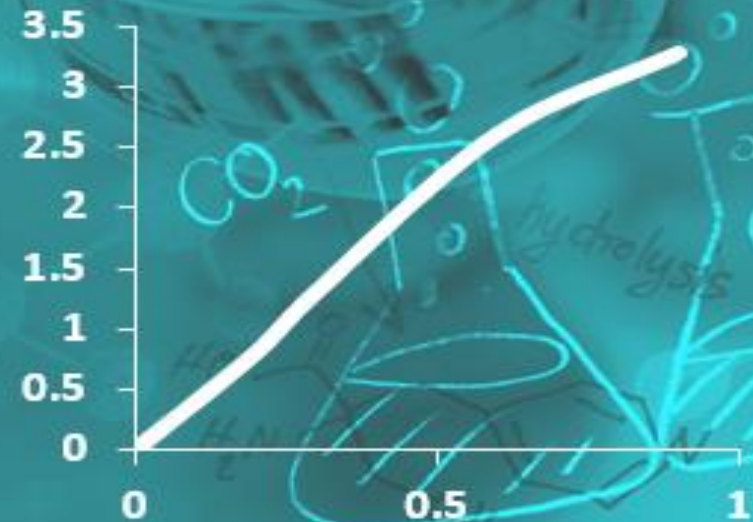
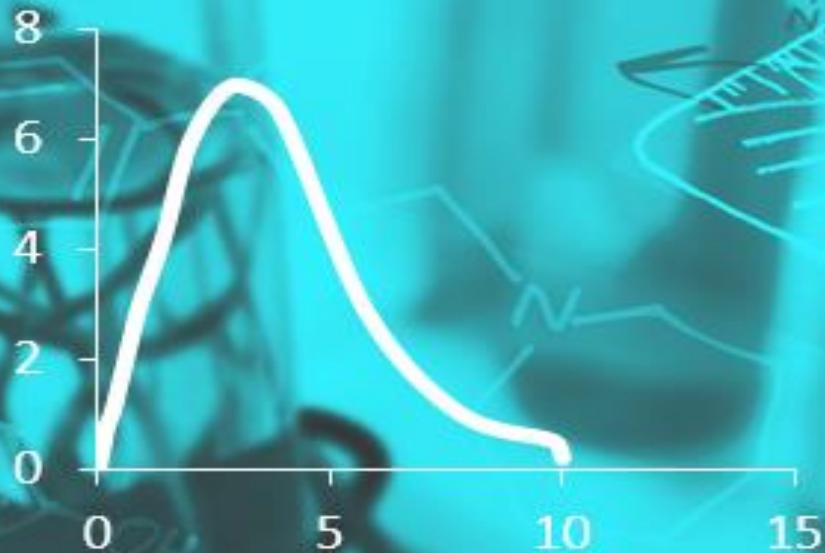


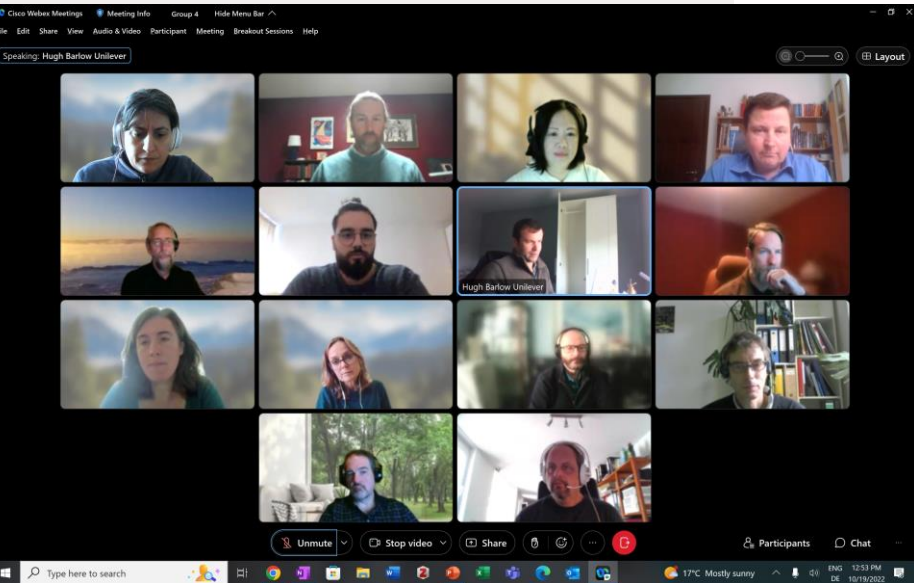
WORKSHOP on Quantitative Response – Response Relationships (qAOPs)

