is a threshold during development.

Uncertainties:

- Several experts expressed the view that, although thresholds may exist, it might be difficult to estimate with any confidence the biological thresholds of adversity based on currently available standard tests.

Expert views:

Critical window of exposure:

- Agreement, that development is a very sensitive life stage, general agreement that this implies that it might be very difficult to determine a threshold with sufficient confidence, disagreement if this implies that no threshold exist.

Low dose effects:

- non consensus on the evidence of low dose effects, but if they exist, agreement that current tests systems might not adequately detect them**.**

Non-monotonic dose responses:

- no consensus if non-monotonic dose responses are relevant with regard to adversity. But if they exist, agreement that current tests systems might not adequately detect them.

Expert views:

Limitations of experimental approaches :

- Current tests may not cover sensitive endpoints and uncertainties might be higher compared to other modes of action (some experts).
- different opinions on whether or not it would be feasible to overcome the limitations in the near future in a way that the uncertainties discussed would be appropriately addressed.

Mixtures:

- There is evidence that EDs can act together in additive manner (not specific to EDs) and it was agreed, that estimation of an experimental threshold is challenging in case of mixed exposure.

Expert views – overall uncertainties:

Uncertainties highlighted by some experts:

- Binding to different receptors may lead to different effects at different dose levels.
- Effects may differ depending on the environmental conditions
- Uncertainties related to inter- and intra-species extrapolation
- Exposure during sensitive windows may result in delayed effects
- Limitation of methods sensitivity and possible lack of sensitive endpoints

Agreement:

- there are many uncertainties in carrying out a risk assessment. Many are not specific to EDs but some factors may be particularly relevant to some EDs.

Different views:

- Some experts considered uncertainties were higher for EDs, other experts considered that the uncertainties were not specific for EDs and not necessarily higher than for other types of toxicants acting via non ED MoAs.

Summary:

- It is likely that, from a mechanistic point of view, thresholds exist but may be very low (most experts).
- Several reasons may make it difficult to derive such a threshold:
  - Low dose effects and non-monotonic does responses may be difficult to be detected if they exist (agreement)
  - Mixture toxicity makes it difficult to detect real life thresholds (agreement)
  - Tests may not be sensitive enough especially during critical life stages (agreement)
  - Sensitivity differences with regard to different receptors, individuals and species may result in difficulties in extrapolating from standard tests to human populations and wildlife (some experts)
- Different view how relevant these uncertainties are and whether or not it would be feasible to overcome the limitations in the near future in a way that the uncertainties discussed would be appropriately addressed

Conclusion:

- The ED EAG was asked to consider the key aspects related to the appropriateness of following either a threshold or non-threshold approach to the evaluation of EDs.

- As reflected in this presentation, there were both points of agreement as well as diverging views between the members of the group on key scientific issues.

- Therefore no consensus was reached on which approach to follow.

Thank you for your attention

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