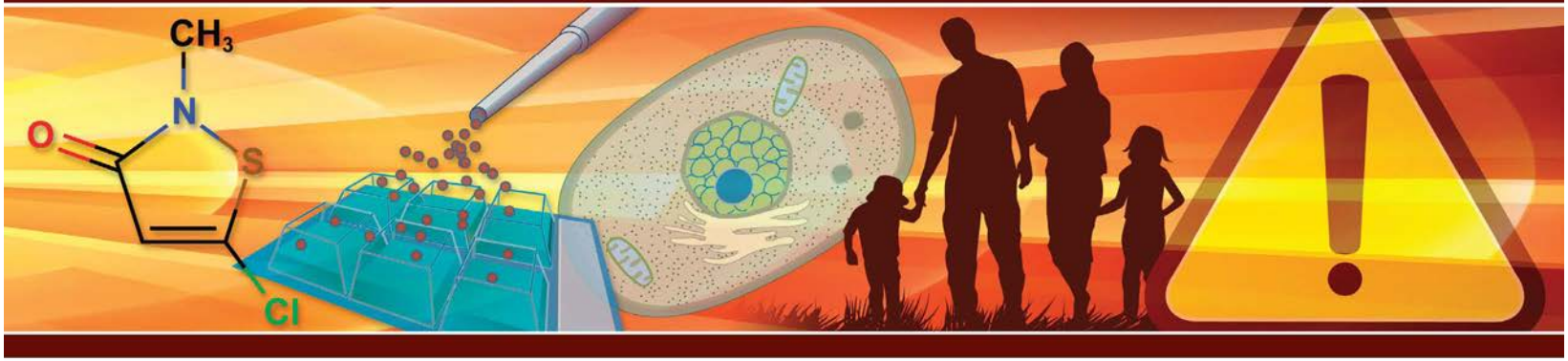
Scientific Workshop



Adverse Outcome Pathways: From Research to Regulation

September 3-5, 2014

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

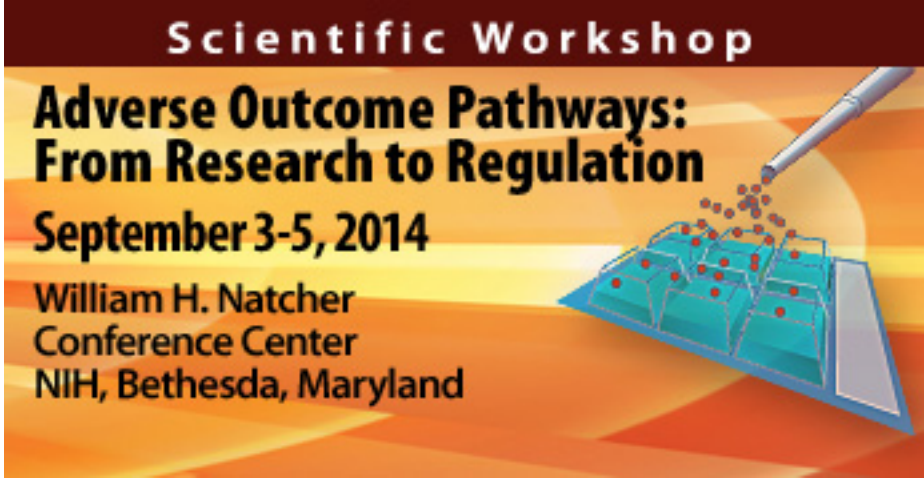
SOT | Society of Toxicology
Creating a Safer and Healthier World by Advancing the Science of Toxicology