BREAK-OUT GROUPS

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Q3

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

What does the “**fit of purpose**” mean? Performance standard or we could follow OECD TGs following normal assay variation. PURPOSE needs to be defined upfront and the domain of the qAOP. → Assay performance Criteria and identification of stressors to be able to evaluate.

Quality assurance → std reporting metrics, reporting framework and criteria already available could be interesting to explore to apply to qAOP. Follow up record about published work that could give feedback and assure evaluation/quality. We need to understand the assays and how interaction is taking place, where the underlying information and assay is coming from (e.g. comparative studies). What are the data that have been already curated and if these can be reused, how to FAIR search for these data. Understand range of variabilities and uncertainties (how much variability do you get biological and technical replicates, how much precision do we get from our readouts and need in the modeling). Understanding the variability, you can enter this piece of information in the overall context.

FAIR

Ensure **Accessibility** how it will be easily transferred (limitation to certain expertise's) ex. Model experts vrs others that do not have the knowledge.

Userfriendly & opensource software → Github sharing for follow up and develop further these models. **Findability**, tool from Nicoleta and how she made her work and analysis. Commission just started a new project at OECD about maximizing the data from academia for regulatory purposes... (what std are available) how do regulators find the data. How to find and make the tools available. A catalogue of model components, from literature make a good strategy, qAOP are difficult to **reproduce**, code should be published in order to be able to reproduce. All the steps that are made, choices are made at each step of model development, but what is the framework we need to record this choices. (q)AOP agnostic or not it should be taken into account for reproducibility. (CHECK CHAT)


Interoperable → Ontologies/terminologies/vocabulary should be harmonised.

PBK modelling and other computational modeling experience could be used like characterization and description of the PBK model be used in similar way for qAOP.

Confidence in the underline AOP itself (upstream analysis), how confided are we on the AOP from which we would be the models → qAOP (retrospective evaluation, for now we are limited to the data but not form the information)

No open std available at present so needs to identify this. (response-response, ODEs etc)

Quality of model and quality of data – quality metric in vitro assay system → GIVIMP, DNT OECD.



Q2

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

“Fit for purpose” some time the most appropriate is the cheapest and some time the most appropriate is the most accurate model. There is a need to test the model empirically (against “real-world” observation), but we cannot test all scenarios.

Leveraging the past data making these models and testing them. What can we leverage from different chemicals to other for which we do not have, confidence is key, (RX).

How much confidence do we need for developing models when we need to develop for a large number of chemicals that we need to test and assess, so a possibility is not to develop a full qAOP but focus on KE translatable to AO.

But we need to build trust and is difficult when we want to translate all KE in an AOP since we need to elaborate complex models and these needs some sort of evaluation before extrapolate and scaling between species and other populations.

How faithful we need to reproduce the qAOP, it should not be an exact replica of the qualitative AOP, just address the purpose to predict the AO (we can skip intermediate KE)!

As an example of qAOP - ODE modeling approach can be more valuable to describe KE with a clear description of time dynamic included. To fit these models you need data to parametrize these models and also to evaluate.

Q1

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



Evidence from the qualitative AOP should be used to model, but how complete the qAOP should be in describing the biology depends on the purpose (regulatory or research). Not all KE need to be included to describe the processes identified in the AOP. Be aware that the simplicity can be affected by other features like for instance modulating factor (that can influence upstream and downstream events) and kinetics.

Chemical agnostic versus non agnostic, at what point is the chemical informing the processes interplay between the biological system and the chemical and is not restricted to the MIE!

AOP is chemical agnostic and needs to be linked to kinetics, to describe dose response.

Response-response models can be developed using assays (e.g. Knockdown assays) that are measured without chemicals.


