National Institute of Environmental Health Sciences
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Methods2AOP: An International Collaboration to Integrate Assay Annotations into the AOP Key Event Descriptions

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Background: Adverse Outcome Pathways (AOP)

- New approach methodologies (NAMs) in biological and computational sciences can generate mechanistic information which can be used to support safety assessments of chemicals.
- The adverse outcome pathway (AOP) is a conceptual construct that portrays existing knowledge concerning the linkage between a direct molecular initiating event and an adverse outcome at a biological level of organization relevant to risk assessment (Ankley et al. 2010; doi.org/10.1002/etc.34).
- While key events (KE) in an AOP are well-described, users and regulators may not be aware of specific methods that inform on that KE that can be deployed to interrogate chemical-AOP linkages.

Figure 1: Adverse Outcome Pathway Framework. The AOP framework links molecular initiating events (MIE) to and adverse outcome (AO) through a series of KE. One of the fundamental principles for the AOP framework is that AOP's MIEs and KEs must be detectable and measurable in order to substantiate proper linkage(s) between possible real-life stressors and effects on a particular KE.

AOP-Wiki

- The AOP-Wiki (aopwiki.org) is the primary repository of qualitative information for the international AOP development effort. The AOP-Wiki project is coordinated by the Organisation for Economic Co-operation and Development (OECD).
- The AOP-Wiki is hosted by the Society for the Advancement of Adverse Outcome Pathways (SAAOP) and serves as one component of the larger OECD-sponsored AOP Knowledgebase (AOP-KB; https://aopkb.oecd.org/index.html).
- The AOP-Wiki provides access to AOP information via a web interface that supports browsing and searching for AOPs, KEs, key event relationships (KERs), and stressors known to perturb the AOPs. It provides programmatic access to all information via web services as well as downloadable files containing all content in XML format.

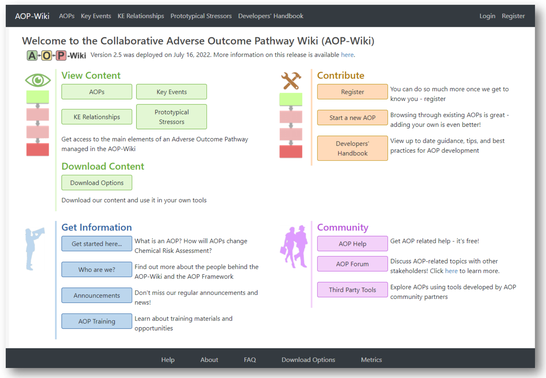


Figure 2: AOP-Wiki Homepage. Screenshot of the AOP-Wiki homepage showing the breadth of AOP information and resources available through this platform.

Goals of this Project

1. **Establish a dynamic collaboration: Methods2AOP**
   Key stakeholders joined an international collaboration to tackle challenges of mapping methods to AOPs.

2. **Develop framework to communicate NAM methods and integrate into AOP-Wiki**
   Aim to keep information requirements straightforward and non-prescriptive while prioritizing easy adoption among information providers, and collecting requisite details on test methods to increase the overall trustworthiness and utility of a methods-annotated AOP.

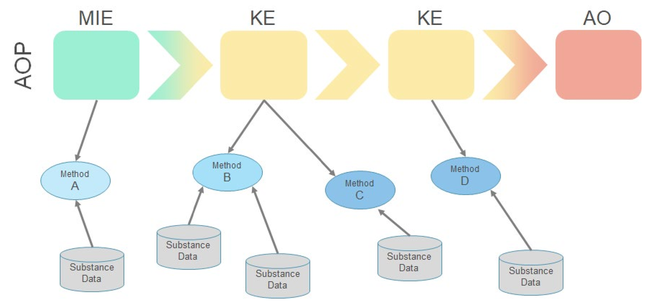
Methods2AOP Collaboration

Integrating Standardized Methods Tables

The Methods2AOP collaboration seeks to develop an infrastructure to accommodate the integration of defined methods details being provided and associated with specific MIE/KE components of AOPs.

Methods2AOP Vision for Method Integration

Adding methods tables to the AOP-Wiki will support development of associations between substances tested and methods used for informing on MIE/KE steps in AOP pathways (shown in Figure 3 below).



Scoping Content for Methods Tables

Identifying Minimum Necessary Fields for Annotating Methods to AOPs

The key focus of the Methods2AOP project is annotation of NAMs to relate them to KEs in AOPs. To effectively relate methods to KEs, developers must provide the detail required to bolster regulatory acceptance. At the same time, information requirements must be simple, concise, and minimally laborious. To accomplish these goals, two tables have been conceived. Table 1 includes fields that are critical to the interpretation of assay design and association to the AOP MIE/KEs while Table 2 provides additional technical information and insight into the regulatory status of the method. These tables represent a draft list of elements and will undergo refinement.

Table 1: Method Details for Establishing AOP Links

- Detection technology (ontologized)
- Experimental setting (ontologized)
- Method type (ontologized)
- Targeted biological endpoints (three ontologized fields)
  - Process or pathway
  - Gene or protein
  - Metabolites
- Complexity level
- Species specificity
- Tissue or cell type specificity
- Summary (free text)
- References (list of URLs)
- Other KEs this method has been applied to
- Relevance to the AOP KE (Boolean, or subjective ad hoc list, one per linked KE)
- Preference ranking among methods for this KE (KE-specific data)

Table 2: Technical and Regulatory Insights

- Relationship between detection technology and measured endpoint (Boolean)
- Measured observation (ontologized, opens if Relationship is indirect)
- Method trade name and provider (free text)
- Standard protocol availability (list of URLs)
- Factors to be considered for applicability to IVIVE (ad hoc list)
- Status of the method (ad hoc list)
- Limitation (free text)
- Window of sensitivity (free text)
- Duration of treatment (ad hoc list)
- Interferences or confounder (ad hoc list)
- Other factors to be considered (ad hoc list)
- Popularity (ad hoc list)

Implementation

Creating Interactive User Dialogue Boxes for Input

The AOP-Wiki will ultimately have interactive input forms to allow method developers and AOP authors alike to populate methods information.

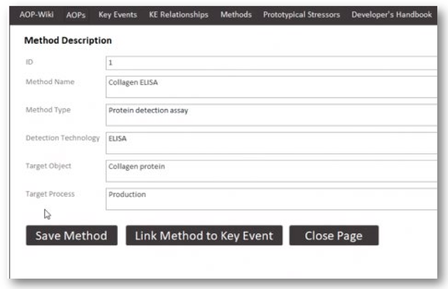


Figure 4: Example of a dialog box for Method Description input.

Summary

- The Methods2AOP collaboration has been formed to help integrate harmonized, ontologized, annotated methods description fields into the AOP-Wiki to support robust association of methods to MIE and KE.
- Defining methods that are relevant to defined AOPs can help bolster confidence in the use of NAM data within the AOP framework for regulatory purposes.
- The Methods2AOP collaborative is actively working to identify minimal information criteria and organization of relevant methods inputs into an approachable, intuitive, and actionable format.

Join the AOP-Wiki Community!
aopwiki.org

Acknowledgements

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