EURION
Stakeholders feedback

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Q1 (AT)

From your perspective, what are the needs and expectations on EDC test method development in EURION?

- Taxa extrapolation
- Thyroid modalities including DNT
  - Endpoints that are population relevant
- Complementarity of test methods e.g. test battery, including prediction model
- Novelty e.g. KEs related test methods
- Non-EATS mediated pathways

Q2 (NA)

- **What seem to be largest obstacles/challenges for the uptake/use of new test methods?**
  - The regulatory problem formulation
    - Screening for prioritization of chemicals for future testing.
    - Screening of small numbers of structure/class specific chemicals.
    - Single chemical hazard assessments
    - when no in vivo data exist, testing can be used to determine if, and what, follow-up testing should be run.
    - when existing in vivo data is equivocal, testing can be used to inform the Weight of Evidence (WOE) based assessment for ED.
    - when ED in vivo data exists and is negative, but concern exists from new or novel molecular initiating event (MIE)-based assay or from the published scientific literature, a regulatory choice could be to run testing to inform the WOE based assessment.

NAMs should <u>fit for purpose</u> to address the different regulatory needs

Q2

- **What seem to be largest obstacles/challenges for the uptake/use of new test methods?**
  - Accessibility (available in contract laboratories)
  - Availability of a users test guidance
  - Uncertainty analysis as part of the test guidance (more uncertainties can be accepted depending on the regulatory problem formulation.

Q3 (AT)

What type of validation is needed for in vitro screening assays and in silico methods?

- Define a road map for test validation in advance (Develop with regulators a clear implementation plan with specific goals for its roadmap; define the goals of the roadmap and identify specific actions to reach these goals)
- Based on a mechanistic understanding and that the endpoint measured is representing a fundamental step in the pathway
  - Define test performance criteria
  - Test how many compounds as possible
  - Define positive and negative
  - Include development of a prediction model
- Develop a classification model for compound classification (i.e. what is a hit)
- Provide case studies (IATA) including IVIVE modelling

Q3

What type of validation is needed for in vitro screening assays and in silico methods?

- Provide interpretative guidance
- Provide training to regulators
- Uncertainty analysis as part of the test guidance.
- Use of harmonized template for reporting NAMs (OECD 201)

Q4 (NA)

What type of specific endpoints should be added to existing OECD guidelines?

- In vivo GD (level 4 and 5) are designed to explore adversity /toxicity and for this, if dose is correctly selected, they are generally considered as appropriate. ED related additional endpoints for mammalian tox are likely represented by intermediate KEs which are better addressed in specific mechanistic studies (which can be guideline e.g. new GD)
- For non mammalian species, T-mediated parameters (population relevant) in fish guidelines (on-going) and others for intermediate KEs
- A tiered approach can be an option, but this needs to be contextualized

Q5 (AT)

What is your opinion on the addition of molecular readouts to existing OECD guidelines?

- Preferred option is to be part of the mechanistic studies
- Option to include biomarkers in the in vitro studies

Q6 (NA)

What is your view on the usefulness of AOPs in the context of developing ED tests?

Relevant

- Anchoring testing to an in-vivo AO
- In-vitro to in-vivo correlation
- Test for intermediate KEs (hormonal changes (defined when hormonal changes are adverse))

Q6 (AT)

What should be the benefit of grouping and read-across in ED assessment? [e.g. cumulative risk assessment]

- To be discussed, different approaches based on different contexts.