Topical Scientific Workshop on
New Approach Methodologies in Regulatory Science
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Break-out session 1

Case study from SEURAT-1

Perfluorinated alkyl acids: direct acting toxicant category supported by ToxCast evidence

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Question block 1: Case description

1. Are the chemical structures from the source substances and target substances sufficiently described to determine the structural (dis)similarities?

Yes, impurity profiles would be needed though (no further consideration for the current case)

2. What is the regulatory purpose for which the case is prepared?

Filling data gap for 90-day RDT in the context of REACH registration

3. What is the property for which a prediction is attempted?

90-day RDT with the critical effect liver toxicity with the purpose to identify a NOAEL and subsequently derive a DNEL

4. What is the hypothesis under which the prediction is attempted?

Parent substance is the acting chemical structure, no metabolism. Liver toxicity as key effect mediated via receptor interaction (PPAR). Variation in strength of effects

Case description (2)

- 5. What information obtained in animal studies is provided to support the prediction?

90-day study with source substance, "flanking information" on C 6, C11, C12 supporting the prediction, but not in the category.

- 6. What are the weak points of the justification, which are identified by the assessment according to the RAAF?
  - Borders of the category; justification could be improved for the selection of category members.
  - C8 selected as worst case for liver toxicity. Really worst case for the set of parameters in a 90-day study? Issues are: toxicokinetic information and possible other effects, e.g. thyroid function disruption, haematological, clear statement missing on effect doses for those possible effects in vivo
  - Documentation of the weight of the mechanistic evidence.

- 7. What supporting evidence is still missing or could be added to increase the confidence in the prediction?
  - Data table for ToxCast, other NAM data; further toxicokinetic information
  - Scientifically relevant question, regulatory-wise obligation met without NAM
  - Systematic assessment of quality of all information provided
  - Further detailed description of the methods used in Toxcast and of the results obtained

Question block 2: Contribution of NAM information

8. What types of NAM information have been used in the case to increase the confidence in the prediction?

Mechanistic understanding of the liver toxicity, ToxCast assays

9. Were the weak points in the prediction addressed or at least partly addressed by NAM, and has the condifence in the prediction increased

Lacking further toxicokinetic information remains a weak point, NAM data currently in the case study not supposed to address this.

Question block 3:
Detailed characteristics of the NAM information provided

10. Are the NAM methods used in the case study generally available?

no

11. What scientific limitations are evident for the NAM information in the case study?

Solubility issues of test substances, applicability domain due to phys-chem issues

12. What could be the barriers in using or generating the necessary NAM data?

Cost currently, expected to decrease in importance in future , time, uncertainty on acceptance (from the panel discussion), missing reporting standards, potential for predicting absence of effect