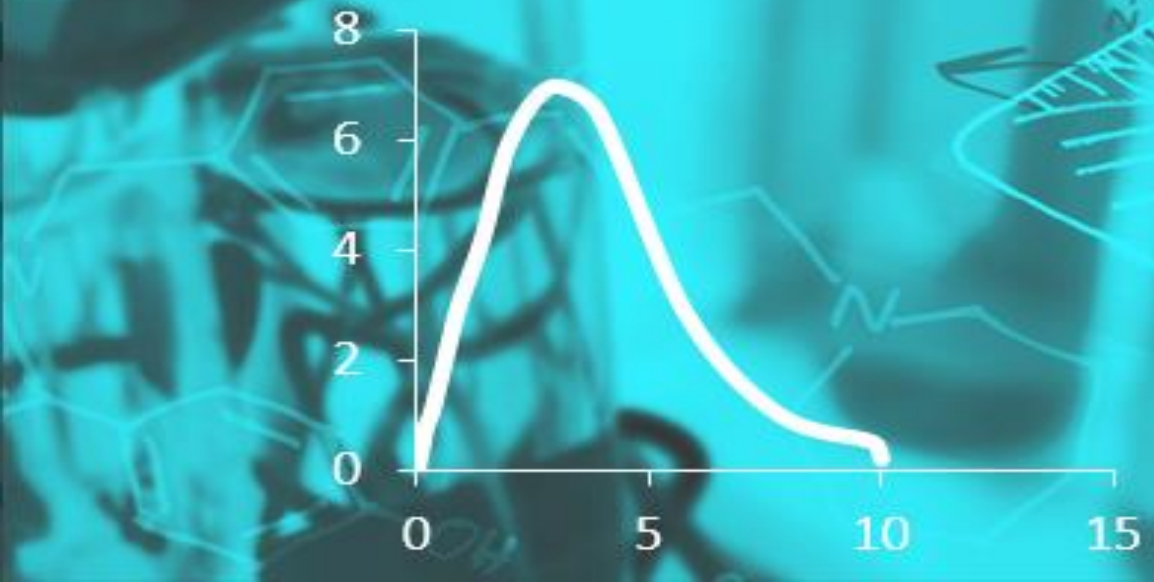
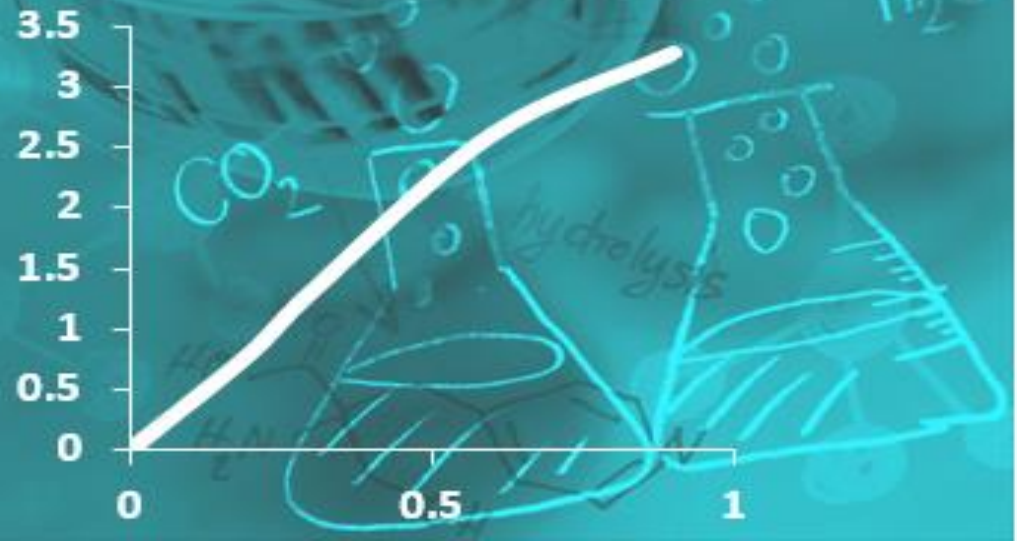
WORKSHOP on Quantitative Response – Response Relationships (qAOPs)

BREAK-OUT GROUP 3

19th October 2022





General thoughts

- **Context dependency is key to all questions set!**
  - Context: quantitative risk assessment…
- **Hence problem formulation should be the starting point**
  - But if end-users (regulators*) do not know why they need qAOPs then how do to do that?
- …
- …

* Note: risk assessors in industry are also end-users!

Q3

How do we ensure the quality assurance and accessibility of qAOP models and their predictions?

What would be the quality assurance criteria for the underlying data?

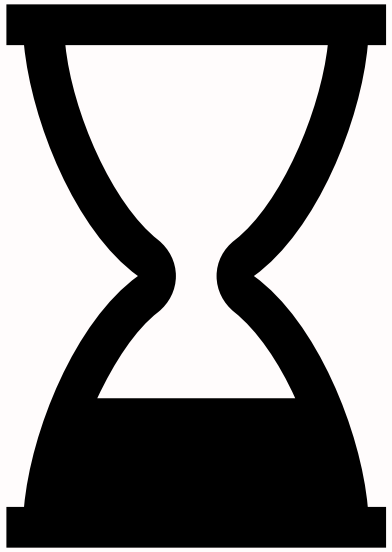
- **Context dependent, problem definition first!**
- Define QA criteria first (minimal criteria)
  - Model overview, problem definition, application area, parameters, documentation
  - Separate: model – parameters – data
  - and check match to problem definition, incl. causality linking!
  - Model AOP or one or more KERs?
  - How much lower level detail is needed? → Context/question dependent.
  - Calibration, validation
- Existing QSAR, PBPK & EFSA ecological modelling guidance as starting points

Q3

How do we ensure the quality assurance and accessibility of qAOP models and their predictions?

