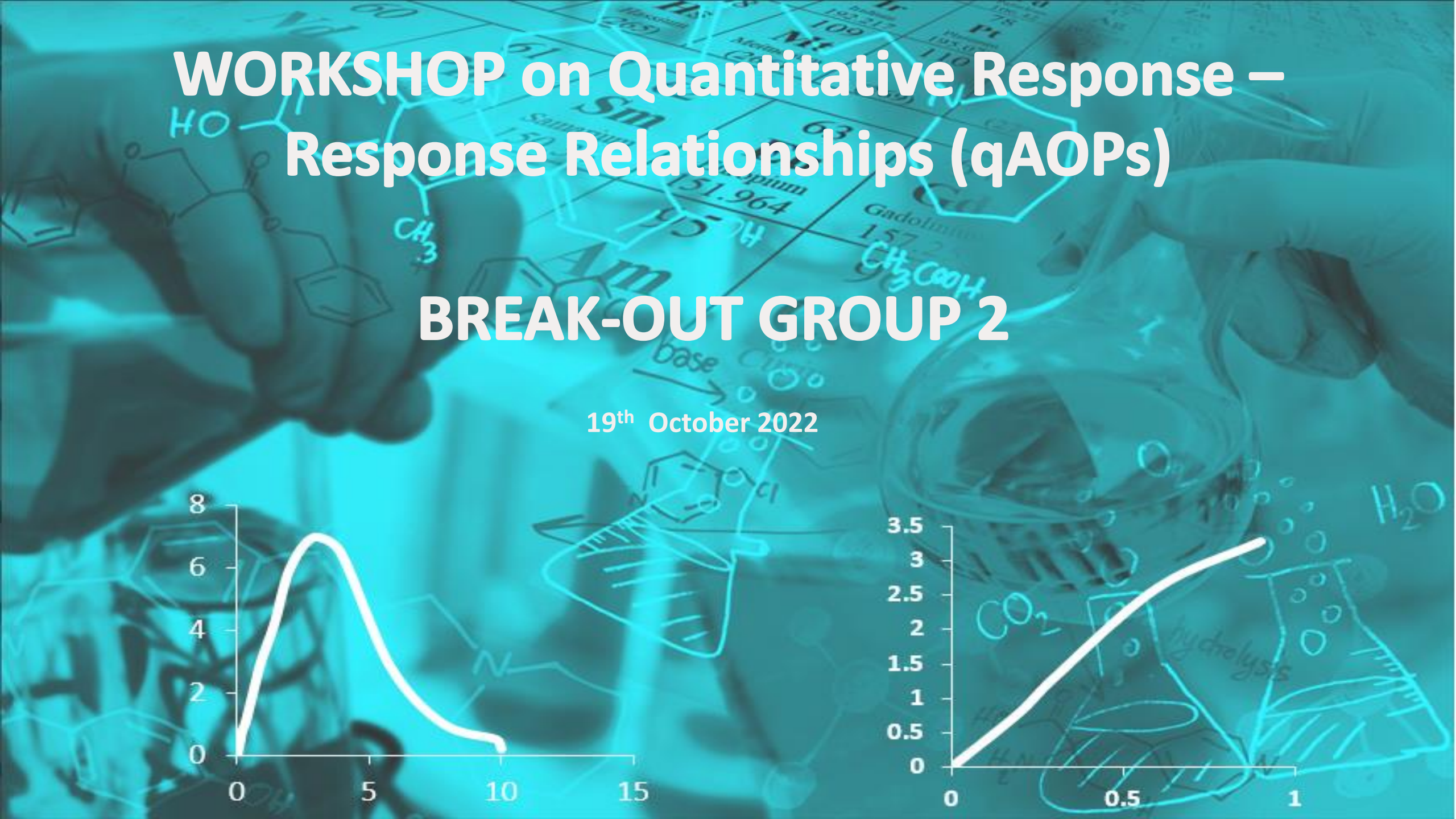
WORKSHOP on Quantitative Response – Response Relationships (qAOPs)

BREAK-OUT GROUP 2

19th October 2022



Participants

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- Magda Sachana, OECD
- Caroline Gomes, BASF
- Phil Botham, Syngenta
- Audrey Phan, RECETOX
- Marvin Martens, MU
- Steven Webb, Syngenta
- Joost Beltman, LU
- Prakash Patel, Cyprotex
- Bennard van Ravenzwaay, WU (moderator)
- Nynke Kramer, WU (rapporteur)

Q2

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

- What are the pros and cons of different modelling approaches?
- What are the methods for extrapolating from short-term to longer term exposures?
- How faithful should the model structure be to the qualitative AOP?

