Abstract #3090

Enhancing the FAIRness (Findability, Accessibility, Interoperability, and Reusability) of the AOP-Wiki

Virginia K. Hench[1], Stephen W. Edwards[1], Travis Karschnik[2], Dan Villeneuve[2], Jason O'Brien[3], Clemens Wittwehr[4]
[1]RTI International, RTP, NC, [2]US EPA, Duluth, MN, [3]Environment Climate Change Canada, Ottawa, ON, Canada , [4]European Commission Joint Research Centre, Ispra, Italy

Background

The AOP-Wiki provides a central repository for development of adverse outcome pathways (AOPs) and the dissemination of AOP information.

What's an AOP?
An AOP describes a sequence of events commencing with initial interaction(s) of a stressor with a biomolecule within an organism that causes a perturbation in its biology (i.e., molecular initiating event, MIE), which can progress through a dependent series of intermediate key events (KEs) and culminate in an adverse outcome (AO) considered relevant to risk assessment or regulatory decision-making.
- AOP Developer's Handbook v2.5

Read more about AOP's in the AOP Developer's Handbook

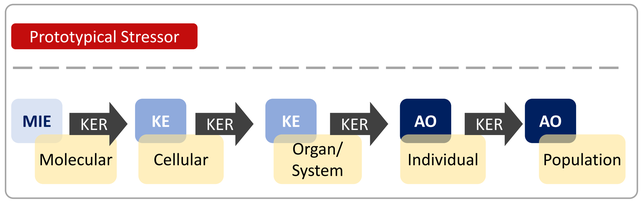
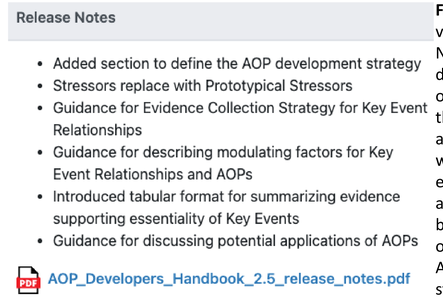


Figure 1: A visual representation of an AOP with the level of biological organization indicated for each event. The dashed line separating the Prototypical Stressor from the AOP is meant to acknowledge the role that stressor's play in shaping our understanding of evidence used to shape and support AOPs, while reinforcing the fact that AOPs are stressor agnostic.

Recent AOP-Wiki Feature Highlights

AOP Developer's Handbook

The AOP Developer's Handbook is now an integral part of the AOP-Wiki (since June 2022), making AOP guidance immediately accessible to AOP-Wiki users through links in the main navigation bar and from within instructional text, highlighted by the icons embedded throughout the core entity pages – the AOP, Key Event (KE), and Key Event Relationship (KER) pages.


Release Notes

- Added section to define the AOP development strategy
- Stressors replace with Prototypical Stressors
- Guidance for Evidence Collection Strategy for Key Event Relationships
- Guidance for describing modulating factors for Key Event Relationships and AOPs
- Introduced tabular format for summarizing evidence supporting essentiality of Key Events
- Guidance for discussing potential applications of AOPs

AOP_Developers_Handbook_2.5_release_notes.pdf

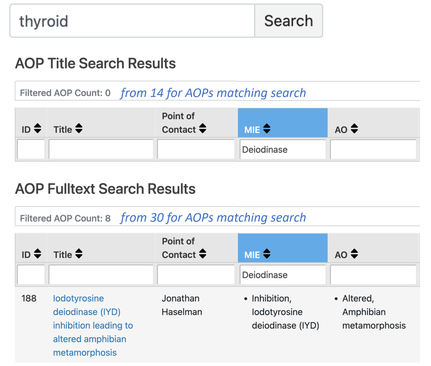
Figure 2: Handbook version 2.5 Release Notes. The release notes draw attention to aspects of the AOP framework that are evolving to accommodate integration with data sources external to the AOP-Wiki and to better bridge between multiple types of AOP-Wiki users and AOP community stakeholders.

Strategy Fields to Improve Interoperability and Reusability

- The context and strategy fields were introduced to illuminate the *why* and *how* behind an AOP.
- The AOP **context field** should be used to explain why an AOP was developed, for example to address key research questions or meet specific regulatory needs
- The **strategy fields** are critical to increasing transparency around the workflow used to identify and assemble relevant evidence.

Filtering to Improve Findability

Filtering on AOP search results enables more targeted options when browsing through both Title and Full text Search Results.


thyroid Search

AOP Title Search Results

Filtered AOP Count: 0 *from 14 for AOPs matching search*

ID	Title	Point of Contact	MIE	AO
			Deiodinase	

AOP Fulltext Search Results

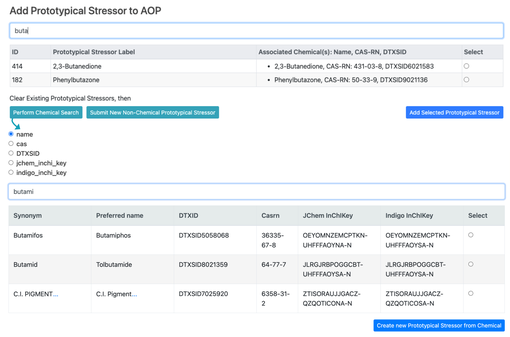
Filtered AOP Count: 8 *from 30 for AOPs matching search*

ID	Title	Point of Contact	MIE	AO
			Deiodinase	
188	Iodotyrosine deiodinase (IYD) inhibition leading to altered amphibian metamorphosis	Jonathan Haselman	• Inhibition, Iodotyrosine deiodinase (IYD)	• Altered, Amphibian metamorphosis

Figure 3: Result counts and first row of full text results when searching for AOPs matching "thyroid", then filtering on the "thyroid" search results to find AOPs with "Deiodinase" in the MIE name.