Which open standards support qAOP development? Are there any gaps?

- …

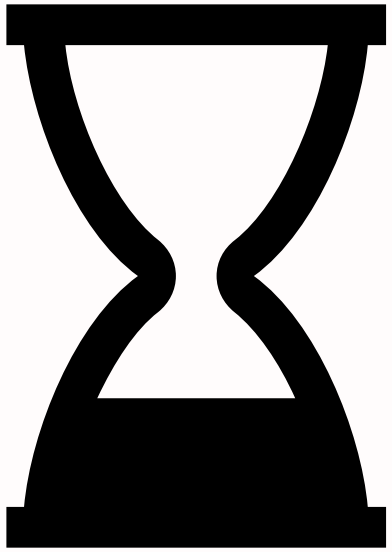


Q3

How do we ensure the quality assurance and accessibility of qAOP models and their predictions?

How do we ensure the FAIRification of qAOP models and underling data?

- …



Q1

How would you choose the most appropriate level of biological detail to include in your qAOP?

What data should we get and how to organise it? Data requirements?

- Relevance
- Quantitative
- Cover key events
- Structural identifiability analysis
- Reproducibility

- Reporting requirements, standard protocols, … reliability scoring (Klimisch criteria?)

- Comparability? How much of the AOP in one experiment? Adjacent KERs?

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Q1

How would you choose the most appropriate level of biological detail to include in your qAOP?

What data should we get and how to organise it? Data organisation?

- Follow data reporting guidelines, standardised
  - Bottom up may not work, patterns more important, we are looking for particular types of information (not just everything)
- Role of canonical information?
- **Organising data around certain organs or pathways?**
- **Quantitative threshold effects + need to collect below that level?**
- Is not all this data available?

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Q1

How would you choose the most appropriate level of biological detail to include in your qAOP?

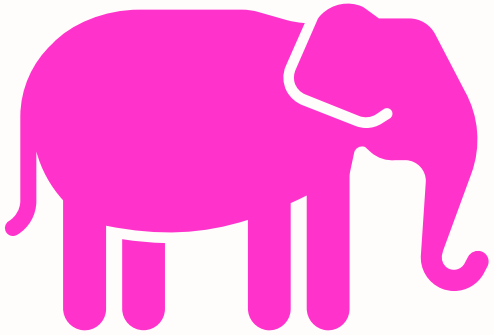
How do you judge how complete (in term of the number of key events required to describe the toxicological response) a qAOP needs to be?

Or

What is most appropriate level of detail for qAOP?

- **Depends on current understanding & data**
- **Depends on question / problem definition**
- Need temporal data
- Cell, organ, organism specific, is level of KE important?
- Equivalency between cell types and species? If yes, modular modelling approach!

- ***Parsimony principle, start simple***



Q1

How would you choose the most appropriate level of biological detail to include in your qAOP?

How do you judge the level of complexity (in terms of detailed biochemical/physiological/biological mechanisms and feedbacks) that is required?

- **See previous slide…**

Q2

How and why would you choose the most appropriate modelling approach?

What are the pros and cons of different modelling approaches?

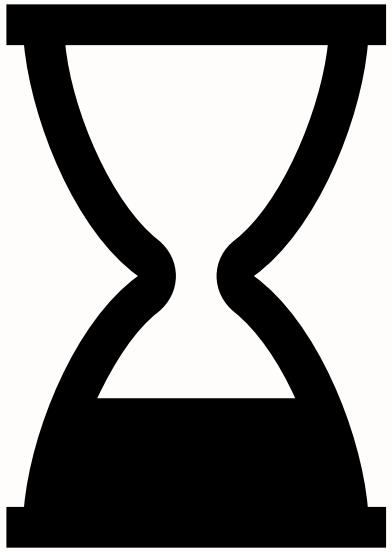
- **Not just one approach, use complementary approaches**
- **More important to characterise the KER**, e.g. Linear, non-linear, feedbacks yes/no, thresholds, temporal scale, …
- Model education may be important
- (Some) qsar modellers use a battery of models
- **Modelling approach is not so important, building trust and confidence is more important** → How do you know the model is good enough?
- 3 groups: modellers, regulators, risk assessors
- Training in model approaches & uses is critical
- Role of (research) funders, incl. regulators?

Q2

How and why would you choose the most appropriate modelling approach?

What are the methods for extrapolating from short-term to longer term exposures?

- …

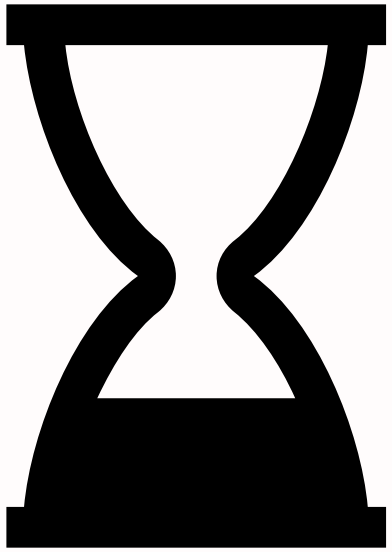


Q2

How and why would you choose the most appropriate modelling approach?

How faithful should the model structure be to the qualitative AOP?

- …



Q3

- How do we ensure the quality assurance and accessibility of qAOP models and their predictions?

•What would be the quality assurance criteria for the underlying data?

•Which open standards support qAOP development? Are there any gaps?

•How do we ensure the FAIRification of qAOP models and underling data?