
Webinar on recent improvements and future challenges for the Adverse Outcome Pathway (AOP) framework and the AOP-Wiki
WHEN: 14 December 2022
13:00 - 14:30 CET
07:00 - 08:30 EDT
OECD
BETTER POLICIES FOR BETTER LIVES

Agenda

- Introduction
- AOP-Wiki 2.5 and 2.6:
  Rationale behind added features, hands-on technical implementation
- Beyond AOP-Wiki 2.6:
  Challenges ahead and how to address them
- Q&A and discussion
- Outlook and next steps

Panelists and speakers

• Clemens Wittwehr • Brigitte Landesmann	European Commission, Joint Research Centre (JRC), Ispra, Italy
• Dan Villeneuve • Michelle Angrish	United States Environmental Protection Agency, Center for Computational Toxicology and Exposure, Great Lakes Toxicology and Ecology Division
• Jason O'Brien	Ecotoxicology and Wildlife Health Division Environment and Climate Change Canada
• Bette Meek	University of Ottawa
• Annamaria Carusi	Interchange Research
• Shihori Tanabe	National Institute of Health Sciences, Japan
• Ginnie Hench • Steve Edwards	GenOmics, Bioinformatics, and Translational Research Center, RTI International
• Nathalie Delrue	OECD, Environment Health and Safety division, Environment Directorate

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- AOP-Wiki 2.5 and 2.6:
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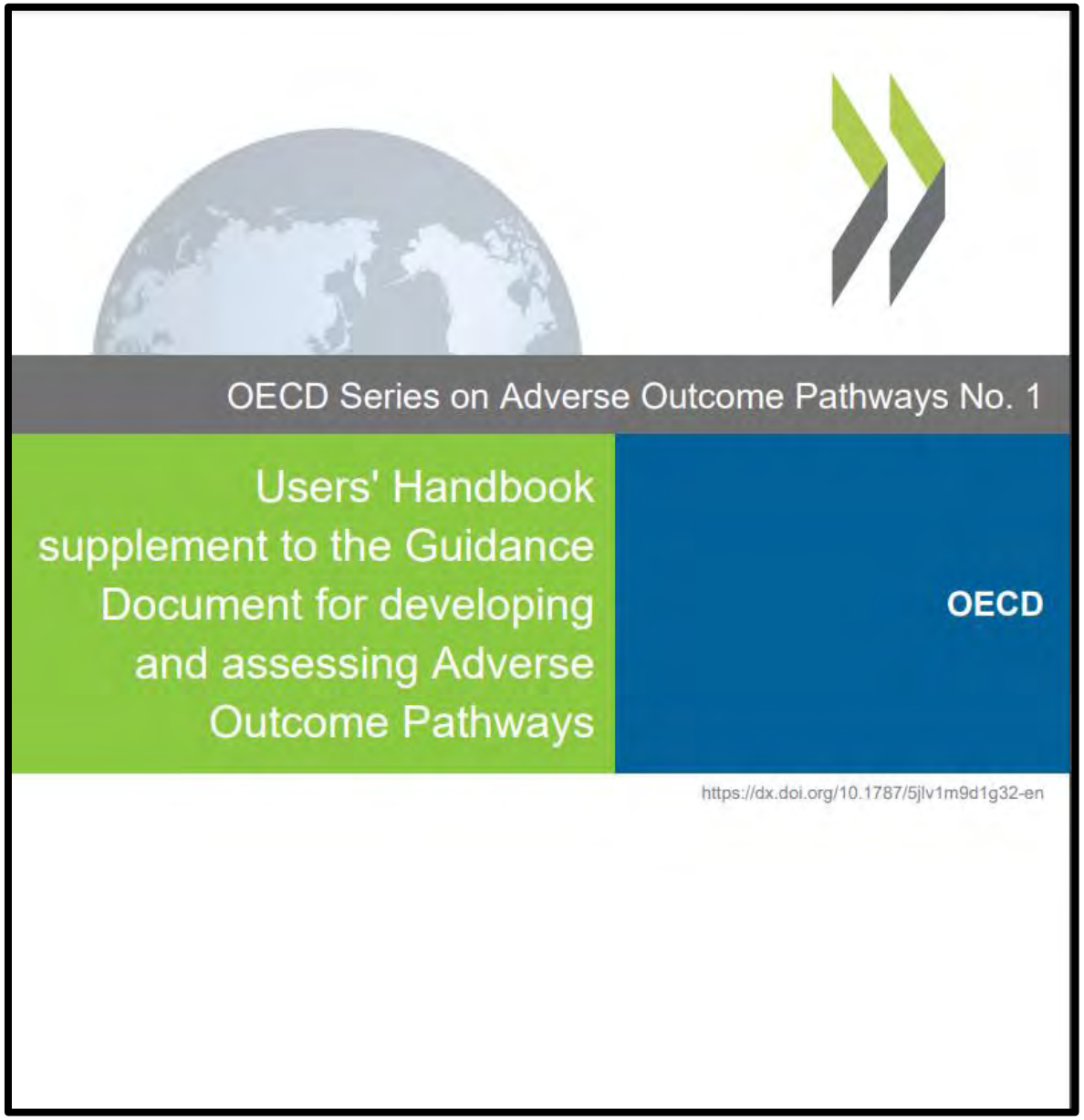
Resources for AOP Developers

Users' Handbook

- "How to" guide for development/description of AOPs in the AOP-Wiki.
- All previous versions reviewed and approved by working parties and published in OECD series on AOPs.
  - Time-consuming
  - Some content becoming out of date as framework evolves
  - Link to pdf from AOP-Wiki
- Foundation for help-text in AOP-Wiki



Next generation Handbook (version 2.5)

1. Re-named as “AOP Developers’ Handbook”
   - better reflects content and target audience.
2. Fully electronic, navigable version added to AOP-Wiki
   - Easier access for AOP developers
   - More seamless integration with AOP-Wiki help text
   - When handbook text updates, relevant AOP-Wiki help information updates
   - Streamlined – no longer a need to link to “implementation in the AOP-Wiki” sections in the handbook
3. More rapid updates are now feasible
   - Current version in the AOP-Wiki is the officially recognized version of record
   - All previous versions are archived with release notes

Electronic AOP Developer's Handbook

Table of Contents

Archived Handbooks Download PDF

Developers' Handbook 2.5

Released July 15, 2022

FOREWORD

This document is the AOP Developers' Handbook supplement to the Guidance Document for developing and assessing Adverse Outcome Pathways (AOPs) [ENV/JM/MONO(2013)6, Second Edition]. The Guidance Document provides a historical background for the AOP development programme, and outlines the elements required to construct an AOP as well as the principles of the AOP framework.

The AOP Developers' Handbook (previously "Users' Handbook") supplement was prepared initially in June 2014 by a subgroup of the Extended Advisory Group on Molecular Screening and Toxicogenomics (EAGMST). At that time it was acknowledged that the Handbook should be revised as expert groups and member countries acquire experience in developing, assessing, and applying AOPs. The present version of the AOP Developers' Handbook reflects the most recent principles, practices, and recommendations pertaining to AOP development as implemented and supported via Release 2.5 of the adverse outcome pathway Wiki (AOP-Wiki; aopwiki.org)

The Handbook was reviewed and discussed by EAGMST at the 15th meeting of the EAGMST, in June 2022, and endorsed by EAGMST through written procedure.

Contributing Authors: Daniel Villeneuve, Bette Meek, Barbara Viviani, Tanja Burgdorf, Carlie LaLone, Jason O'Brien, Dries Knapen, Michelle Angrish, Rex Fitzgerald, Shihori Tanabe

Archived Handbooks

Developers' Handbooks

Ver.	Release Date	View	Download	Release Notes	Forum Links
2.5	July 15, 2022	Digital Copy, v2.5		• 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	https://aopwiki.org/forums/forumdisplay.php?fid=19
2.0	February 14, 2018	AOP_Handbook_release_2018.pdf		OECD (2018), "Users' Handbook supplement to the Guidance Document for developing and assessing Adverse Outcome Pathways", *OECD Series on Adverse Outcome Pathways*, No. 1, OECD Publishing, Paris, https://doi.org/10.1787/5jlv1m9d1g32-en.	
1.0	September 25, 2014	AOP_Handbook_September_25_2014_release.pdf		This document is a supplement to the Guidance Document for developing and assessing Adverse Outcome Pathways (AOPs) [ENV/JM/MONO(2013)6] (AOP guidance hereafter). The AOP Guidance, published in 2013, only one year after the OECD programme on the development of AOPs was initiated, was considered a first version which would be revised as expert groups and member countries	

- All previous developer's Handbooks are available.
- AOPs need to be compliant with the Handbook version associated with creation date or newer.
- Release notes documenting significant changes to each version are provided.
- Forum link to provide feedback

Coaching

- Even with the handbook as a guide, AOP development can be challenging – especially for first-time developers
- OECD established a “coaching” program to pair new with experienced developers
- Coaches are available to answer questions and provide guidance
- Coaches assure compliance with guidance and handbook during the development process
- Coaching avoids discouraging rejection of AOPs after extensive work has been done

Coaching-related documents are available at threads of AOP FORUM in AOP-Wiki.

[Announcements]
AOP COACHES CHECKLIST AND FINAL REVIEW REPORT <Updated 11-29-22>
Guide for Coaches <Updated 11-24-22>

[Coaching Forum]
Coaches (OECD EAGMST AOP Coach Status) <Updated 11-29-22>

Revision of Guide for Coaches (version 11-24-22)

- Part V. AOP Follow-up
- 1) How can Coaches follow-up the development of AOP?

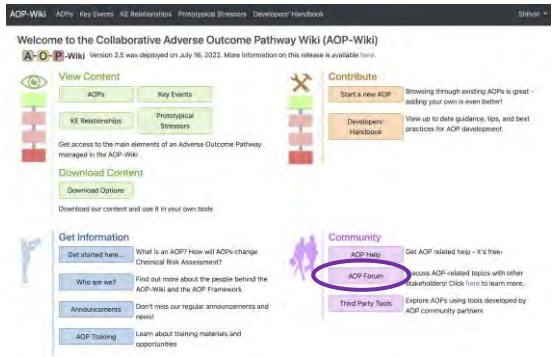
Coach lead will ask all the Authors/Developers in coaching whether AOP development will be continued or not around October every year. Authors/Developers are asked to tell Coaches whether it is okay to stop following up the AOPs if Authors/Developers don't have any intention to develop the AOP furthermore, since Coaches are worried about development status of the AOPs. Coaching of the AOPs in active development will continue as before.