Prototypical Stressor Updates

Prototypical stressors are stressors for which responses at multiple key events in addition to the MIE have been well documented. AOPs may be annotated with prototypical stressors that may serve as positive controls for the KEs along the pathway and serve as a reference for comparing potencies along the pathway.


Add Prototypical Stressor to AOP

butaj

ID	Prototypical Stressor Label	Associated Chemical(s): Name, CAS-RN, DTXSID	Select
414	2,3-Butanedione	• 2,3-Butanedione, CAS-RN: 431-03-8, DTXSID6021583	
182	Phenylbutazone	• Phenylbutazone, CAS-RN: 50-33-9, DTXSID9021136	

Clear Existing Prototypical Stressors, then
Perform Chemical Search | Submit New Non-Chemical Prototypical Stressor | Add Selected Prototypical Stressor

name
cas
DTXSID
jchem_inchi_key
indigo_inchi_key

butami

Synonym	Preferred name	DTXID	Casrn	JChem InChIKey	Indigo InChIKey	Select
Butamifos	Butamiphos	DTXSID5058068	36335-67-8	OEYOMNZEMCPTKN-UHFFFAOYNA-N	OEYOMNZEMCPTKN-UHFFFAOYSA-N	
Butamid	Tolbutamide	DTXSID8021359	64-77-7	JLRGJRBPOGGCBT-UHFFFAOYSA-N	JLRGJRBPOGGCBT-UHFFFAOYSA-N	
C.I. PIGMENT...	C.I. Pigment...	DTXSID7025920	6358-31-2	ZTISORAUJJGACZ-QZQOTICONA-N	ZTISORAUJJGACZ-QZQOTICOSA-N	

Create new Prototypical Stressor from Chemical

Figure 4: The *soon-to-be-released* workflow for adding a Prototypical Stressor to an AOP demonstrates how Prototypical Stressors can be created from chemicals or as non-chemical stressors. First, AOP developer users should search to see if an existing Prototypical Stressor already exists in the AOP-Wiki. If not, the user can create a new Prototypical Stressor that is based on a chemical or non-chemical entity.

Licensing to Support Reusability

Historically, most content in the AOP-Wiki has been governed by a Creative Commons, Attribution License (CC BY), which will soon be transitioned to an Attribution, Share-Alike License (CC BY-SA) with upcoming release 2.6. Also, creators of new AOPs will have the option to choose an "All Rights Reserved" license, that essentially allows the AOP pages to function as a pre-print server, until the author is ready to publish the content.

Integrating with Third Party Tools

Figure 5: The AOP-Wiki now supports link-outs to third party tools, with the Wiki Kaptis tool from Lhasa Limited being the first tool directly embedded within the main AOP page. Other third-party tools that are featured on the AOP-Wiki Tools page include the Adverse Outcome Pathway Database, AOP-helpFinder, AOP-Wiki RDF, and Biovista Vizit.

Evidence Map Prototype

Entries in the Evidence Map and Observation form images below are for illustrative purposes only. They are not meant to reflect information curated by AOP developers with domain expertise.

A) Supporting Evidence | Conflicting Evidence | NR Not Relevant | Not yet assessed

Evidence Map

Title	First Author	Biological Plausibility	Dose Concordance	Temporal Concordance	Incidence Concordance
Oocyte maturation: Converting the more	Woodar	✓			
Ovotoxicity in Female Mice Following more	Thomas	✓	✓	NR	×
A time-course analysis of effects of more	Bartke		✓		
Fungicide Impacts on Ovary Culture more	Humphr		✓		
Effects of a short-term exposure to more	Pennam		✓		

Add New Evidence Row

B) **Dose Concordance Evidence**
- in vivo experiments in male mice demonstrated dose concordance (Thomas, 2001)
- in vitro experiments in zebrafish demonstrated dose concordance (Bartke, 2006)
- ovarian culture experiments demonstrated dose concordance (Humphr, 1997)
- Experiments in female fathead minnows demonstrated dose concordance (Pennam, 1999)

C) Evidence metadata

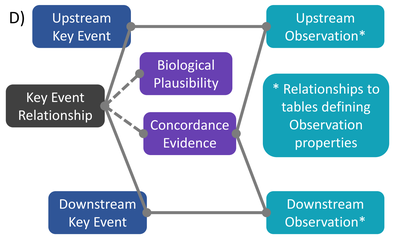
Upstream Event Observation Property Fields | Downstream Event Observation Property Fields

