Adverse Outcome Pathways: From Research to Regulation

The Process of Regulatory Acceptance

Breakout Group 1

Moderators
David Dix, U.S. EPA
Craig Rowlands, The Dow Chemical Company

Aim

This breakout group aims to consider themes relevant to the regulatory acceptance of AOPs and tools and strategies based on accepted AOPs.

Speakers

- Rick Becker (ACC)
- Christine Olinger (EPA)
- Melissa Panger (EPA)
- Ruthann Rudel (Silent Spring Institute)

How are the critical relationships between chemical availability, activity, and adversity established within an AOP in a way that protects the most sensitive subpopulations? (part 1)

- AOP provides a framework to assess cumulative risk from multiple stressors on an outcome
  - Tool for identifying and assessing risks to sensitive populations
- AOPs should include a specific section to identify and discuss potential sources of population variability in response
- Exposure needs to be included to assess risk
- The example of how PBPK is used in risk assessment may be applicable to AOPs
- AOPs generating discussion about adverse vs. adaptive outcome
  - On a population level, not likely to be a bright line between these, since an exposure that produces an adaptive response in one individual will produce an adverse response in a susceptible individual
  - Depleting an individual's capacity to respond to the next stressor is an adverse outcome.
  - Irreversibility not required for adversity, since many exposures are continuous and we don't want biological stress during exposure

How are the critical relationships between chemical availability, activity, and adversity established within an AOP in a way that protects the most sensitive subpopulations? (part 2)

- Strengths of the linkages should be assessed based upon different factors (e.g., life stages)
- May need to use uncertainty factors as a default factor for sensitive populations
  - Need grounding for these factors
  - Difficult for certain agencies to include non-chemical factors into assessments
- Legal barrier to use some factors; needs to be defensible in court

How do we establish scientific confidence in AOPs?

- Need a systematic, transparent process engaging all stakeholders
- Sliding scale of confidence could be appropriate depending on the intended purpose of the AOP (e.g., prioritization, exposure levels)
- Therefore, AOP rationale is important to determine and communicate
  - AOP can be hypothesis generating, not necessarily for predicting
  - Connecting test method endpoints/evaluations to KE to assist in identifying data gaps
  - AOP can also be used to identify which endpoints/KE give you the “best bang for your buck”

Scientific Confidence Framework for AOPs

(adapted from Cox et al. 2014 Reg Tox Pharm)

1	**Develop the AOP**
2	**Develop new (or map existing) specific assays to key events within the AOP**
3	Conduct (or document) **Analytical Validation** of each assay
4	Develop new (or map existing) models that predict a specific key event from one or more pre-cursor key events. (The input data for the prediction models comes from the assays described in Steps 2 and 3 above.)
5	Conduct (or document) **Qualification** of the prediction models
6	**Utilization**: defining and documenting where there is sufficient scientific confidence to use one or more AOP-based prediction models **for a specific purpose** (e.g., priority setting, chemical category formation, integrated testing, predicting *in vivo* responses, etc.)
7	For regulatory acceptance and use, processes need to be agreed upon and utilized to ensure robust and transparent review and determination of fit for purpose uses of AOPs. This should include dissemination of all necessary datasets, model parameters, algorithms, etc., to enable stakeholder review and comment, fully independent verification, and independent scientific peer review. While these processes have yet to be defined globally, in time, these should evolve to enable scientific confidence and credible and transparent use of AOPs.

This framework was presented at 2014 SOT: The Toxicologist, Abstract 2253, page 602.

Scientific Confidence Framework for AOPs

Utilization

- Contextual and weight-of-evidence analysis of the use (qualitative or quantitative) of the prediction model for a specific purpose.
  - Defining the intended purpose of the prediction model
  - Documenting/justifying applications, based on weight of evidence, of the scientific confidence to support the use of the AOP
    (1) priority setting, where the model is used to identify priority substances for more detailed evaluation;
    (2) chemical categorization for subsequent read-across
    (3) screening level assessment of a biomarker, where model is used as a surrogate data point for a biochemical endpoint or a biomarker;
    (4) integrated testing strategy, or where the model is used to describe/predict a hazard property in lieu of a traditional tox study
    (5) to predict an adverse outcome.

What is the process for AOP development, peer review and application within OECD? (part 1)

- AOPs should be generic and evolving
  - Agency specific determination as to applicability of the AOP to decisions are needed
  - Risk assessors and managers need to be included in review process
  - More ways to increase involvement of relevant experts in review process are needed
  - Public input is needed – Wiki needs to be publicized so that communities that aren't typically involved in OECD procedures can become involved in reviewing and comments on draft AOPs
  - Crowd sourcing?
- A key point is that the AOP under review needs to fit the purpose that it is being validated for
  - Regulatory
  - Hypothesis generation

What is the process for AOP development, peer review and application within OECD? (part 2)

- An AOP is not a test guideline; but it has an ongoing relationship with test guidelines and other data sources
- Should a methods page be included with the AOP wiki to map methods to KE?
  - Could Effectopedia have something like this?
- Care needs to be used in terminology
  - Separate development of AOP from development of assays that describe the key events in the AOP
- AOPs could be viewed as a guidance document
  - Not legally binding, but provides a framework that can evolve
  - It can be viewed as a set of separate tests that could be part of an overall guidance that is informed by an AOP
- As the process evolves, a more formalized process should be put into place increase transparency and confidence in outcomes

How do you go from OECD acceptance to agency acceptance?

- Agency specific determination as to applicability of the “approved” AOP to decisions then will allow agencies to determine which ones are useful for specific purposes
- Risk assessors and managers should be included in the review process since they are the ones that will be implementing them for decision making
- Quantitation also is needed to increase confidence in predicting adverse effects
  - This may be needed for an AOP to be useful in a regulatory context
  - But this may not be possible for all relationships

Does one validate an AOP? Or the tools that come from it?

- AOPs aren’t validated, the KE and tests that identify those KE are validated
- AOPs should be generic and evolving as our understanding of biology evolves

Final Points

- Need to incorporate how to handle variability and uncertainty around exposure, kinetics, and dynamics of AOPs
- Systematic, transparent framework for developing confidence in AOPs across all stakeholders
- OECD offers a path for international cooperation in the development, evaluation, and application of AOPs