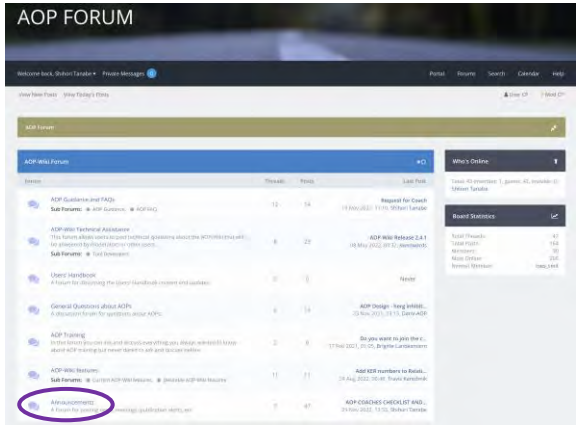
- 2) How can we know whether the KE/KER have been reviewed by EAGMST?

It can be found in Key Event / Key Event Relationship Overview in each KE or KER page. If OECD Status is "WPHA/WNT Endorsed", it has been reviewed by EAGMST.

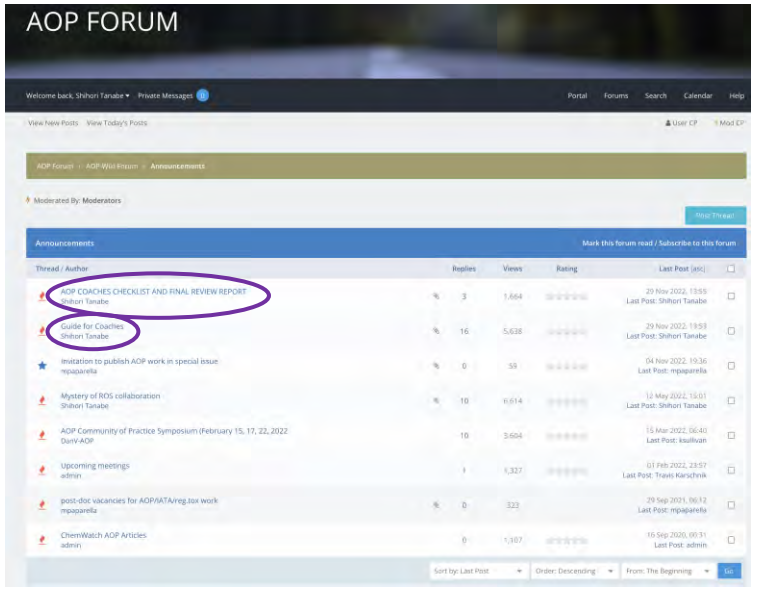
---As of November 24th, 2022

Prepared by: Shihori Tanabe, Dan Villeneuve, Rex FitzGerald, Magdalini Sachana, Jason O'Brien, Nathalie Delrue, Cinzia La Rocca, Carlie LaLone, Judy Choi, Andrea Terron, Jinhee Choi, Kristie Sullivan, Jung-Hwa Oh, Julija Filipovska, Tanja Burgdorf, Dries Knapen, Vinita Chauhan, Kevin Crofton, Travis Karschnik, Olga Tcheremenskaia, Coaching Team, and Handbook Guidance Gardening, AOP Knowledge-Base, and External Review Subgroup members.





https://aopwiki.org/forums/forumdisplay.php?fid=6



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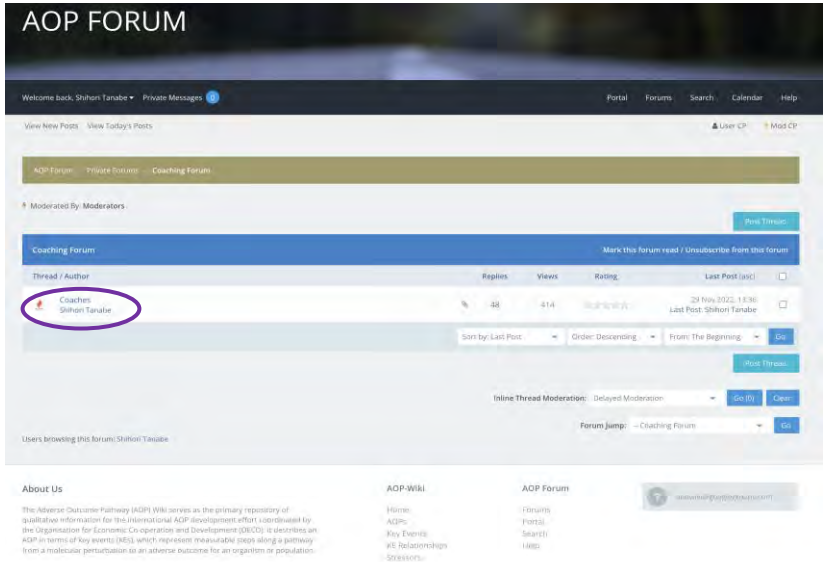


https://aopwiki.org/forums/forumdisplay.php?fid=15

Coach identification will be added to AOP page

- Rationale:
  - Increased visibility for the contributions of coaches
  - Incentivization – coaching can be cited as professional achievement/contribution
  - Reminder for developers
  - Ability to search for AOPs by coach

Coach identification will be added to AOP page

Authors

Text

Point of Contact

Text

Contributors

Tagged | Tagged | Tagged

Coach(es)

Tagged | Tagged

Implementation

- Coaches user ids will be tagged similarly to those of contributors
- Requires coaches have author access in AOP-Wiki (to be confirmed)

Training resources

- OECD EAGMST Education, Communication, and Training Subgroup (ETC)
    - Organizes, manages and makes available, training courses, materials
    - Develops communications materials
    - Recently reviewed/catalogued/organized OECD program training materials, to:
        - Categorize (Basic, Advanced, Editors and Reviewers)
        - Update
        - Stream to most relevant and current
        - Describe and time stamp
    - CE course at ICT/Eurotox (quantitative AOPs) to be posted shortly
    - CE course at SOT 2023 (Nashville, March 19th – 23rd)

- Available via AOP-Wiki training page/posted on the AFSA website

Get Information

Get started here...	What is an AOP? How will AOPs change Chemical Risk Assessment?
Who are we?	Find out more about the people behind the AOP-Wiki and the AOP Framework
Announcements	Don't miss our regular announcements and news!
AOP Training	Learn about training materials and opportunities

AOP Training

Help and Guidance

General

The AOP-Wiki help pages provide descriptions of each field in the wiki and includes links to the relevant sections in the AOP Developers' Handbook for more information.

The online AOP Developers' Handbook contains all the information from the OECD AOP Developers' Handbook in a web accessible format. The original document is still available for download.

If you have any **questions** that are not addressed below please check the AOP Forum and/or Frequently Asked Questions page.

Training Wiki

We have launched a training wiki to allow users to learn the new system before making changes on the new production wiki. You do not need to be an author on this wiki to be granted author status on the training wiki, but all information in the training wiki is purged periodically and no mechanism exists to migrate information from that system to this one. If you would like to request author privileges on the training wiki, please contact us at aopwiki@googlegroups.com.

Training Events

Request Training

A community of AOP developers and users is available to develop trainings for groups, projects, and institutions. If you are interested in exploring the possibility or setting up a training, please fill out this form and someone will respond to your request.

OECD AOP Webinars

The OECD has hosted a series of webinars focused on a variety of aspects related to Adverse Outcome Pathways. Topics include journal review of AOPs, training needs and opportunities, tips for AOP development, assembling and evaluating weight of evidence, and the AOP framework. The webinar recordings and slides can be found in the middle of this page.

Upcoming Events

Checking in on Adverse Outcome Pathways (AOPs): Evolving Development, Evaluation, and Application. Society of Toxicology Annual Meeting, March 19th, 2023, Nashville, U.S. (Fee for course) More information

Training Materials

Catalog of Training Materials and Resources

A variety of presentations, recordings, and other resources created by the AOP Community have been collected by the Animal Free Safety Assessment Collaboration. The collection can be explored here: https://www.afsacollaboration.org/tox21/get-trained/#training-resources.

AOP Wiki Training Page linked to AFSA Webpage - AOP Training Resources Roadmap and Organization

AOP resources

The OECD AOP development programme is overseen by the Extended Advisory Group on Molecular Screening and Toxicogenomics (EAGMST). Their website describes the programme and contains many valuable resources, including a series of webinars [link]. The AOP concept can also be applied as a framework to develop Integrated Approaches to Testing and Assessment (IATA) and the OECD website on IATA again contains many links to informative resources.
The following materials have been assembled to provide information about the development and application of AOPs, ranging from introductory to more advanced and those tailored specifically for AOP reviewers and journal editors.

Introductory Resources

No.	Title	Description	Year	Type	Notes
1	The concept and all basic principles of an AOP	This video describes the concept and all basic principles of an AOP. This was presented by Brigitte Landesmann (JRC) within Session 1 (Introduction to AOPs) of a workshop organised by the Institute of Radioprotection and Nuclear Safety (IRSN) under the mandate of MELODI, in collaboration with the ALLIANCE and the contribution of EURADOS, OECD/NEA/CRPPR/HLG-LDR and Health Canada.	2021	Video	Timestamp: 3min. Length: 27min.
2	The Adverse Outcome Pathway Framework: The Foundation for	This short course is a brief, high-level (beginner) overview of the value of AOPs and their contribution to toxicology. Topics covered are as follows:	2018	Video	Note: Scroll down to access other videos. Length: 7min, 5min, 10min, 6min, 4min.

Introductory n = 7

More Advanced n = 10

Reviewers & Journal Editors n=4

https://www.afsacollaboration.org/tox21/get-trained/

Third Party Tools

- The AOP-Wiki cannot possibly cover all functionalities that the stakeholder community might request
- A series of pilot collaborations with outside software providers was initiated.
- Connections to their systems are now integrated into the AOP-Wiki:
  - Novel ways of graphical AOP depictions
  - support in identifying literature that strengthens the evidence behind AOP elements are now provided by third party tools
- Based on these pilot experiences, more possibilities for such collaborations will be identified in the future.