Support status selection menu

Summary text

Submit

D)



E) Observation Form fields, with field type and data table source:

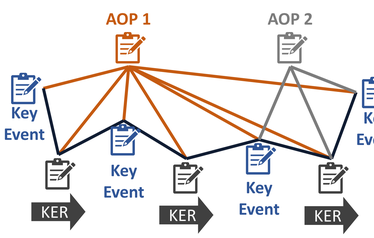
Effect: increased	Menu options from Event Component Actions
Endpoint: cholinergic synapse	Autocomplete from Event Component Objects
Experiment Type: in vivo	Menu options from *experiment_types*
Stressor: Benzo(a)pyrene	Autocomplete from *chemicals*
Taxon Term: Mus musculus	Autocomplete from *taxon_terms*
Life Stage: Select life stage	Menu options from *lifestage_terms*
Sex: Select sex term	Menu options from *sex_terms*
Organ	Autocomplete from *organ_terms*
Cell	Autocomplete from *cell_terms*

Figure 6: User interfaces and data models developed for the Evidence Map prototype project: A) An Evidence Map table on a KER page populated with details collected through associated forms, represented in panels C & D. Each table row holds a single reference with columns for biological plausibility and each empirical evidence type, that are given a support status score based on the evidence in the reference. B) Details submitted through the evidence forms populate the relevant section of the KER page. C) The Concordance Evidence Form includes 2 subforms, one for each upstream and downstream Observation, along with a support status selection menu and a free text summary field. D&E) The data model representations shows how the Observation and Evidence entities are connected to Key Event and Key Event Relationships, respectively. Importantly most Observation properties are defined based on associations to tables with predefined terms, which are referenced in E next to the Observation form detail.

Future Direction: AOP-Wiki 3.0

Current Wiki-inspired Data Model Structure

A significant amount of content for the 3 main entities – AOPs, KEs, & KERs – is stored in free-text format with a limited set of subsections that use tabulated data formats.



Tabulated Data fields

AOPs
- Prototypical Stressors
- Taxonomic Applicability, Life Stage, and Sex Applicability

Key Events
- Level of Biological Organization
- Event Components
- Taxonomic Applicability, Life Stage and Sex Applicability

KERs
- Taxonomic Applicability, Life Stage and Sex Applicability

Challenges associated with the existing data model

- Related KEs and KERs have no way of sharing common information
- Narrative format is good for humans to read but impossible for computers to use

→ Proposed Solutions:
- Use controlled terminologies & ontologies to capture discrete information with structured forms
- Minimize free text fields on all entities except for AOPs

- Similar information is captured on different pages, which leads to inconsistencies among authors in terms of information that gets included on each entity page

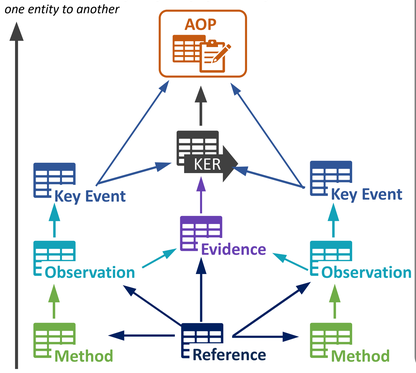
→ Proposed Solutions:
- Design data model so that information captured at granular levels rolls up to higher levels to avoid duplicative and/or inconsistent information submission

- The relationship between supporting evidence and source references is entirely dependent upon citations stored in free text fields at the database level, rather than as structured metadata

→ Proposed Solutions:
- Explicitly capture references as discrete entity instances linked to evidence and method-related entities along with capturing the strategy used for assembling the literature

Desired Data Structure

Direction of arrows reflects flow of information from one entity to another



Guiding Principles informing data model revision

- Increase FAIRness
- Capture information in a single place, but allow sharing of information between entities
- Allow for *related* Key Events to share information
- Harness benefits of working with controlled vocabularies and ontologies
- Enhance provenance tracking throughout the system

Ongoing and Upcoming AOP-Wiki Input Opportunities

Numerous international efforts have informed current thinking or are underway to collect additional input from the AOP-Wiki user community on the future design:
- Evaluate FAIRness and provide recommendations for improvement led by Clemens Wittwehr, Penny Nymark, and Luiz Bonino
- Improve AOP visualizations led by Anna Maria Carusi
- An upcoming SAAOP Workshop series in the spring/summer of 2023
- Methods2AOP collaboration, represented at SOT as abstract 3643/poster P125
- CIAO, led by Clemens Wittwehr, Penny Nymark, and Laure-Alix Clerbaux
- AOP Forum developed and maintained by Anthony Coe

Acknowledgements

The contents of this poster neither constitute, nor necessarily reflect the policies of US EPA, ECCC, or the EU JRC. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

OECD AOP-KB subgroup & in-kind contributions

Financial contributions

Explore the AOP-Wiki

For more Information, contact Virginia "Ginnie" Hench at vhench@rti.org