We need to clearly communicate what is described with the model and assumptions made.

Sens Analysis can be used to check if you have appropriate level of biological detailed.

Iterative processes between qualitative and quantitative AOP development, so are data collection and model development.

Hypothesis → irreducible simple → test → refine and add complexity... understand of biology and simplify it (iteration loop).





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?

Two levels, how complete the qAOP should be. Sufficient KE to describe the processes and are confident that all is covered. Modulating factor can influence and rely on the existing events down up streams... this could end up in having non good predictions. Evidence from the qualitative AOP what should be used to model.

Chemical agnostic versus non agnostic, at what point is the chemical informing the processes interplay between the biological system and the chemical and is not restricted to the MIE. QAOP is chemical agnostic (need to take into account kinetics) and we need to gain confidence both at the kinetic and dynamic processes. Up stream kinetic modelling (if there is not kinetic info used) these needs to be reported to justify why. K+D should be coupled. Separate the response modelling but when we go to the regulator we can couple them. Chemical Agnostic and type of data for the response response data where assays can be used without application of chemicals

What is the most relevant, but most of the time is iterative processes since you do not know what is biological relevant until you start. And if they do not describe the processes as one established it then we need to understand why this takes place. Model needs to represent as accurate as possible the biology but we need to fit the regulatory purpose. Model development.

More complexity when we enter modulating factors are introduced. We need to clearly communicate what is described with the model.

Need to add extra complexity, is there a way on how to report them or criteria to report these, SA example. How much detail to introduce. What is the minimum information required, and then how much work you need to translate this or characterising it. Extrapolate from different set of assays to more broadly applicable to effects.

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

Q2

- 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?

WHY → how to justify the use of one model as compared to another approach.

Not the one but the Best model, costly and time to develop the model.

What is the purpose you will use the qAOP model. → ideal world, we would go on the KE event level, and this is translated to AO. But we need to build trust, and KE translated into AOP and we need to elaborate complex models. → need to make extrapolation and scaling between species and other populations. Measure KE are chemical specifics look at the population you are studying.

How faithful we need to reproduce the qAOP (it should not be an exact replica of the qualitative AOP just address the purpose to predict the AO (we can skip intermediate KE)

Fit for purpose is the most appropriate the most cheap, what is the appropriate use of different models is tricky to test and evaluate can we do that we need empirical data to gain confidence in models. (make a predictions with model and test empirically). WE cannot test all scenarios, to we still need to do in vivo testing.

AOP → qAOP for regulatory use e.g. find a PoD.

What do you have? Data we have is limited in to how much data is collected and measured, high amount of information in the AOP but then you need to translate this into the model, the model is very complex and is not then possible to ... Best modeling framework qualitative AOP take a subset. Do not add extra complexity. Think what you really need to model.

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

Q3

- What would be the quality assurance criteria for the underlying data?
- Which open standards support qAOP development? Are there any gaps?

Database system presented by Jason

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

What are the data that have been already curated and if these can be reused, how to FAIR search for these data, do we have a DB?

Ontologies/terminologies/vocabulary should be harmonised

We need to understand the assays and how interaction is taking place, where the underlying information and assay is coming from (e.g. comparative studies).

Understand range of variabilities and uncertainties (how much variability do you get biological and technical replicates, how much precision do we get from our readouts).

Agree which assay are appropriate for measuring KE. What is **fit for purpose** for measuring a particular KE, but increase quality and acceptability.

What does the "fit of purpose" mean? Performance standard or we could follow OECD TGs following normal assay variation. Luckily to have multiple AOP for any purpose of application, and this needs to be clearly defined. PURPOSE needs to be defined upfront and the domain of the qAOP. → Assay performance Criteria and identification of stressors to be able to evaluate. Express things based on this.

Quality assurance → std reporting metrics, reporting framework and criteria already available could be interesting to explore to apply to qAOP. Follow up record about published work that could give feedback and assure evaluation/quality.

PBK model experience could be used like characterization and description of the PBK model be used in similar way for qAOP.

Understanding the variability, you can enter this piece of information in the overall context.

What is the dynamic range of a specific measure and do we have a specific NAM