Exploring hazard for Endocrine Active Substances

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- ED definition and related concepts
- The scientific foundations of regulatory decisions
- ED criteria
- OECD GD 150 as a matter of hazard identification
- The complexity of hazard identification
  - Effects secondary to other toxicity effects
Definition of ED and related concepts

- An ED is an exogenous substance or mixture that (1) **alters the function(s) of the endocrine system** and consequently causes (2) **adverse effect** in an (3) **intact organism**, or its progeny, or (sub) population.

1. Interaction with synthesis, release, transport, metabolism, receptor binding, action or elimination of the endogenous hormones (explorable in vitro/in vivo)

2. WHO definition for adverse effect (explorable in vivo)

3. Intact organism
   1. The effect would occur in vivo (test animals, epidemiology, clinically)
   2. But can be shown in alternative test systems predictive of the adverse effect
Definition of ED and related concepts

- Free hormone and receptor concentrations are variables depending on cells, tissues and development stage and this accounts for the difference in sensitivity (relevant for HI)

- Programming role of hormones during pre and postnatal development can accounts for latency in the occurrence of the effect (relevant for HI)

- Disrupting the programming functions of hormones during development induce adverse effect (relevant for HI)
Scientific foundations of regulatory decisions

- Identify ED is an HI procedure
  - Timing of exposure relative to life stage
- Effects secondary to another toxic effect
- Effects observed in the presence of excessive toxicity
  - High dose effects
  - Above 1000 mg/kg
- Lack of validated tests for a number of MoAs
  - More guidance are needed
ED criteria

- It shows an adverse effect
- It has an endocrine activity i.e. it has the capacity to alter the function(s) of the endocrine system
- The adverse effect is a consequence of the endocrine activity- there is a biologically plausible link between the endocrine activity and the adverse effect
- **Identify ED is not only a matter of HI but rather a more complex Weight of Evidence based exercise**
Starting point for ED hazard identification

- Data requirements in line with the ED criteria
  - All available relevant scientific data
    - Scientific data generated in accordance with internationally agreed study protocols (standard studies)
    - Other scientific data selected applying a systematic review methodology
  - Additional information may be required if there is indication of ED properties in order to:
    - Elucidate the MOA
    - Provide sufficient evidence for relevant AEs
Standard studies

- Designed to explore and possibly identify hazards
  - Relevance of the dose (e.g. MTD considerations)
    - High dose effects as confounding factors
  - Relevance of the study design
    - Internationally agreed study protocols
    - Use of the latest version of the corresponding test guideline (e.g. OECD TG 443)
Five-level organised “toolbox” listing assays able to provide information regarding potential ED properties for a chemical substance.

- Is not a tiered testing strategy
- Limited to the investigation of EATS mediated modalities
Provide guidance about results interpretation in light of the data that may or may not be available from in-vivo or in-vitro studies

Based on WHO definition of adversity; consequently can only suggest that a chemical is an ED if adversity in-vivo is plausibly linked to an ED mode of action

Does not present a testing strategy as is restricted to a single step when further testing is recommended or proposed for consideration
OECD GD 150 and ED criteria fit (not only studies included in the DR)
The complexity of hazard identification

- Few examples on “effects secondary to other toxicity”
Thyroid histopathology; primary or secondary to other toxicity?

Normal rat thyroid

Rat follicular cell hypertrophy; thyroid
MOA analysis, primary vs. secondary

Hepatic tissue dose → CAR/PXR activation → Hepatic phase I/II induction → Decrease in T4, increase in TSH → Thyroid histopathology changes

Hepatic tissue dose → CAR/PXR activation → Hepatic phase I/II induction → Liver centrilobular hepatocyte hypertrophy → Liver hepatocellular adenoma

Hepatic tissue dose → CAR/PXR activation → Hepatic phase I/II induction → Decrease in T4, increase in TSH → Thyroid histopathology changes
Weight of evidence/human relevance

- Is the pathway human relevant?
  - YES
- Is the rat more sensitive than human?
  - Generally accepted
- Demonstrate the human relevance by providing data and weight of evidence
  - Hormonal analysis and dose response
  - Comparative studies on liver enzyme induction (including human and negative species)
  - Exclude other possible thyroid-disrupting moas (e.g. NIS or TPO inhibition)
Testicular tox. Primary or secondary?

Vidal et al. 2014
MoA

- OECD GD 150: Testis histopathology E,A,S; following the guidance, multiple putative MOAs can be proposed and the substance identified as ED by coherence analysis.
- 2,5 hexanedione cause germ cell apoptosis, occurring by means of up-regulation of the Fas ligand by the Sertoli cell stimulating the Fas receptor on spermatocytes.
SOME CONCLUSIONS

- Hazard identification is a complex exercise and difficult to regulate
- Considering the physiological role of hormones in development process, is the use of OECD GD 150, sufficient for HI?
- Guidance and regulations should consider update to incorporate “validated” test systems for ED, particularly for the ED pathways insufficiently investigated
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