European Commission

Third Party Tools listed within AOP-Wiki

AOP-DB

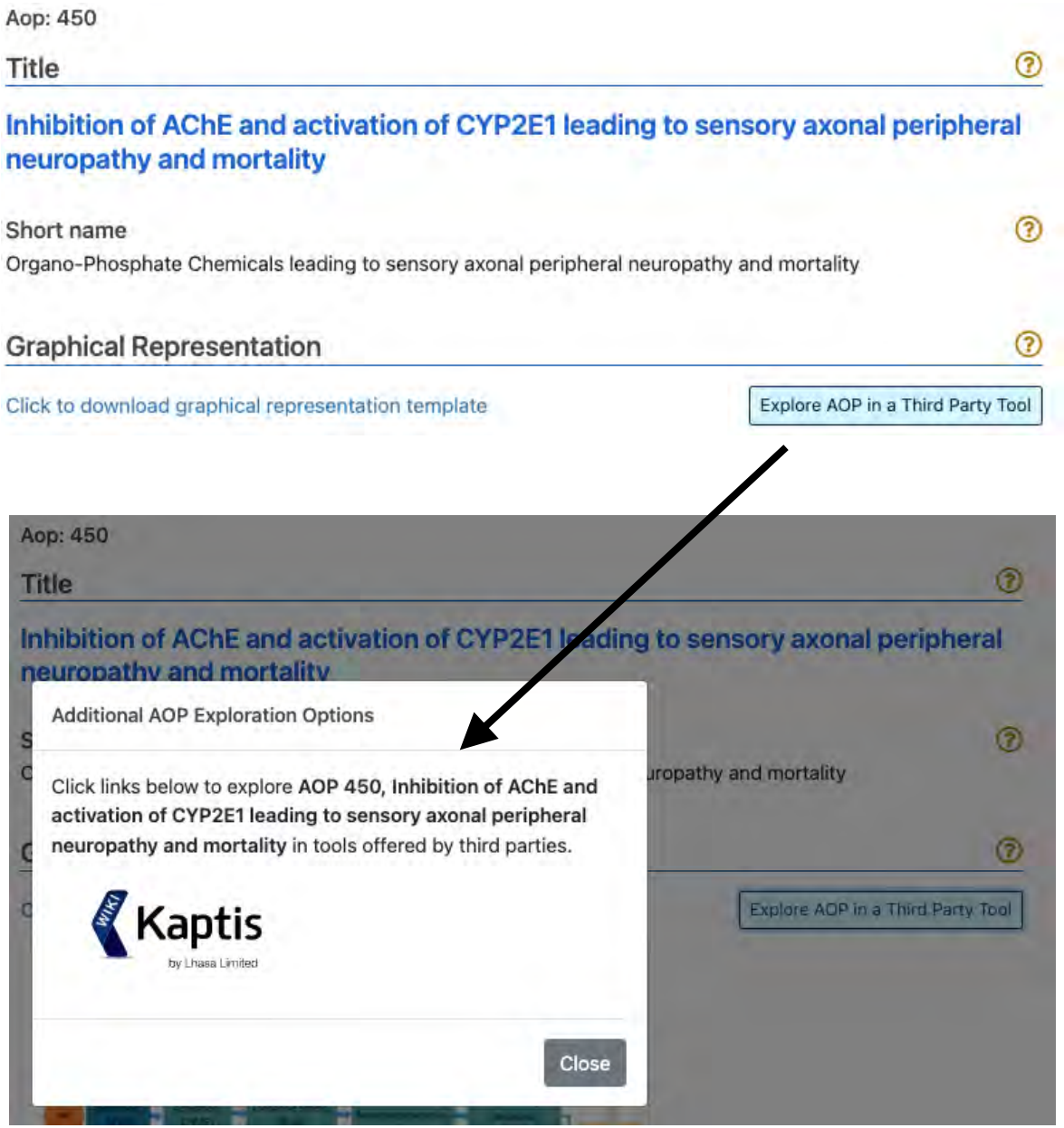
Vizit
A Biovista product

AOP-helpFinder

AOP Wiki RDF

Kaptis
by Lhasa Limited

First third-party tool to be integrated into AOP page



Updates to the Framework

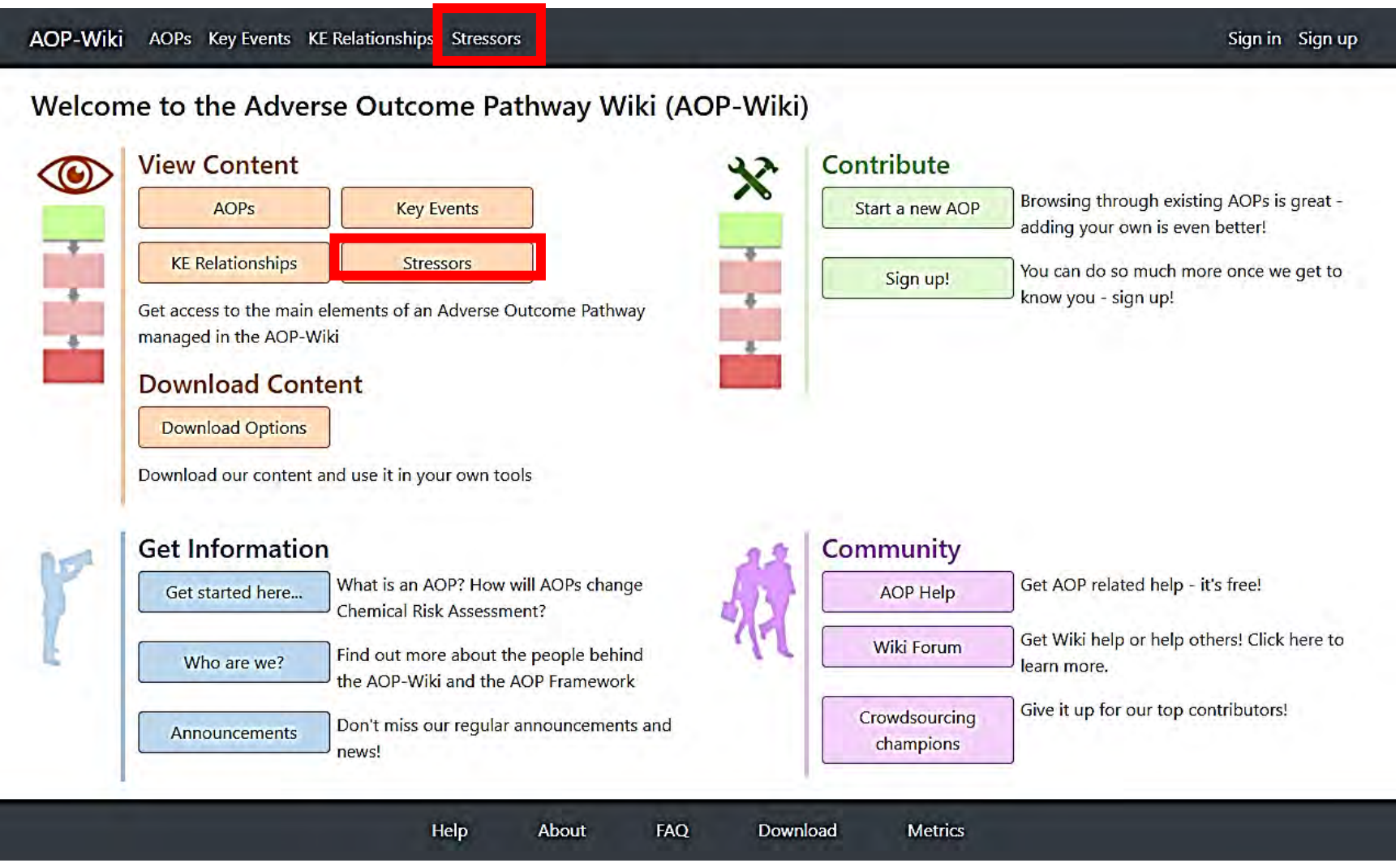
Stressors and the AOP-Wiki

- AOPs are not specific to stressors
- Intended for AOP-Wiki to be search by bioactivity/biological effect

- Risk assessments and chemical safety decision-making tend to be chemical specific

Users have wanted the ability to search the AOP-Wiki by stressor

Stressors and the AOP-Wiki



In previous version of the AOP-Wiki, Key Events could be annotated with lists of stressors (that activate that KE)

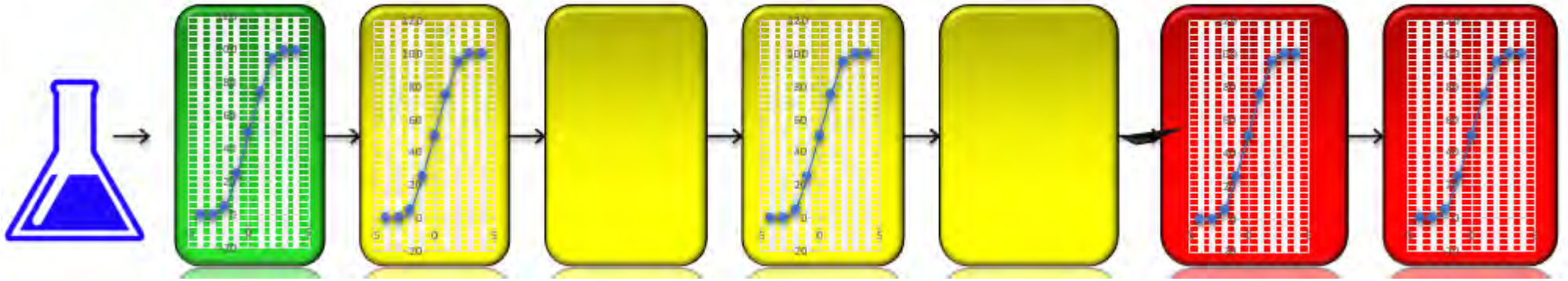
There was a stressor list, and ability to search by stressors

Problems

- Stressor lists are not comprehensive
- Credibility requires evidence
- Evaluating evidence that a stressor activates a KE and/or associated AOP becomes a de facto hazard assessment.
- Not the role of AOP developer

Stressors and the AOP-Wiki

- After considerable debate/discussion within EAGMST decided to remove stressors from AOP-Wiki
- Instead focus on **Prototypical Stressors**

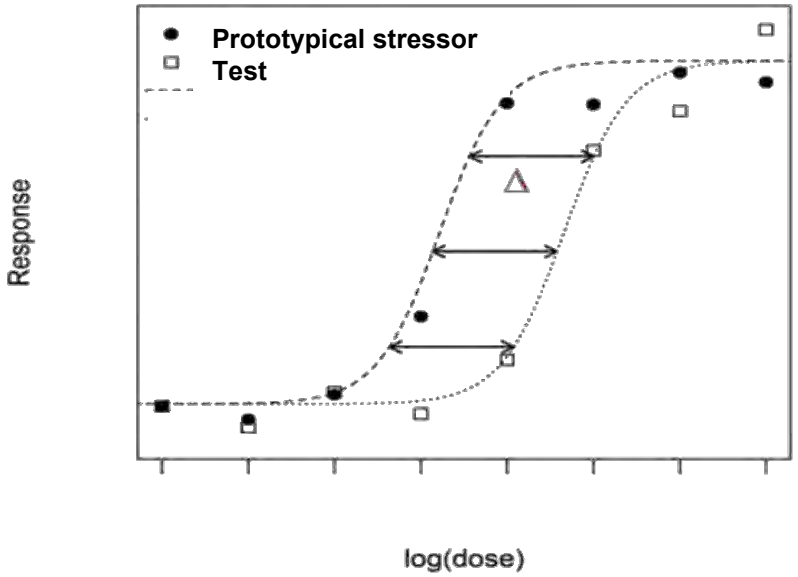


Prototypical stressor: A stressor that is known to trigger the molecular initiating event (MIE) (or the earliest key event in the pathway) and for which there is an extensive database with respect to its impacts on the downstream key events (KEs) such that experimental evidence related to that stressor's effects provided considerable support for key event relationships (KERs) along the pathway and the AOP as a whole.