NIH National Institute of Environmental Health Sciences

PCRM Physicians Committee for Responsible Medicine

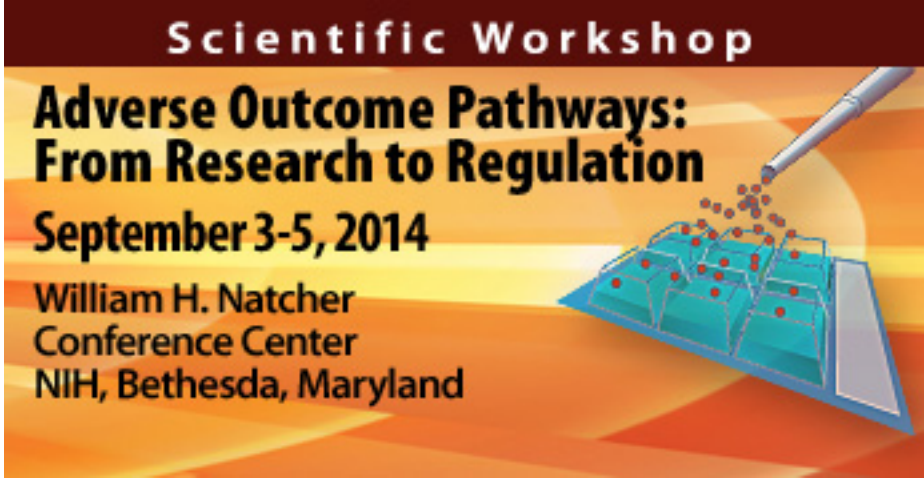
European Commission

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



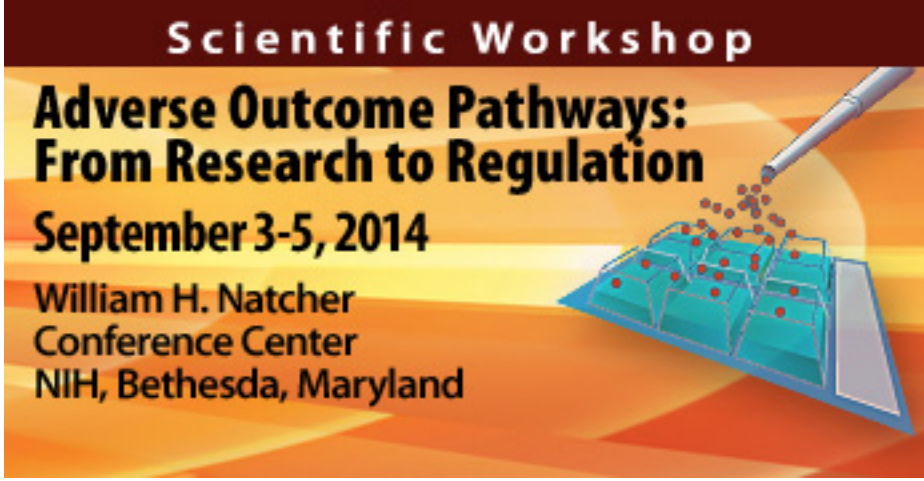
- Attendees/Speakers:
  - Research scientists
  - Regulatory decision-makers
  - Industry stakeholders
  - Nonprofit groups
  - Test method developers
  - Computational modelers
  - Epidemiologists
  - Informaticians
- Format:
  - Symposium talks
  - Discussion forums
  - Poster sessions
  - Junior investigator awards
  - Hands-on demonstrations
    - AOP Wiki/Effectopedia
  - Rotating breakout groups
    - Case study presentations
    - Charge questions

What is an Adverse Outcome Pathway (AOP)?



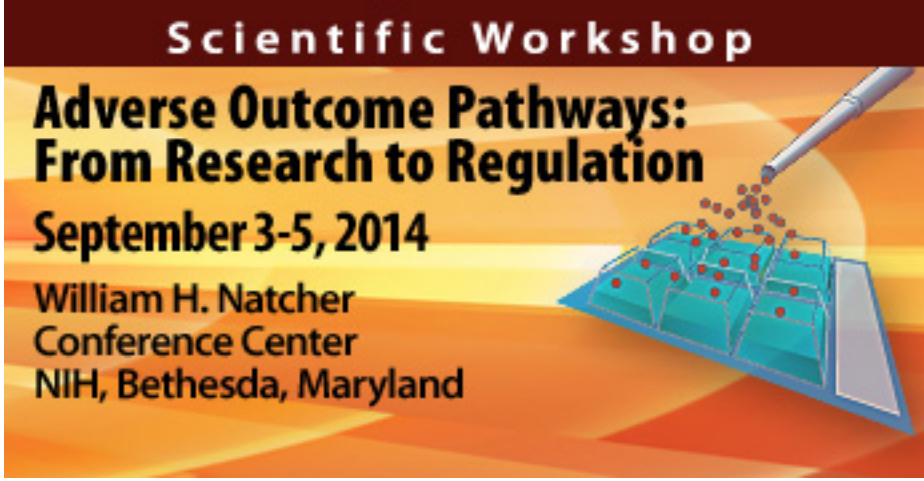
- AOP:
  - Conceptual framework linking molecular initiating events to cellular/tissue effects to adverse outcomes
  - Facilitates better mechanistic understanding of human and ecological toxicities
  - Helps relate exposure to a potentially toxic substance to an actual illness or injury
  - Provides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

