

# Adverse Outcome Pathways: From Research to Regulation

## Using AOPs for Regulatory Decisions: Confidence and Criteria Breakout Group 2

### Moderators

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# Background - 1

Adverse Outcome Pathways (AOP) are conceived as a general framework that allows the placement of available information on a particular biological pathway into an organized, usable format. Information in an AOP format could be used for assessing chemical risks in a number of ways, including:

1. Deciding which chemicals among a large set deserve additional attention (priority setting/screening/ranking)
2. Informing Integrated Approaches to Testing and Assessment (IATA)
3. Qualitative or quantitative hazard characterization
4. Quantitative risk assessment

The use of an AOP can be informed by the completeness and maturity of the knowledge underpinning the AOP and the extent to which the links between each key event are understood.

## Background - 2

- Most agree that an AOP can be at least somewhat useful at any stage of development, and that the effort, time, and cost required to develop a fully mature, quantitative AOP must be balanced by the immediate regulatory need for better predictive toxicology tools. The Bradford-Hill criteria for evaluating the weight of evidence underlying the elements of an AOP have been implemented into the OECD AOPs program.
- However, unified criteria have yet to be suggested that would help to determine a particular AOP's usefulness, given a particular stage of its development or verification and the regulatory context in which it is intended to be applied (“fit for purpose”).

## Background - 3

- This breakout group will explore the development of criteria for evaluating specific AOPs in specific use contexts from a variety of regulatory perspectives.

## Case Study Presenters

- Strategic Adverse Outcome Pathway Analysis to Inform Human Health Risk Assessment: An Example with Inorganic Arsenic
  - Christina Powers, U.S. Environmental Protection Agency
- Considerations for using AOPs in Human Health Risk Assessment of Environmental Contaminants
  - Annie Jarabek, U.S. Environmental Protection Agency
- Using Evidence-Based Toxicology to Evaluate AOPs
  - Thomas Hartung, Center for Alternatives to Animal Testing (CAAT)

# Charge Questions

## Criteria an AOP should fulfill

- The level of confidence needed for each of the following uses will vary
  - Priority-setting
  - IATA Development (note: an IATA is a tool that can be used for all of these purposes)
  - Hazard Characterization
  - Risk Assessment (dose response and exposure)
- Need to distinguish between developing the AOP and how/when it is actually applied
  - *Hierarchy of knowledge building – the use of this knowledge will vary depending on the application*
  - Also important that the regulated community understands what the expectations are
- Breadth of the data available will likely impact the level of confidence, as will the maturity of the AOP
- There will be steps in an AOP that are not defined but it will still be useful for priority setting
- Exposure also will factor into priority setting and risk assessment
- Consider cost/resources to evaluate AOPs for these applications

## Criteria an AOP should fulfill (continued)

- Need some threshold for amount of info needed (i.e., what is the minimum info needed before starting the process?)
  - Defining minimum info is difficult and will be case specific
    - Suggested minimum requirement: need at least 2 papers for a KE (i.e., reproducibility)
    - Establish relevance to humans
    - Don't necessarily need to include everything – need to include the minimum necessary information
    - Need to clearly define what the data are being used for
  - New info vs mining the literature – need to ensure adequate quality
    - Must be aware of biases that exist in literature
  - Systematic review and mechanistic review of assays utilized

# What are priority pathways? Should priorities be apical endpoint-specific? What are the research needs?

- Priority pathways (non-pharma applications):
  - Those with legislative mandates (e.g., EACs)
  - For assessment: Most prevalent diseases/largest public health threats
    - Cardiovascular; respiratory; cancer; diabetes; autism; hepatotoxicity; neurodevelopmental
    - Pathways that hit the most apical endpoints
  - Priorities in screening: ToxCast/ExpoCast approach to id exposure and activated pathways
  - Based on chemical class (e.g., metals)
  - “Lowest hanging fruit” (i.e., those we have the most information about already); building the library of key events
  - Critical path analysis – key controlled pathways that can be most disrupted in a robust system
- Research needs:
  - EACs – very little data on females and how to interpret (including life stage)
  - More wildlife representation and data is needed and also pathways not conserved in humans

## **How can AOP development incorporate information on biomarkers (exposure, effect, susceptibility) or bioindicators? Would bridging between environmental and clinical arenas accelerate development or provide other benefit (e.g., verification)?**

- They should be linked
- Must have a framework to incorporate metabolism
- Need to make sure that events between exposure and MIE are accounted for (dosimetry)
- Biomarkers of effect and exposure – datasets should be available to determine exposure and effect
- Molecular key event could serve as a biomarker – in vitro to predict in vivo
- Diagnostic codes (e.g., IDC and CPT codes) could inform cost-benefit analysis and could also serve to direct AOPs

## How do the particulars of the pharmaceutical R&D process impact this conversation? Are AOPs useful for pharmaceutical companies? Regulators?

- AOPs are a very useful conceptual model for pharma
  - Repository of knowledge
  - Captures key events in toxicological processes
- Getting putative AOPs out for comment/discussion will ultimately generate additional support (will also be more cost effective to share this information)
  - The concepts associated with AOPs have been used by pharma for a long time – just haven't been called AOPs
  - Early discovery applications
  - Identify targets for developing compounds for a specific disease process
- Critical path initiative (public/private partnership for biomarker qualification)

## What do you need to replace a test (or test guideline, from an OECD perspective)?

- Need to explicitly justify how the method is better/advantages offered
- As good as or “better”
  - More predictive, faster, cheaper, increased relevance to humans/target population
- Fit for purpose validation – focus on regulatory questions to be addressed
- Predictivity of endpoint of interest needs to be sufficient to provide high confidence to justify replacement
  - Will need to justify why it is different than the current standard (may or may not be the same)

# Can we envision a set of AOP-based assays replacing a test guideline, or will regulators move away from “OECD-approved” test guidelines, in favor of an IATA-based approach, completely?

- Not necessarily mutually exclusive
- Regulators are actually encouraging IATA/alternate testing approaches (which may be “IATA-like”) if they are adequately justified/provides sufficient confidence in the prediction
  - NOTE: The group discussed the different jurisdictions that would actually be involved in these decisions
- Toolbox of OECD TGs that are validated and would be used in the IATA based approach
- IATA will leverage best available methods – may often be OECD TG methods
  - Some OECD TGs are actually simple IATAs (e.g., eye irritation/corrosion)
  - Do we need OECD guideline IATAs?

## What external factors are important?

- Education
- Information technology
- Policy or legislative considerations
- Communication
- Terminology is a stumbling block
- Linkage to specific decisions