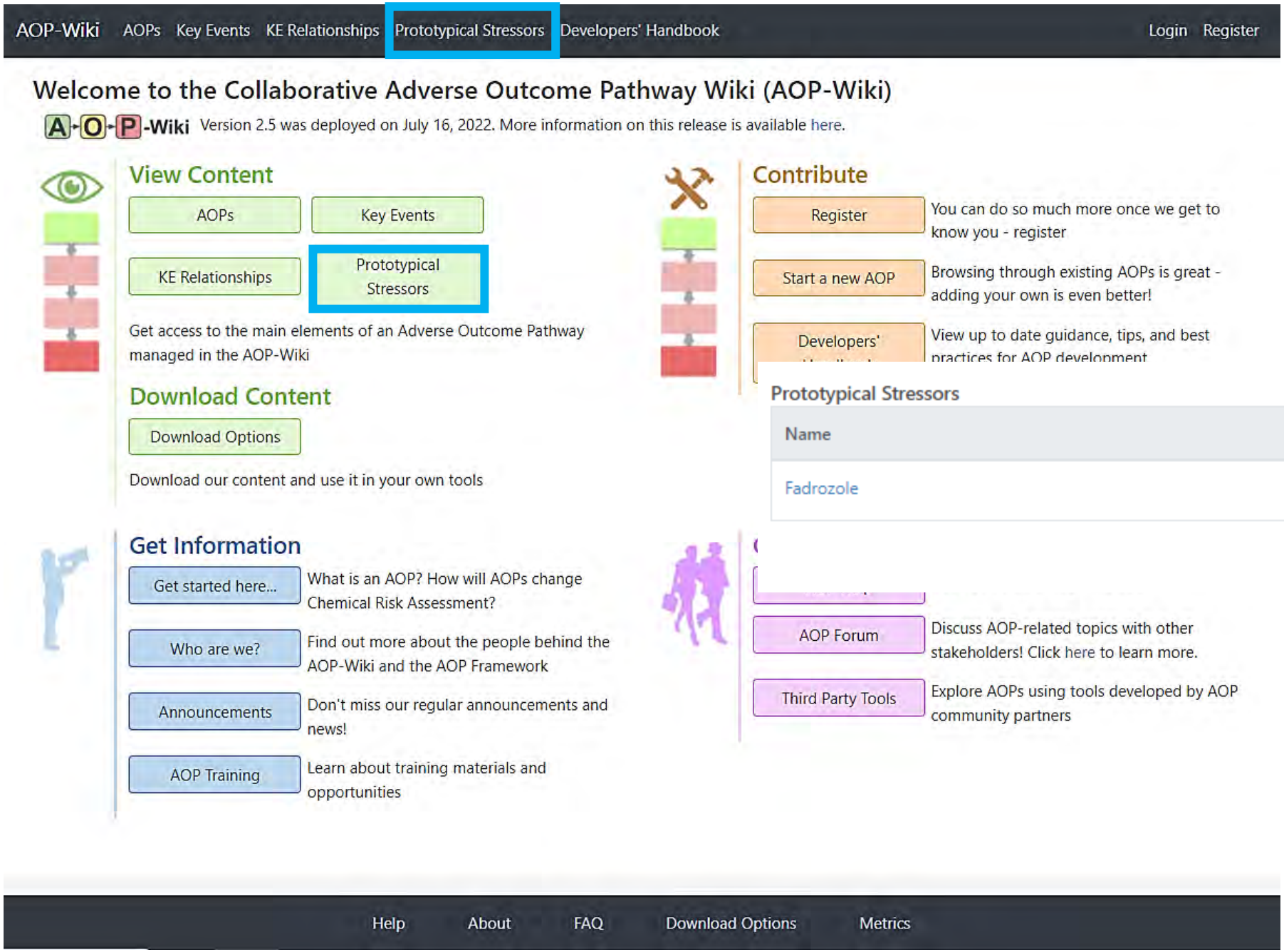
- Prototypical stressors often serve as a focal point for literature searches and other assembly of empirical support
- Prototypical stressors are not necessarily chemicals (e.g., radiation)

Prototypical Stressors

- Linked only to a full AOP (AOP page), not to individual key events
- Can serve as a “positive control” for the pathway
- Can serve as a reference for **quantitative understanding** of “how much perturbation will drive this path to the AO”



- Potency of a “test” compound relative to the prototypical stressor can be used to estimate concentration that would elicit adverse outcome (based on series of assumptions).
  - Similar fate/distribution and ADME over relevant dose range
  - Dose response curves are parallel and efficacy is the same
  - Actions on the downstream events are mediated through the same sequence of KEs
  - Effects are essentially additive at sub-maximal levels of exposure (following adjustment for diff potency)


AOP-Wiki
AOPs
Key Events
KE Relationships
Prototypical Stressors
Developers' Handbook
Login
Register
Welcome to the Collaborative Adverse Outcome Pathway Wiki (AOP-Wiki)
A-O-P-Wiki Version 2.5 was deployed on July 16, 2022. More information on this release is available here.
View Content
AOPs
Key Events
KE Relationships
Prototypical Stressors
Get access to the main elements of an Adverse Outcome Pathway managed in the AOP-Wiki
Download Content
Download Options
Download our content and use it in your own tools
Contribute
Register
You can do so much more once we get to know you - register
Start a new AOP
Browsing through existing AOPs is great - adding your own is even better!
Developers'
View up to date guidance, tips, and best
Prototypical Stressors
Name
Fadrozole
Remove
Add Prototypical Stressor
Get Information
Get started here...
What is an AOP? How will AOPs change Chemical Risk Assessment?
Who are we?
Find out more about the people behind the AOP-Wiki and the AOP Framework
Announcements
Don't miss our regular announcements and news!
AOP Training
Learn about training materials and opportunities
AOP Forum
Discuss AOP-related topics with other stakeholders! Click here to learn more.
Third Party Tools
Explore AOPs using tools developed by AOP community partners
Help
About
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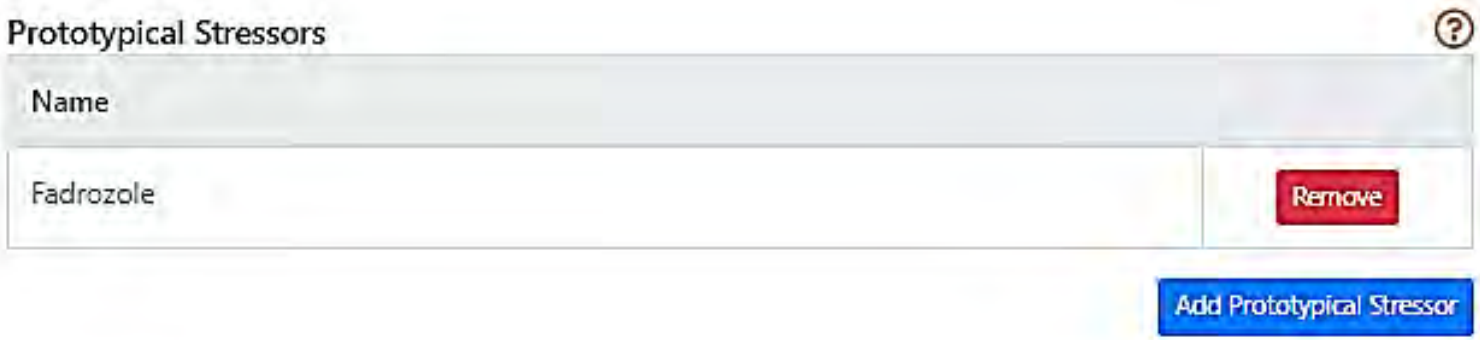
Download Options
Metrics



Prototypical stressor(s) can be listed on AOP page

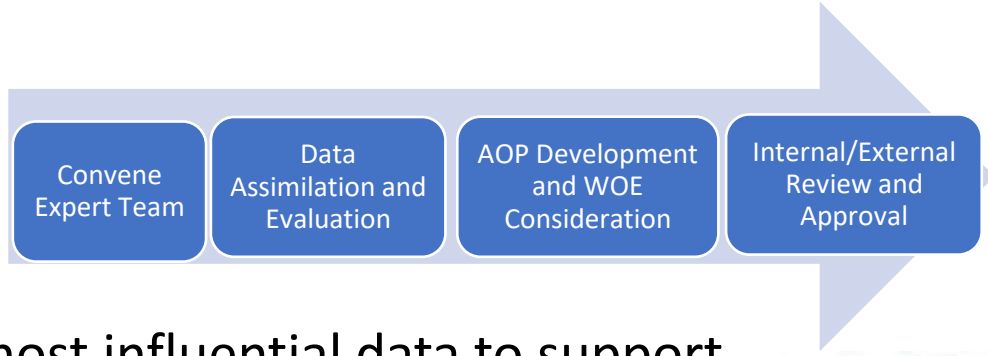
Prototypical Stressors

ID	Prototypical Stressor Name	Associated Chemical(s): Name, CAS-RN, DTXSID	Associated AOPs
2	(2-ethylhexyl) hydrogen phthalate	• MEHP, CAS-RN: 4376-20-9, DTXSID2025680	
3	1-Methylsulfonyloxyethane	• Ethyl methanesulfonate, CAS-RN: 62-50-0, DTXSID6025309	
4	17beta-Estradiol	• 17beta-Estradiol, CAS-RN: 50-28-2, DTXSID0020573	314
5	17beta-Trenbolone	• 17beta-Trenbolone, CAS-RN: 10161-33-8, DTXSID0034192	23, 376
6	2(3H)-Benzothiazolethione		
7	2-mercaptobenzothiazole	• 2-Mercaptobenzothiazole, CAS-RN: 149-30-4, DTXSID1020807	
8	Aceytlsalicylic acid	• Aspirin, CAS-RN: 50-78-2, DTXSID5020108	
9	Allyl Alcohol	• Allyl alcohol, CAS-RN: 107-18-6, DTXSID8020044	38

AOP-Wiki contains a list of prototypical stressors and their associated AOPs.

