Adverse Outcome Pathways: From Research to Regulation

Taking Qualitative AOPs to the Next (Quantitative) Level
Breakout Group 3

Moderators
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Background - 1

At its most basic level, a useful AOP links a Molecular Initiating Event (MIE) convincingly and qualitatively to an Adverse Outcome (AO). Adding information about the linkages between the intermediate Key Events (KEs) along a pathway expands the usefulness further, perhaps to the level where evidence provided by mechanistic tests querying those particular events can characterize chemical hazards.
Background - 2

- However, to be most useful, the linkages between MIEs and KEs, and among KEs, must be understood quantitatively. These questions and others should be considered and outlined to the extent possible during construction of an AOP.

  - What is the dose that activates the pathway, and is it relevant to human/eco exposure scenarios?
  - What is the threshold of activity that pushes the pathway onward from one key event to the next?
  - Is each KE governed by a threshold mechanism or is constant perturbation required?
  - How does the frequency of multiple doses affect the probability of an AO?
  - Are certain KEs necessary and sufficient to result in the AO?
This breakout group explored scientific and policy initiatives that can be pursued by various stakeholders to encourage and facilitate quantification of existing and new AOPs, and to identify resources and methods for doing so.
Thank you to our presenters

• Case study presentation: A Quantitative AOP for Skin Sensitization
  - Gavin Maxwell, Unilever

• A Conceptual Model that Enables Quantitative Integration of Data into an AOP
  - Catherine Willett, Humane Society of the United States

• Applying Semantic and Network Methods in AOP Knowledge Discovery
  - David J. Wild, Indiana University, School of Informatics and Computing
Why do we need quantitative AOPs? What would they be used for? Would you always need quantitative information for an AOP?

• Risk assessment vs. risk management; may need different levels of quantitation

• Prioritization important part of regulation, does not require detailed quantification

• Put in context for risk assessment (POD for endpoint of regulatory concern)

• Human vs. rodent; focus on human relevance
What are the specific investment/research/IT tools needs?

- IVIVE considerations; DB of existing in vivo data - need to acquire additional kinetic data
- Case study based approaches
- Critical missing areas include developmental toxicity
- Prevalent endpoints related to HPV/industrial chemicals (SEURAT-1 approach) can also guide work
- Standardized approaches to developing/testing network structures
- How do we connect the information from semi-automated literature curation to AOP building tools
- Need to invest in outreach and familiarization; need to work with people who know the subject; need to show people how to use databases
How do we best capture quantitative and kinetic information? How do you take linkages between various pathways into account? What about species differences? Metabolism?

- Interspecies comparisons and measurements at macro molecular stage
- Consider potential activity for all metabolites against AOP
- Network structural similarities of AOPs
- Further information on metabolic enzyme expression levels and profiles across species to facilitate extrapolation
- Database that capture key species differences; will need sharing of data between groups
What are the quality criteria (or grading) that should be applied to existing/new data to support a quantitative AOP?

- Bradford-Hill criteria (Reproducibility, etc.)
- Database of assays and which AOPs they map to/toolboxes of methods
- Utility of AOP depends on characterizing reliability of assays
- Relevance to regulatory endpoint of concern
Is it possible to identify general rules for when “threshold” vs. “non-threshold” linkages are likely to occur?

- Nonlinearity, reversibility, feedback loops require a high degree of mechanistic knowledge
- Static process
- Thermodynamics amenable to quantitative analysis; biochemical networks; get physical chemists interested in AOPs
- Have defensible science for regulatory use; biology is non-equilibrium systems
- Can you identify a rate-limiting step for an AOP?
- How to define threshold of recoverability/reversibility
How can we take advantage of various sources of information and literature mining tools? Improvements/connections needed?

- Use case studies to build on these arguments; human health and disease; get input from other fields, e.g., histopathology; get more human health info
- Case studies with multidisciplinary teams; identify assumptions and uncertainty
- There are tools currently available to pull together data from a variety of sources, (e.g., disease pathway databases)
- Need more information about the data, not necessarily more data
- Need expert insights/experience into the data
How can we design assays to generate quantitative information on KE linkages?

• Some assays should be metabolically competent
• Learn from sensitive subpopulations
• Need to consider spatial aspects and tissue relevant concentrations
• In vivo assays may not be demonstrating effects of the parent chemical
• Look at acute verses chronic/cumulative exposure; Lifespan vs short timeframe; accumulation of drugs/metabolites in organ for toxicity
What are likely stumbling blocks?

• Lack of sharing assumptions/lessons from building AOPs; need centralized storage that is universally accessible (AOP wiki?)

• How to implement a peer review process

• Need to identify correct cell system (primary vs cell line); time and duration of exposure

• How to address lack of time and resources with tractable solutions

• Inter-species differences in mechanism of action and key events
How should the quantitative nature of an AOP be characterized? What questions should the supporting data answer?

- Data driven vs expert driven
- Shifts in distribution of processes over populations
- Risk assessment-quantitative endpoint; a key event could be your AO of interest
- Reversibility; point of departure not reversible; peak and area of curve; AOPs need number; quantitative; anchor to real data
- Lifestage and lifespan for AOP developmental risk assessment; separate AOPs for different lifestages
How can we best integrate quantitative tests into decision strategies and map those to AOPs?

- Identify no effects level specific to AOPs
- Capturing assumptions and applicability domains of decision strategies
- Create guidance on developing qAOPs; lessons learned from QSAR validations
How important is it to quantify uncertainty and be able to characterize it for each step in the AOP, and for overall predictions?

- Level of validation and acceptable uncertainty depends on ultimate use
- Characterizing uncertainty in a transparent increases comfort level and utility
- Trajectory analysis; recovery; state changes; robustness vs homeostasis
- Regulatory decisions being made using AOPs; risk assessment approach
- Need to consider ensembles of AOPs; manage AOPs in isolation and hierarchy
- Look at case studies and see where you get; figure out case studies needed; put teams together and see what can happen