Q2

Choosing the most appropriate modelling approach

What are the available modelling approaches?

Approach dependent on the question to answer, data availability (incl. animal data needed for validation and defining applicability domain (species relevance), phenotype anchorage)

Tiered approach

Approach complexity dependent on data availability (time, concentration, response relationships, feedback mechanisms, knowledge of AOP): linear, networks, mechanistic (TK-TD) vs systems biology approach, scale and not binary, from linear non-temporal data vs neural network modelling

Need to specify what we model: what are we modelling? Use requires more than qAOP sec, not stand-alone in case when used (exposure modelling).

qAOP: KER determination – which means AOP and KEs are defined

qAOP predict the incidence of an AO from an observed change in MIE

Species extrapolation is not part AOP, but in qAOP can be made species specific

Q2

Choosing the most appropriate modelling approach

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

- AOP for hazard identification, qAOP for hazard characterization but cannot be used by itself to do so and required chemical specific data and kinetic modelling
- Precautionary approach through hazard identification, tipping point
- Chronic vs acute adverse outcomes (complexity, MDMA receptor perturbation associated with neurodegeneration).

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?

Q3

Ensuring quality

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

- OECD reporting template for modelling, similar for reporting KER
- Curation not fixed with reporting templates, database for appropriate curation, focus on transparency – once you have the model someone should be able reproduce the figure, system for systematic curation in AOP wiki
- Difficulty bespoke models compared to PBK models, assumptions explicit
- Data quality used to derive response-response relationship (KER)
- Hypothesis that sits behind data more generally quality concern for AOPs, not specific to qAOPs, with biological plausibility, empirical support, incidence accordance (modified Bradford Hill criteria). Levels of quality assurance in qAOP development.

Q3

Ensuring quality

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

- more accurate identification of information gaps, a warning sign.
- qAOP is a form of quality check for AOP (and its application domain)
- "Post validation" validation, define applicability domain, centrally reported
- There is a chemical applicability domain, if not chemical specific; should be refined as more information/validation becomes available
- "Retraction watch", reclassification

Q3

Ensuring quality

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

- Accessibility to the lay person is not required, but accessible to specialist in regulatory body. Provide script that a specialist can reproduce easily. Reporting as transparent as reasonable.
- Knowledge transfer should not be dependent on specific developers.
- Mathematical models can be reported in AOP wiki like the AOPs are reported now (all the input publications, scripts).
- System, biomarker method reported

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

Q1

Appropriate level of biological detail

What data should we get and how to organise it?

• ideally: a validated (Adjusted Bradford Hill criteria), detailed AOP, time-resolved concentration-response relationships with clearly defined, sensitive, specific biomarker of toxicity, several chemicals

• Metadata (experimental setup…. all affect KER)

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?

•Depends on the question (level of uncertainty required) and data availability (see answer Q2), qAOPs are essentially empirical despite the mechanistic basis

•Key event skipping, deminimus qAOP, indirect/non-adjacent KERs: ID rate limiting KEs to include. AChE inhibition – delayed neuropathy, detailed AOP but qAOP can be limited. the AOP helps us ID what are necessary KEs for qAOP

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

•Depends on the question (see earlier comment)

•Centrality measure, Bayesian inference techniques, sensitivity analysis – communicate that developers are expected to do this.

Extra Notes

General discussion after breakout sessions

qAOP is a means to provide confidence in using concentration-biomarkers of KE perturbation for hazard characterisation and chemical risk assessment

Need for case studies for integration of qAOPs in chemical risk assessment to provide confidence in their relevance; consider case study put forward by regulatory community

Possible case studies: genotoxicity (although risk assessment not quantitative), case studies should use well validated, accepted in vitro models and have a simple, well understood AOP, the extension of US EPA qAOPs

Collaboration between AOP developers and qAOP modellers to address data quality and confidence

Consider designing a reporting template for qAOP and apply this to case study and ask others to test reproducibility of qAOP model