AOP Development Strategy
Transparently and Systematically Identifying the Evidence Base for AOP Development

- There is no "right" way to identify data relevant to AOP development
- This varies, depending on, e.g.,
  - scope
  - nature of prior documentation
  - the starting point for development, e.g.,
    - the molecular initiating event or adverse outcome
  - complexity
  - envisaged application(s)
- Needs to take into account:
  - AOP development is an expert driven process



  - The weight of evidence considerations flag the most influential data to support application H M L

- *There is, however, a need to describe the approach to support regulatory application*

Development Strategy (Evidence Identification) in AOP Descriptions

Added to the July, 2022 version of the Handbook/wiki (*intentionally non prescriptive*):

- AOP Page
  - Context (*WHY* the AOP was developed), including
    - Research question / problem formulation
    - Scope
    - Envisioned use (may be different from end use)
    - Funding source(s) and stakeholders
  - Strategy (*HOW* the AOP was developed)
    - Decisions on the level of resolution at which to describe the pathway
    - Overall data search and identification strategy(ies)
      - e.g., prototypical stressors
- KER Page
    - Evidence collection strategy
      - E.g., use of systematic review tools

View history | Discussion | Snapshots | API | XML

This AOP is licensed under a Creative Commons Attribution 4.0 International License.

Aop: 472

Title

DNA adduct formation leading to kidney failure

Strategy

This AOP is being developed as part of the ONTOX consortium. The aim of this consortium is to provide a generic strategy to create innovative new approach methodologies (NAMs) in order to predict systemic repeated dose toxicity effects that, upon combination with tailored exposure assessment, will enable human risk assessment. Part of this approach is the development of physiological maps, quantitative adverse outcome pathway networks and ontology frameworks. This project is funded by the European Union's Horizon 2020 research and innovation programme under grant agreement No 963845. https://ontox-project.eu/project/

Within the ONTOX consortium *in vitro* test batteries are being developed to evaluate toxicity in the liver, (steatosis and cholestasis), kidneys (tubular necrosis and crystallopathy) and developing brain (neural tube closure and cognitive function defects). This AOP focusses on kidney tubular necrosis as a result of exposure to a DNA-adduct forming compound (Pt-based drugs).

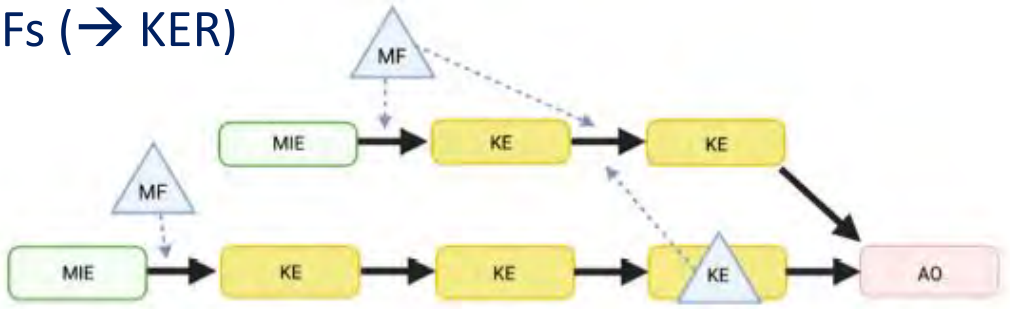
Modulating Factors

Modulating factors (MFs) may **alter the shape of the response-response function** that describes the quantitative relationship between two KES, thus having an **impact on the progression of the pathway or the severity of the AO**.
The supporting **evidence** for an impact of MFs is assembled within the individual KERs.

CIAO as case study (Modelling the pathogenesis of **C**OV**I**D-19 using the **A**dverse **O**utcome Pathway)

Further issues

- Role of time (MF acting)
- Chemicals (or other agents) can be stressors (→ MIE) and/or MFs (→ KER)
- A KE in one AOP might be a MF in another AOP.
- MFs may target several KERs
- Interaction between several MFs

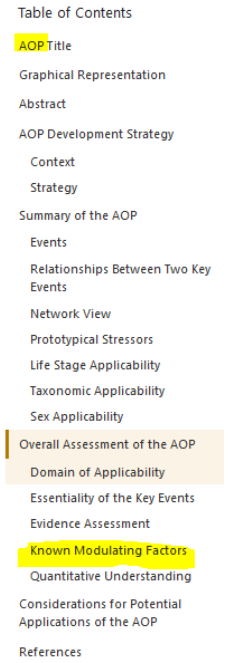


Clerbaux et al., J. Clin. Med. 2022, 11, 4464

Improved visibility

new distinct sections

- Overview on relevant MFs
- Connection to the AO
- Overview on all modulated KERs
- Details on respective KER pages



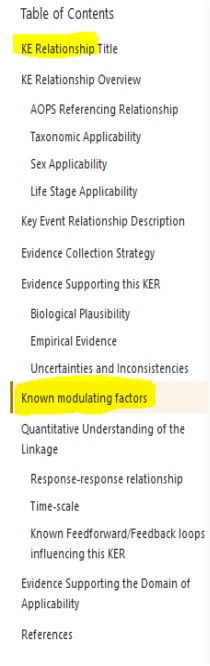
AOP page

MF	Influence on outcome	KER (s) involved

- Definition of the MF
- Specific features of the MF
- How does the MF affect the KER
- Supporting evidence

KER page

MF	MF specification	Effects on KER	References



AOP overview page

Aop: 468

Title

Binding of SARS-CoV-2 to ACE2 leads to hyperinflammation (via cell death)

Overall Assessment of the AOP

Domain of Applicability

Essentiality of the Key Events

Evidence Assessment

Known Modulating Factors

Modulating Factor (MF)	Influence or Outcome	
Sex	Higher risk for sev	
Age	risk for more severe AO increases with age	
Obesity	risk for more severe AO increases linearly with increase, already starting at BMI >23 kg/m^2	2056, 1703, 2354
Vit D deficiency	Low vitamin D status prior to infection increases risk of higher AO severity	2056 , 1703, 2354
Chemicals (PFAS, PFOS, PFOA, PFNA, PFHxS, and GenX)	chemical exposure correlates with higher risk for AO severity	2056, 1703, 2354

Table of Contents

KE Relationship Title

KE Relationship Overview

AOPS Referencing Relationship

Taxonomic Applicability

Sex Applicability

Life Stage Applicability

Key Event Relationship

Evidence Collecti

nce Su

A O P FORUM

Share your experience/opinion

https://aopwiki.org/forums/showthread.php?tid=165

Relationship: 2056

Title

Binding to ACE2 leads to SARS-CoV-2 cell entry

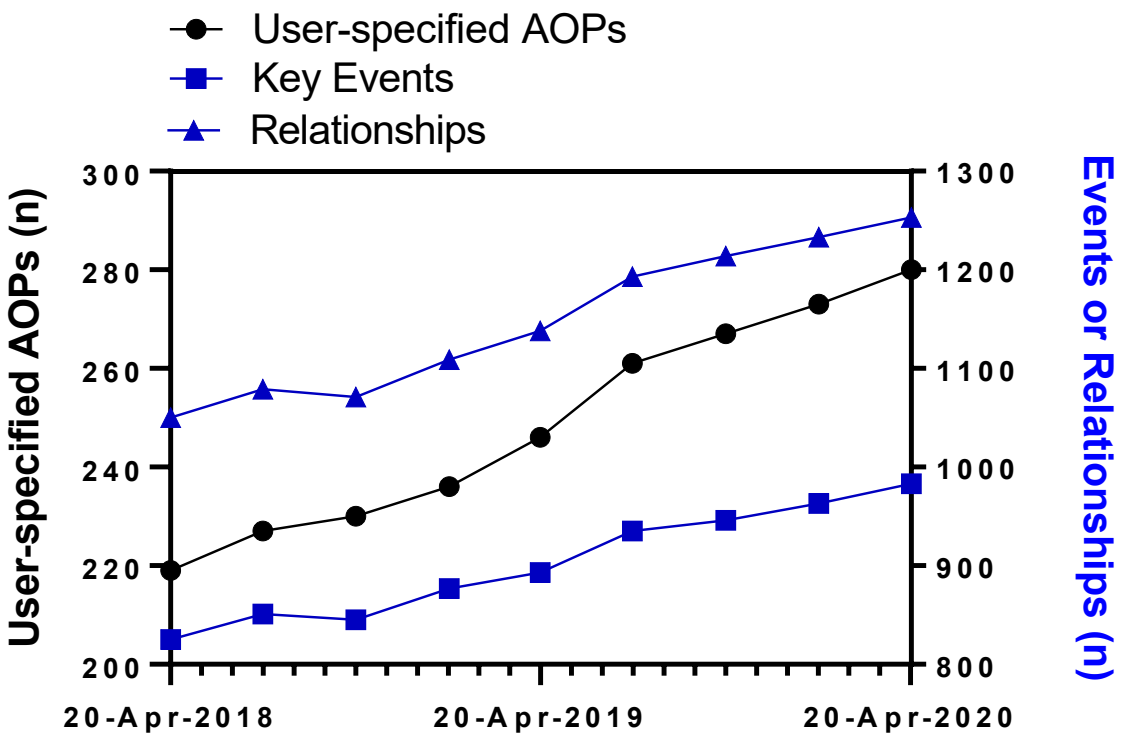
KER page

Known modulating factors

Modulating Factor (MF)	MF Specification	Effect(s) on the KER	Reference(s)
Chemicals (weak evidence)	PFAS (PFOS, PFOA, PFNA, PFHxS, and GenX)	Short-term (10 days), high dose (20 mg/kg/day) exposure to PFOA leads to about 1.6 fold upregulation of the pulmonary mRNA level of *Ace2* and to about 1.5 upregulation of the pulmonary mRNA level of *Tmprss2* in CD1 mice. [1] ...term (12 weeks) of an ...y relevant ...ixture (PFOS, PFOA, PFNA, PFHxS, and GenX; each in 2 mg/l concentration) exposure leads to downregulation of pulmonary ...NA expression of Ace2 ...57BL/6 J male ...reasing trend was observed in PFAS-exposed male mice for *Tmprss2*. [2]	1. doi: 10.1016/j.toxrep.2021.11.014 2. doi: 10.1016/j.taap.2022.116284
Sex (strong evidence)	...sex ...omes)	ACE2 localizes to the X sex chromosome and displays a sex-dependent expression profile with higher expression in female than in male tissues [1,2]. Estradiol inhibits TMPRSS2, needed to facilitate SARS-CoV-2 entry into the cell [3]. Estrogen therapy has been shown to mitigate endoplasmic reticulum stress induced by SARS-CoV-2 invasion through activation of cellular unfold protein response and regulation of inositol triphosphate (IP3) and phospholipase C [4].	1. doi: 10.1177/1933719115597760 2. doi: 10.1016/j.mce.2015.11.004 3. doi: 10.1007/s11033-021-06390-1 4.doi: 10.1016/j.mehy.2020.110148 5. doi: 10.2217/pgs-2020-0092

Improving User Experience

Improved searching, filtering, findability



- Growing numbers of AOPs in AOP-Wiki
  - Increasingly difficult to hone in on AOPs of greatest interest based on text in title or text on page (operation of search function)
- Ability to search, sort, and filter by multiple criteria desired
  - AOP ID
  - Title
  - MIE / AO
  - Point of contact
  - OECD status
  - Etc.

