Scientific Workshop on Adverse Outcome Pathways: From Research to Regulation

Summary

Scientists from 21 countries, representing industry, academia, regulatory agencies, and special interest groups, attended the workshop "Adverse Outcome Pathways: From Research to Regulation." NICEATM co-sponsored the workshop with the Physicians Committee for Responsible Medicine (PCRM). The workshop, held September 3-5 at NIH in Bethesda, MD, considered how the adverse outcome pathway (AOP) concept could improve regulatory assessments of chemical toxicity. An AOP organizes existing knowledge on chemical mode of action, starting with an initiating event such as receptor binding, continuing through key events, and ending with an adverse outcome such as disease or toxicity. AOPs can also help identify knowledge gaps where more research is needed to understand the underlying mechanisms, aid in chemical classification and prioritization for future testing, and guide the development of new testing approaches that use fewer or no animals. Workshop plenary presentations were followed by breakout sessions that considered AOP applications, development and quantification of new AOPs, and challenges to AOP adoption. Several junior investigators with outstanding poster abstracts gave presentations on their work. The closing session summarized the breakout group conclusions and emphasized a need to maintain the collaborations and momentum generated.

Highlights

Plenary presentation topics:

- Coordinating international efforts
- AOPs under development
- Regulatory uses for AOPs
- Incorporating exposure considerations
- Available computational tools and resources

Breakout Group Conclusions:

- Need to incorporate variability and uncertainty around exposure, species differences, kinetics, dynamics, and quantification of AOPs
- Develop systematic, transparent frameworks for creating confidence in AOPs across all stakeholders, based on the application (prioritization, risk assessment, test method alternatives, etc.)
- OECD offers a path for international cooperation in the development, evaluation, and application of AOPs, supported by tools such as the KnowledgeBase and Effectopedia
- Weight of evidence approaches using the Bradford-Hill criteria and reproducibility analyses, combined with databases of validated assays, decision strategies (including assumptions and applicability domains) and AOP networks, will allow fit-for-purpose AOP validation
- Priority pathways were identified based on public health concerns (e.g. cardiovascular, respiratory sensitization, diabetes, developmental toxicity)

Key Messages: People, Process, Priorities, Partnering

- People
  - Expand education and outreach
  - Integrate disciplines beyond toxicology (e.g., medical, IT)
  - Help biologists become more computational
  - Ensure that communication/momentum maintained

- Process
  - Needs to be systematic/transparent
  - Many aren't aware of how to engage in the OECD process
  - Need to distinguish development of AOPs from application of AOPs
  - AOPs are useful even if they are not complete, but should be applied with caution
  - Need to establish what is the minimum info (qualitative vs. quantitative) needed to develop a confidence framework

- Priorities
  - Determine priority AOPs to move forward and focus efforts on those first
  - Facilitate communication between groups (**NICEATM AOP listserve established**)

- Partnering
  - Determine how best to leverage resources to build AOPs and facilitate regulatory use
  - Need to ensure that industry is engaged
  - How sustainable is the current mechanism for getting AOPs done? (they are currently constructed based on "volunteer" efforts)
  - Could establish working groups that could develop AOPs rather than the ad hoc mechanism as currently done.