Breakout Group Conclusions:



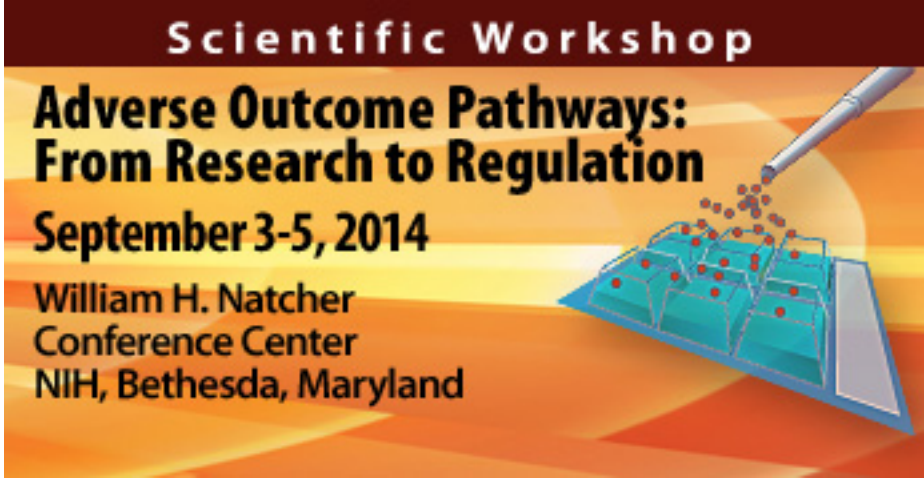
- Need to incorporate variability and uncertainty around exposure, species differences, kinetics, dynamics, and quantification of AOPs
- Develop systematic, transparent frameworks for creating confidence in AOPs across all stakeholders, based on the application (prioritization, risk assessment, test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



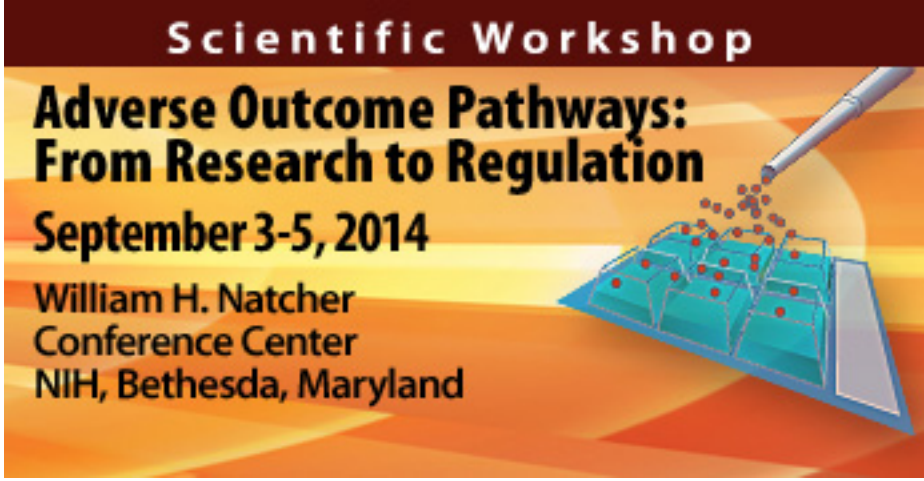
- Weight of evidence approaches using the Bradford-Hill criteria and reproducibility analyses, combined with databases of validated assays, decision strategies (including assumptions and applicability domains) and AOP networks, will allow fit-for-purpose AOP validation
- Priority pathways were identified 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) 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.