Free text entries can be used to filter some columns, as shown for ACE2 in the MIE column

AOPs

Filtered AOP Count: 17

ID	Title	Point of Contact	Author Status	SAAOP Status	MIE	AO	OECD Status	OECD Project
			Clear	Clear	ACE2		Clear	
385	ACE2 binding to viral S-protein leading to microvascular disfunction via ACE2 dysregulation	Julija Filipovska	Under development: Not open for comment. Do not cite		• Binding to ACE2			
427	ACE2 downregulation following SARS-CoV-2 infection triggers dysregulation of RAAS and can lead to heart failure.	Evangelos-Panagiotis Daskalopoulos	Under development: Not open for comment. Do not cite		• Binding to ACE2	• Heart failure		
428	Binding of S-protein to ACE2 in enterocytes induces ACE2 dysregulation leading to gut dysbiosis	Laure-Alix Clerbaux	Under development: Not open for comment. Do not cite	Included in OECD Work Plan	• Binding to ACE2		Under Development	1.96
422	Binding of SARS-CoV-2 to ACE2 in enterocytes leads to intestinal barrier disruption	Laure-Alix Clerbaux	Under development: Not open for comment. Do not cite	Included in OECD Work Plan	• Binding to ACE2		Under Development	1.96

Some columns have drop-down menu options

AOPs

Filtered AOP Count: 17

ID	Title	Point of Contact	Author Status	SAAOP Status	MIE	AO	OECD Status	OECD Project
			Clear	Clear	ACE2			
385	ACE2 binding to viral S-protein leading to microvascular disfunction via ACE2 dysregulation	Julija Filipovska	Under development: Not open for comment. Do not cite		• Binding to ACE2			
427	ACE2 downregulation following SARS-CoV-2 infection triggers dysregulation of RAAS and can lead to heart failure.	Evangelos-Panagiotis Daskalopoulos	Under development: Not open for comment. Do not cite		• Binding to ACE2	• Heart failure		
428	Binding of S-protein to ACE2 in enterocytes induces ACE2 dysregulation leading to gut dysbiosis	Laure-Alix Clerbaux	Under development: Not open for comment. Do not cite	Included in OECD Work Plan	• Binding to ACE2		Under Development	1.96
422	Binding of SARS-CoV-2 to ACE2 in enterocytes leads to intestinal barrier disruption	Laure-Alix Clerbaux	Under development: Not open for comment. Do not cite	Included in OECD Work Plan	• Binding to ACE2		Under Development	1.96

OECD Status dropdown:
- ✓ Clear
- EAGMST Under Review
- EAGMST Approved
- WPHA/WNT Endorsed
- Under Development
- [empty]

Comparison operators can also be used for filtering

Clicking the ? will open the menu listing all filter operators

AOPs

Filtered AOP count: 24

ID	Title	Point of Contact	Author Status	SAAOP Status	MIE	AO	OECD Status	OECD Project
>450			Clear	Clear			Clear	
462	Activation of reactive oxygen species leading the atherosclerosis	Hiromi Ohara	Under development: Not open for comment. Do not cite					
452	Adverse outcome pathway of PM-induced respiratory toxicity	li qing	Under development: Not open for comment. Do not cite		• Non-coding RNA expression profile alteration	• Chronic obstructive pulmonary disease		
458	AhR activation in the liver leading to Subsequent Adverse Neurodevelopmental Outcomes in Mammals	Prakash Patel	Under development: Not open for comment. Do not cite					
459	AhR activation in the thyroid leading to Subsequent Adverse Neurodevelopmental Outcomes in Mammals	Prakash Patel	Under development: Not open for comment. Do not cite					
465	Alcohol dehydrogenase leading to reproductive dysfunction	Donggon Yoo	Under development: Not open for comment. Do not cite		• Increase, Alcohol dehydrogenase			

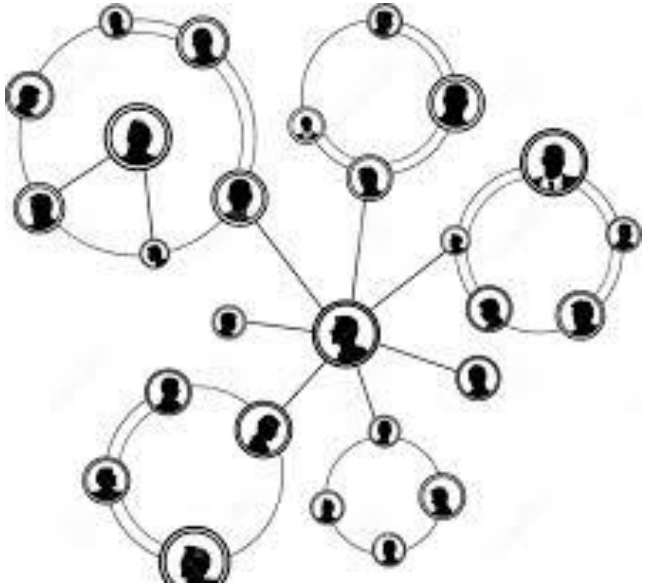
?

Use the filters above each column to filter and limit table data. Advanced searches can be performed by using the following operators:
<, <=, >, >=, =, *, !, {, }, ||,&&, [empty], [nonempty], rgx:
Learn more

TableFilter v0.7.3
https://www.tablefilter.com/
©2015-2022 Max Guglielmi

Close

Protecting content under development



AOP framework and AOP-Wiki were developed based on a crowd-sourcing and open-access ethos

- Ability for multiple authors to contribute to pages
- Ability for anyone to access the information, world-wide

AOP pages: creative commons – open with attribution

KE/KER pages: no rights reserved – no restrictions on use

Protecting content under development

Problem:

Author status may indicate not open for comment, do not cite

No legal backing for restriction on use

Developers hesitant to post content under development – developing off-line

Developers concerned about their work/IP being taken and used elsewhere, including for publication or commercial use without attribution.

AOP Pages Version 2.6

AOP pages

1. Default license will change from CC BY to **CC BY-SA (Attribution, Share-alike)**

- You must not **restrict access** to the work using technical measures, or otherwise attempt to impose limitations on the freedoms to use, study, apply, redistribute, or distribute derivative works.
- You must **give proper attribution to the author and retain the license notice.**
- You must **release derivative works under an identical or similar license**.

2. Authors will have option to override the default AOP page license and select an “All rights reserved” license instead

- *Allows AOP pages in Wiki to function like a pre-print server*

- All rights reserved has to be renewed yearly by author

KE/KER Pages Version 2.6

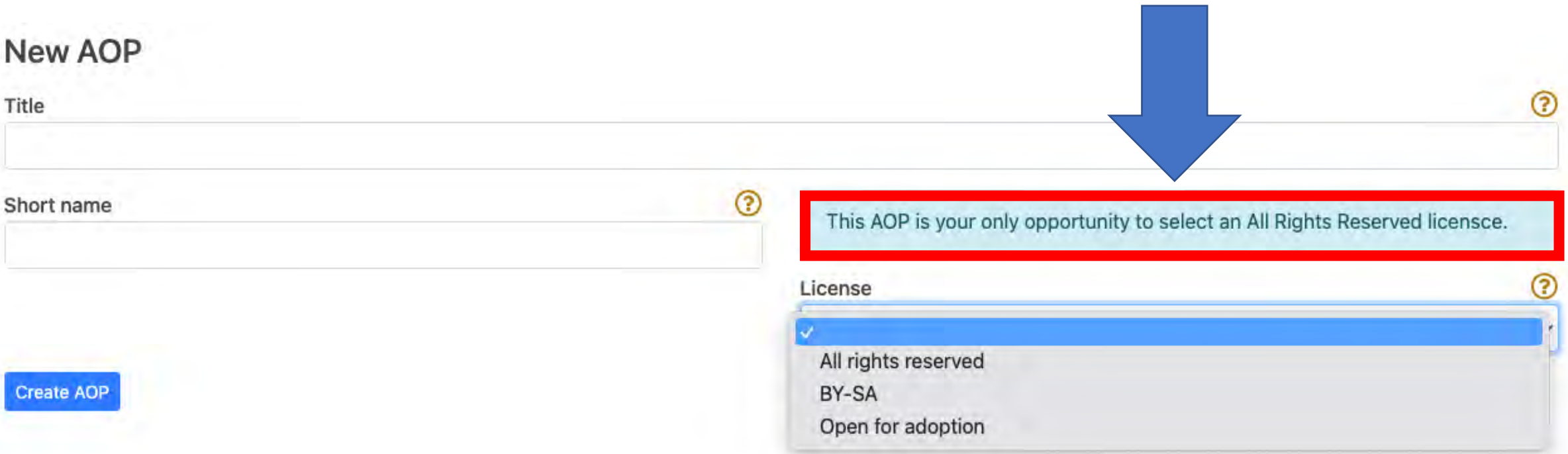
KE/KER pages

AOP pages: only a limited number of pre-defined contributors have write-access

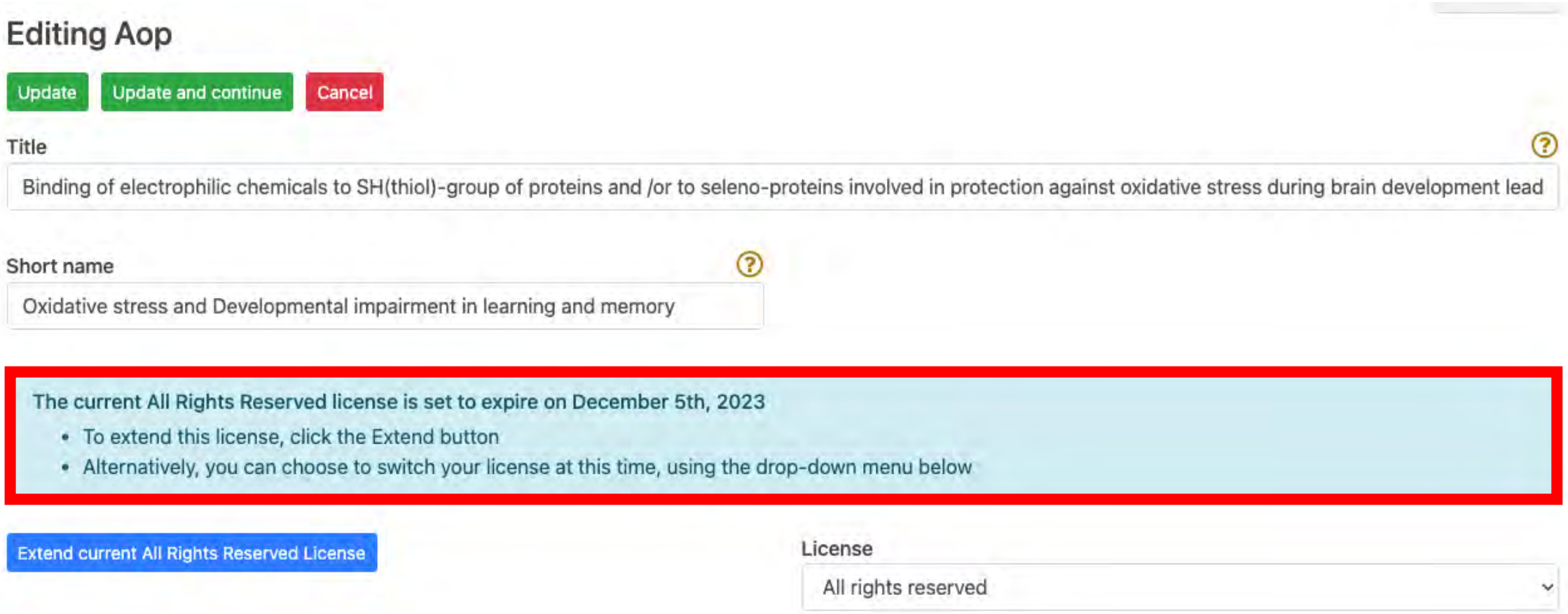
KE/KER pages: every AOP-wiki user with author access is able to edit

