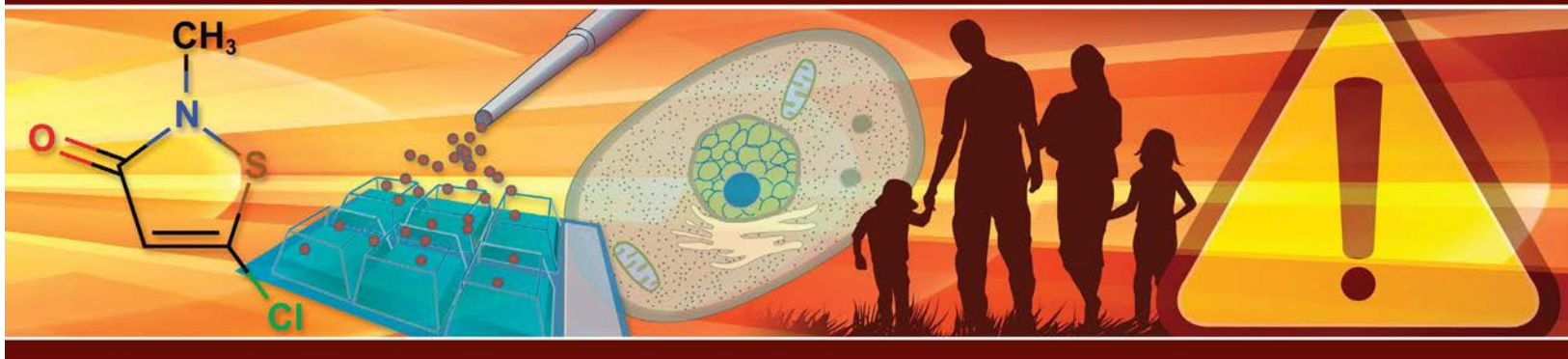


Scientific Workshop

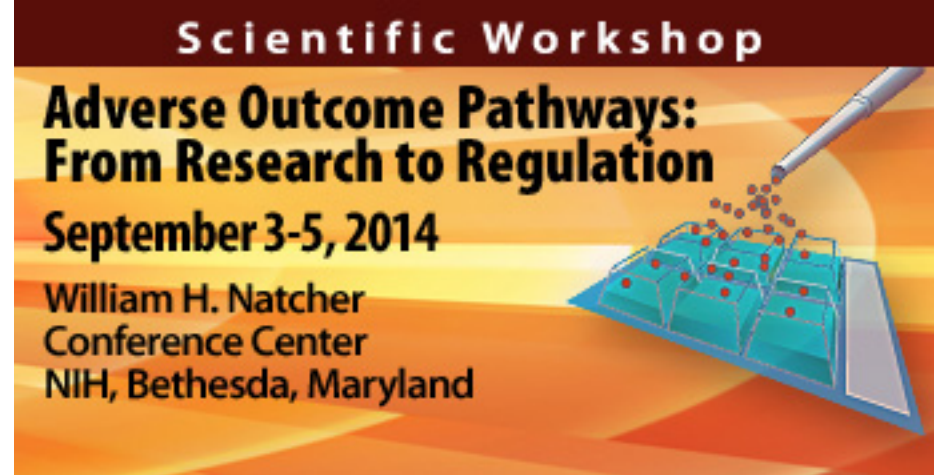


Adverse Outcome Pathways: From Research to Regulation

September 3-5, 2014

William H. Natcher Conference Center
National Institutes of Health
Bethesda, Maryland, USA

