Break-out session 2

Case study from SEURAT-1

β-Unsaturated alcohols: indirect acting toxicant category supported by SEURAT-1

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Major Uncertainties

- Complexity of structures
  → Similarity / category boundaries and members

- Details on study design / quality of *in vivo* data, choice of NOAEL

- Potency of effects, order of reactivity
  → proving the worst case for source compound

- Transformation mechanism (other than via ADH)/rates?
  → reactive potency vs kinetics (size of the category)

- Variation of metabolic pathways (aldehydes/ketones)
  → possible other effects via further metabolites present (kinetics of transformations)

- Toxic reactivity mechanism? Map on AOP?

Read-across issues discussed:

- Toxicokinetics is challenging also in terms of what data is needed to support a given hypothesis.

- How to identify the category, in reality depending on interest from the manufacturer.

Information Added and Uncertainties Reduced by NAM

- **Metabolism of βOAs to toxicant**, reactivity of metabolites as opposed to parent compounds, link with structure (*ex vivo* perfused liver, *in silico, in chemico*)

- *in chemico* data: only quantitative data available to show **clustering of reactivity potency** (supported by *in silico/in vitro*)

- **Mechanism of adverse effect evidence strengthened** by *in chemico/in silico*/ SEURAT-1 *in vitro* data

- in particular: HSC activation markers in hepatic organoids confirm MoA **hypothesis of metabolic-mediated fibrosis**

How can NAM/non-animal data support read-across? (1)

- NAM is providing mechanistic information that together with other information, e.g. *in vivo* data, assist in establishing the hypothesis.

- Evaluate whether the NAM data is relevant to the specific read-across case.

- To split the case into a two-step procedure:
  - First addressing metabolic rate, e.g. metabolic profile in human hepatocytes or HepRG.
  - Secondly the reactivity, e.g. evidence could be molecular mechanism

How can NAM/non-animal data support read-across? (2)

- Be creative using different evidence, e.g. skin sensitization can be sued to help inform on chemical reactivity and biological availability and activation.

- *In vivo* omics data could assist to bridge in between the in vitro and in vivo situation.

- Evidence from non vertebrate species, knowing which biological pathways are relevant to human. This would be an opportunity to bridge in between cell assays and organism level.

What are barriers and limitation in using NAM in read-across?

- Difficult to make general guidance how to apply NAM evidence and how to understand what is fit for purpose.

- Cost-efficiency, how to stimulate manufacturers to use alternatives, too much expertise and resources needed.

- Almost impossible to get an overview and understanding of all NAM and how they can be applied and provide useful data.

- The adverse effect is a complex process including multiple cellular networks and dose response dependence difficult to interpret as well as relevant time points for sampling.

Conclusions from break-out session 2

How to progress together:

- Template to provide data for read-across assessment.

- Training and education.

- Develop a REACH submission based on a case study developed with NAM for example under the EU-ToxRisk project, but with invitation to other groups of expertise to collaborate.