1. Default license will change from CC0 to **CC BY-SA**
2. Short term (version 2.6): encourage the use of external pre-print servers if users wish to protect their contributions
3. Long term (beyond v 2.6): consider block-level licensing after implementation of contributor tagging

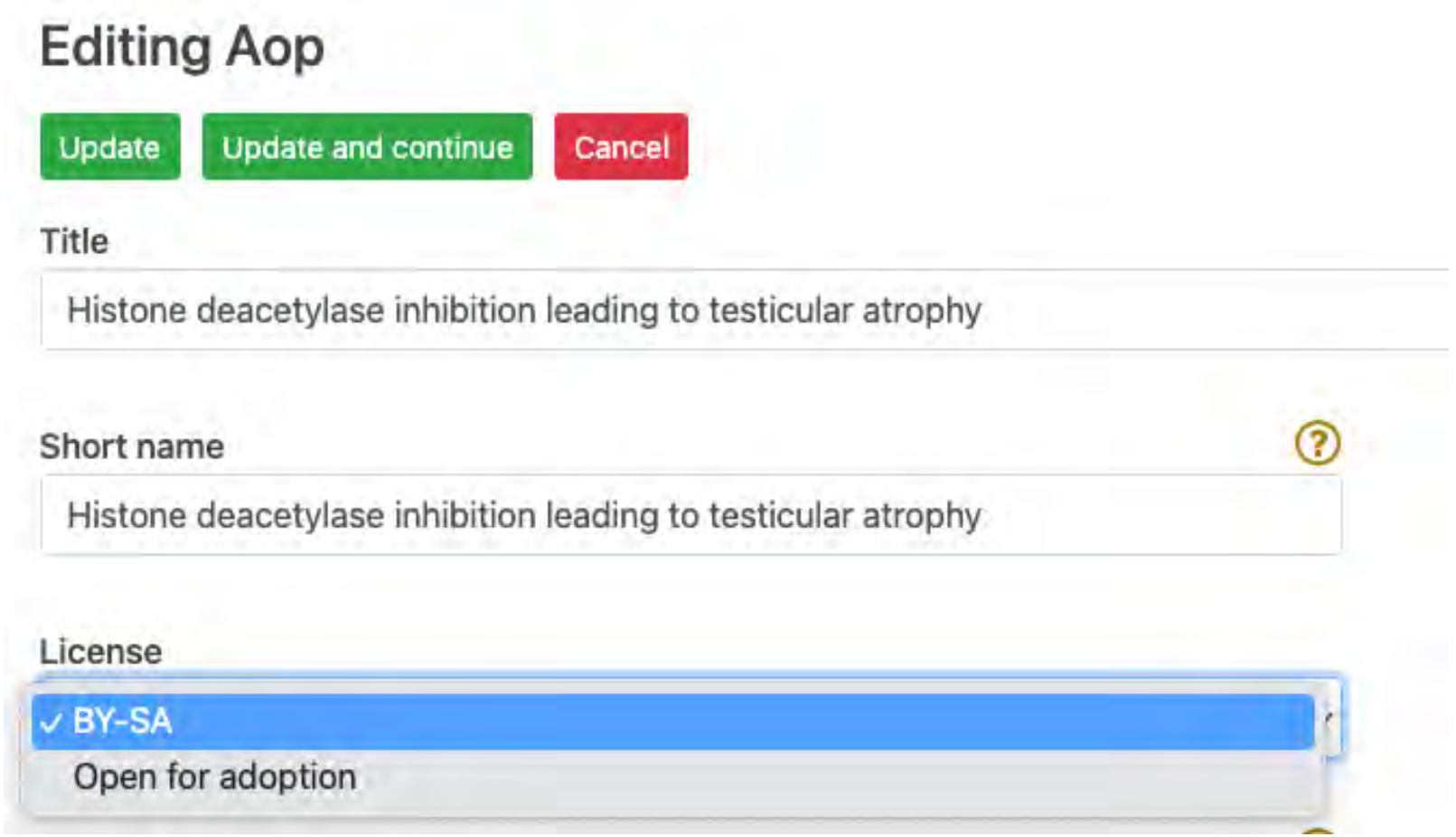
3 options available when creating an AOP page



AOPs with the All Rights Reserved License will have expiration dates lasting one year



The All Rights Reserved license is not available after an AOP has been created and given the BY-SA license



Once the content is opened for use, decision cannot be reversed.

The logo for the selected license will be displayed at the top of each AOP, along with some brief explanatory text regarding the restrictions associated with the license

This AOP is licensed under the BY-SA license. This license allows reusers to distribute, remix, adapt, and build upon the material in any medium or format, so long as attribution is given to the creator. The license allows for commercial use. If you remix, adapt, or build upon the material, you must license the modified material under identical terms.

AOP: 14

Title

Glucocorticoid Receptor Activation Leading to Increased Disease Susceptibility

This AOP is open for adoption and licensed under the BY-SA license. The BY-SA license allows reusers to distribute, remix, adapt, and build upon the material in any medium or format, so long as attribution is given to the creator. The license allows for commercial use. If you remix, adapt, or build upon the material, you must license the modified material under identical terms.

This AOP is open for adoption. Please email aopwiki@googlegroups.com to indicate your interest in becoming the main point of contact for this AOP.

AOP: 19

Title

Androgen receptor antagonism leading to adverse effects in the male foetus (mammals)

Agenda

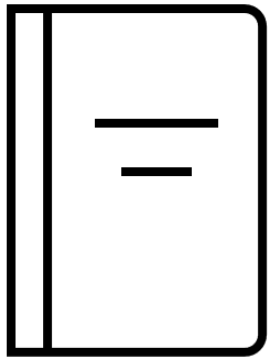
- Introduction
- AOP-Wiki 2.5 and 2.6:
  Rationale behind added features, hands-on technical implementation
- Beyond AOP-Wiki 2.6:
  Challenges ahead and how to address them
- Q&A and discussion
- Outlook and next steps

Suggested Workflow - Developing AOPs

- Expert informed hypothesized AOP (development team)
- Evidence Mapping based on hypothesized KEs, KERs,
  - *Design/streamline to identify most influential datasets*
    - *flagged by weight of evidence considerations*
- Expert informed additional targeted searching in gap areas
- Depending on extent of data identified (i.e., magnitude of the task), consider potential value of using one of the S/R screening tools
- Relevant critical study quality considerations (in AOP context) to be formalized by the AOP development community
  - Many of those currently considered for studies in individual lines of evidence in SR methods *are not relevant to AOP development*
  - *WOE considerations influential*
- Once additionally developed/agreed, designing relevant data entry forms to address

Existing Table of Contents - Handbook

- FOREWORD
- TABLE OF CONTENTS
- ABOUT THIS DOCUMENT
- INTRODUCTION TO AOPs
- OBTAINING AUTHOR ACCESS TO THE AOP-Wiki
- A NOTE ON AOP DESCRIPTIONS IN THE AOP-Wiki



Better frame context for developers – i.e., application, relationship with influential study design

- SECTION 1 – AOP DESCRIPTION
- SECTION 2 – KE DESCRIPTIONS
- SECTION 3 – KER DESCRIPTIONS
- SECTION 4 – OVERALL ASSESSMENT O[illegible]HE AOP

Simplify and address inconsistencies; Delete Section 4; subsumed in Section 1

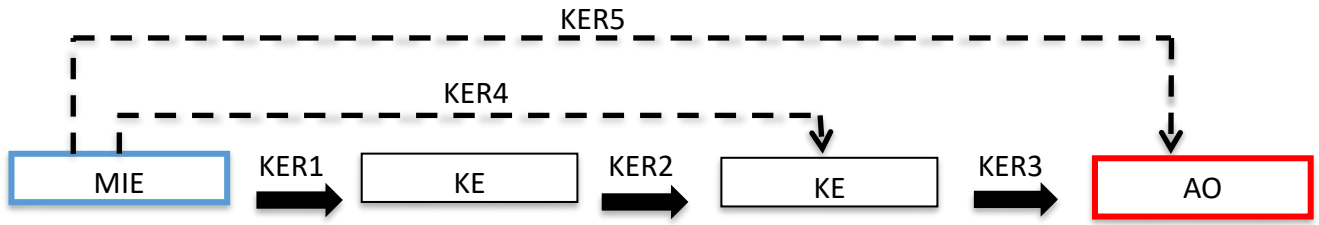
REFERENCES

ANNEX 1: Guidance for Assessing Rela[illegible]vel of Confidence in the Overall AOP

ANNEX 2: General guidance for charac[illegible] the level of quantitative understanding of a KER

Delete both; Annex 1 subsumed in AOP description and assessment; Annex 2 duplicative of confidence determinations for empirical support

1. AOP Graphical Representation, Development Strategy, Support and Assessment



Section 1 AOP Context, Description, Support and Assessment

Section 2 KE Descriptions

- MIE
- KEs
- AO

Section 3 – KER Descriptions

- Key Event Relationships/Associations

KE Pages

- Description
- Measurement/ detection
- Taxonomic applicability

MIE Page

- Description
- Measurement/ detection
- Taxonomic applicability

AO Page

- Description
- Measurement/ detection
- Taxonomic applicability

KER Pages

- Title
- Domain of Applicability
- Evidence Collection Strategy
- Evidence Supporting the KER

Wiki Navigation Guide

- Developing navigation guide to the AOP wiki *for application* (including chemical specific)
  - To *map to basic content on what AOPs are, how confidence is assessed (systematic consideration of data sources and integration)*
    - A *"how to" to navigate/apply the information, including linking to other relevant tools*
- Focus is *AOPs*, taking into account the *needs of the users*, e.g.
      - Chemical specific assessment programs
        - organizing data based on described pathways (data rich)
        - vastly expanded chemical specific mandates (data poor) e.g.,
          - Grouping, read-across
          - Predictive inference
        - IATA
- To involve a working/focus group of *engaged* regulators