AOP workshop was
co-sponsored by:
NICEATM & PCRM
~120 in-person
>350 webcast



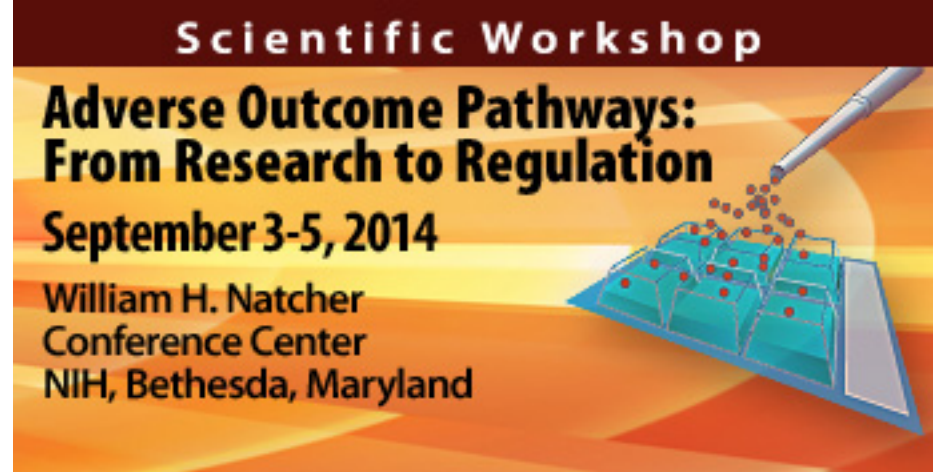
❖ Attendees/Speakers:

- Research scientists
- Regulatory decision-makers
- Industry stakeholders
- Nonprofit groups
- Test method developers
- Computational modelers
- Epidemiologists
- Informaticians

❖ Format:

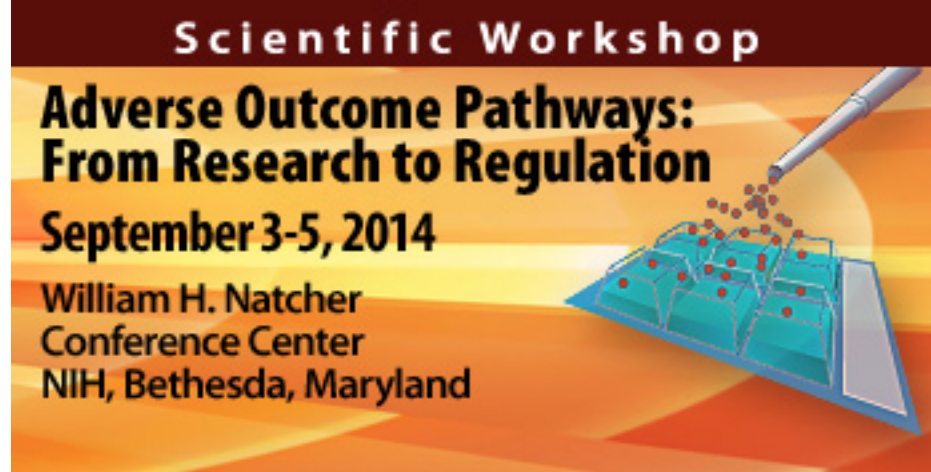
- Symposium talks
- Discussion forums
- Poster sessions
- Junior investigator awards
- Hands-on demonstrations
 - AOP Wiki/Effectopedia
- Rotating breakout groups
 - Case study presentations
 - Charge questions

What is an Adverse Outcome Pathway (AOP)?



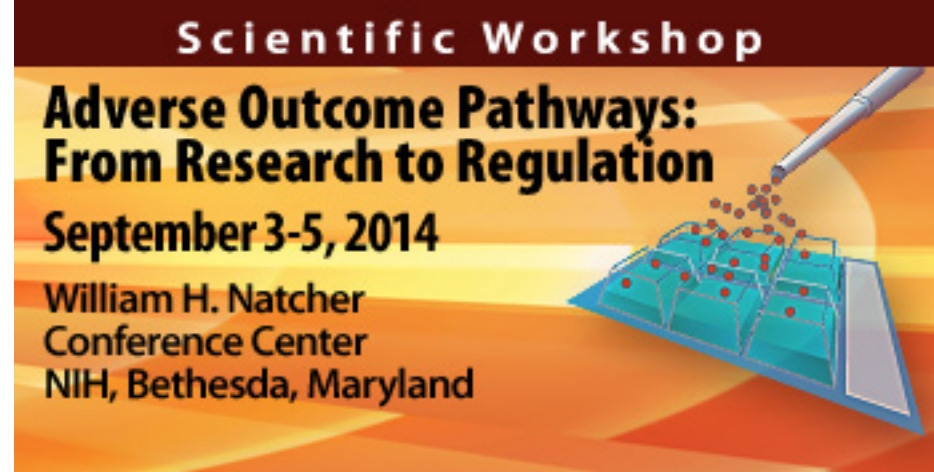
- AOP:
 - Conceptual framework linking molecular initiating events to cellular/tissue effects to adverse outcomes
 - Facilitates better mechanistic understanding of human and ecological toxicities
 - Helps relate exposure to a potentially toxic substance to an actual illness or injury
 - Provides opportunities to map emerging screening technologies (*in vitro* and *in silico*) to endpoints of regulatory concern

Breakout Group Conclusions:



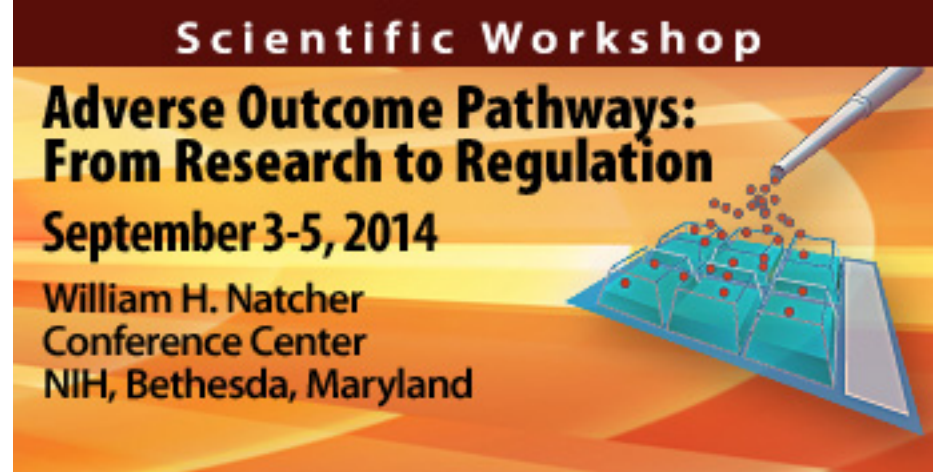
- ❖ Need to incorporate variability and uncertainty around exposure, species differences, kinetics, dynamics, and quantification of AOPs
- ❖ Develop systematic, transparent frameworks for creating confidence in AOPs across all stakeholders, based on the application (prioritization, risk assessment, test 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

Breakout Group Conclusions: (cont'd)



- ❖ 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



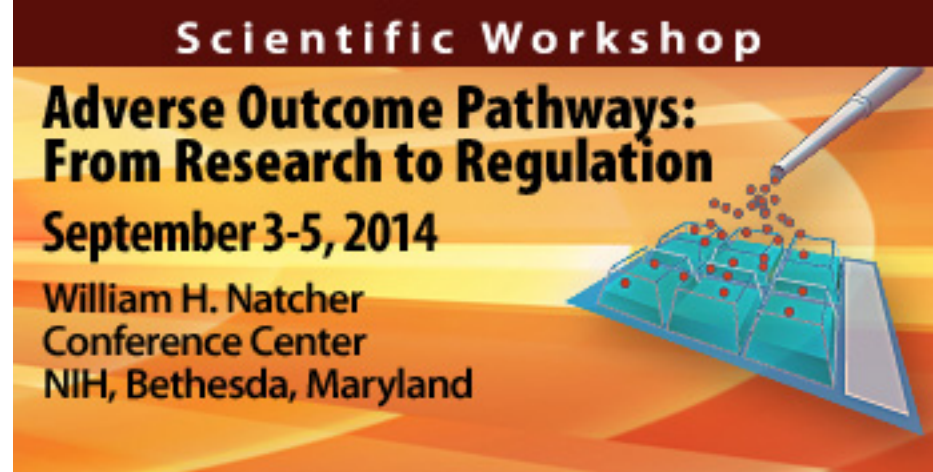
❖ People:

- 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
- Distinguish development of AOPs from application of AOPs
- AOPs are useful even if they are not complete, but should be applied with caution
- Establish what is the minimum info (qualitative vs. quantitative)₆ needed to develop a confidence framework

Key Messages: People, Process, Priorities, Partnering



❖ Priorities:

- Determine priority AOPs to move forward, 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? (currently constructed based on “volunteer” efforts)
- Could establish working groups that could develop AOPs rather than the ad hoc mechanism as currently done.