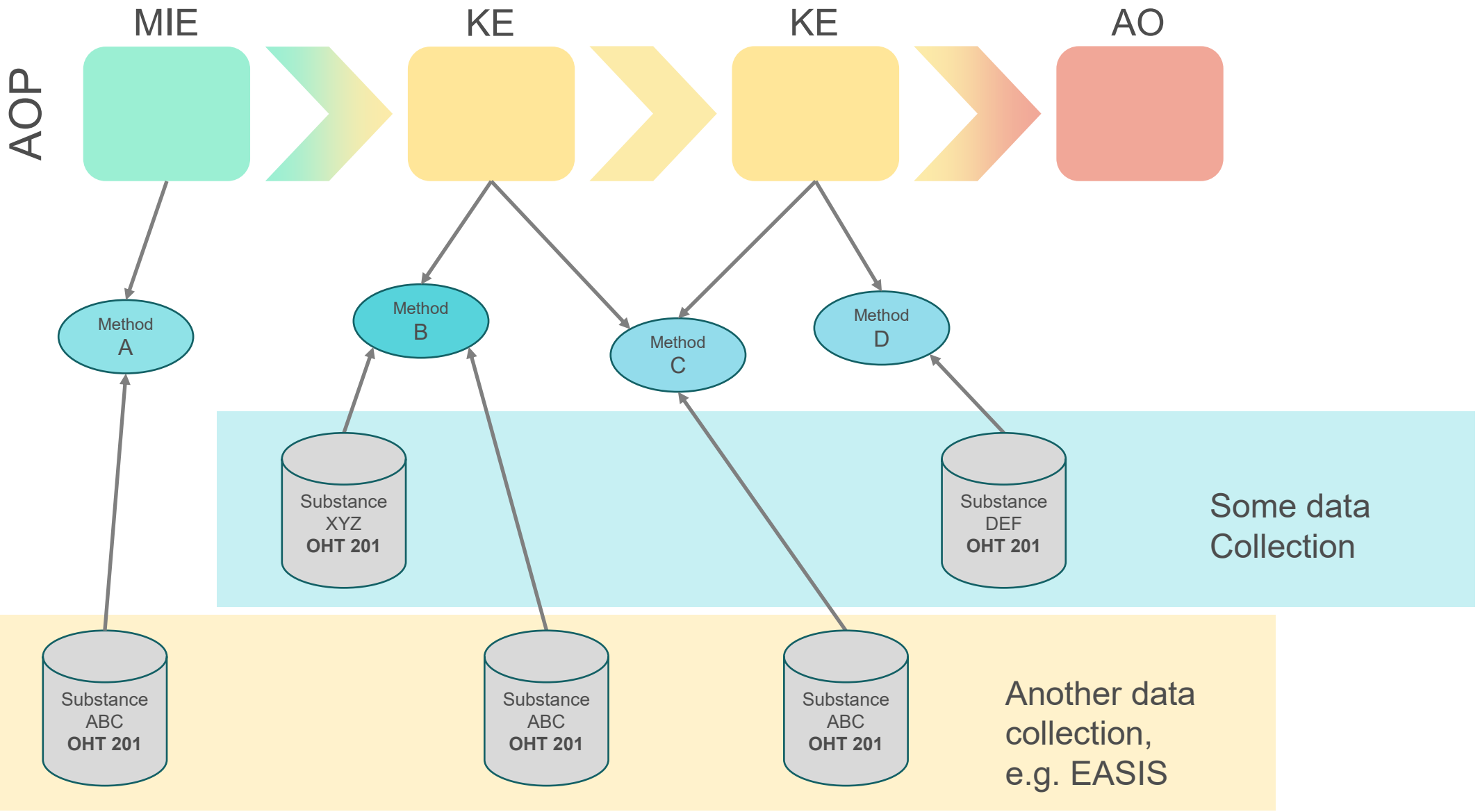
AOPs Moving Forward

- Mode of Action (MOA)/AOPs defined in the context of regulatory application
- Much experience in chemical specific MOA application
- Evolving experience in AOP application (e.g., IATA)
- Greater focus to support regulatory:
  - predictive aspects
  - better documentation
  - more systematic, transparent and consistent consideration of evidence/ assessment
- Regulatory/research Partnerships work best
  - E.g., European Food Safety Agency (EFSA) examples
- Missing?
  - Common understanding for application
  - More input/partnership with regulatory/your ideas

Current role of test methods in the AOP-Wiki

- Current situation:
  - Information about Test Method is freetext on the KE page
  - Very ad hoc and not systematic
  - Connection to stressor?
  - How can we be more **transparent about methods** used in the creation of an AOP and **thereby increase trust in that AOP**?

European Commission



Desired situation…

European Commission

The Methods AOP Initiative

- July 2022 - spontanous initiative of people from

European Commission

NIH National Institute of Environmental Health Sciences

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

Environment and Climate Change Canada
Environnement et Changement climatique Canada

RTI INTERNATIONAL

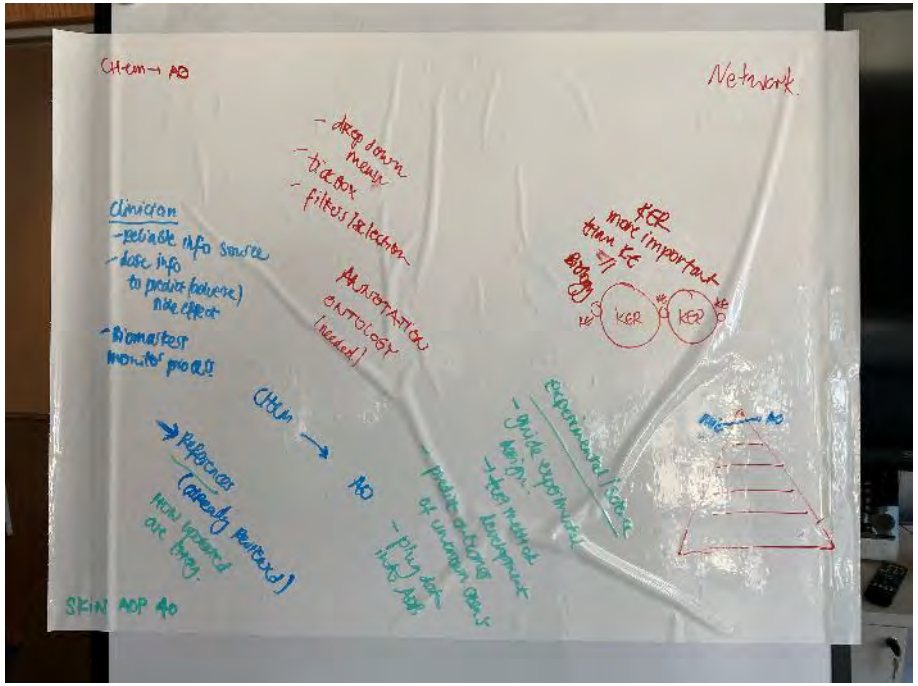
- Objective is to deliver
  - a series of actionable test method related **recommendations** to OECD EAGMST and other affected stakeholders.
  - a collection of implementable **ICT requirements** to the OECD EAGMST AOP-KB subgroup

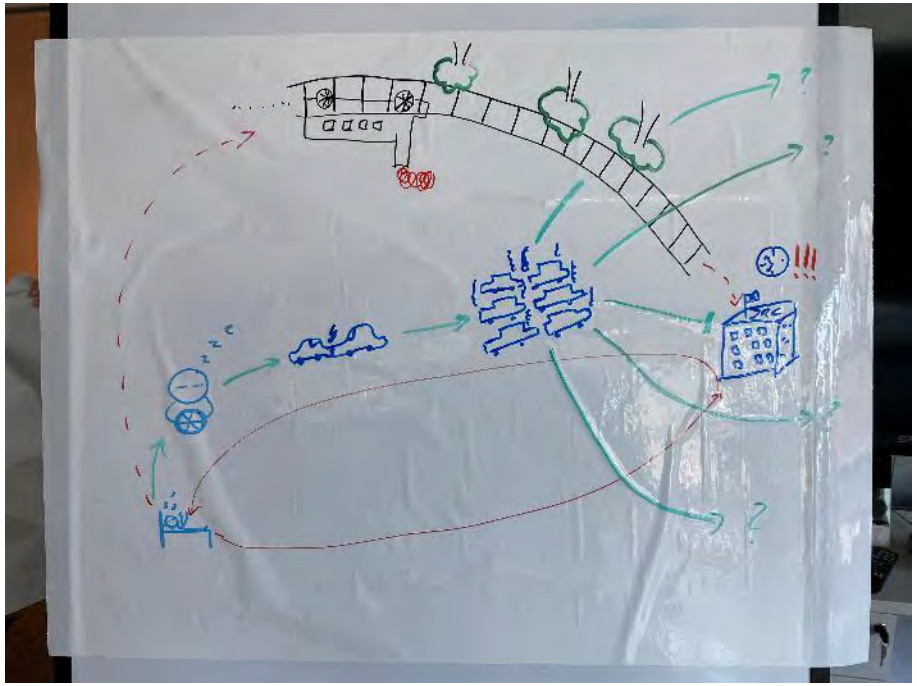
Role of the initiative was acknowledged by EAGMST.

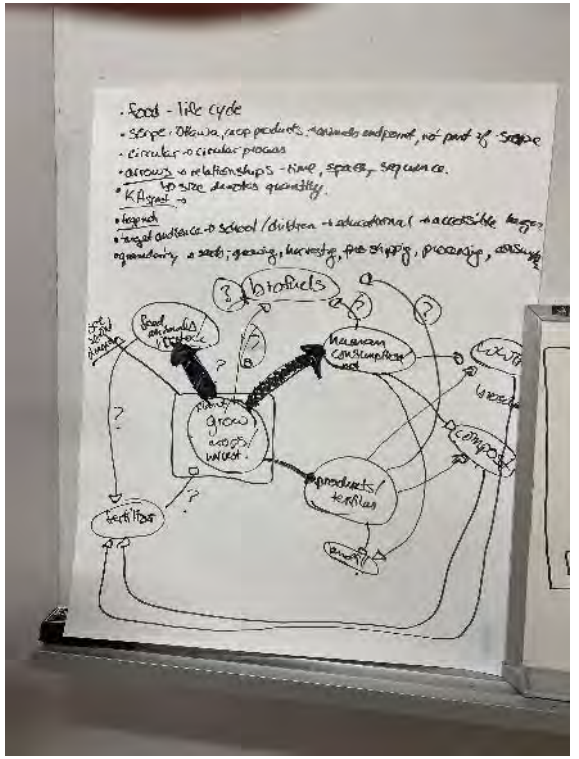
European Commission

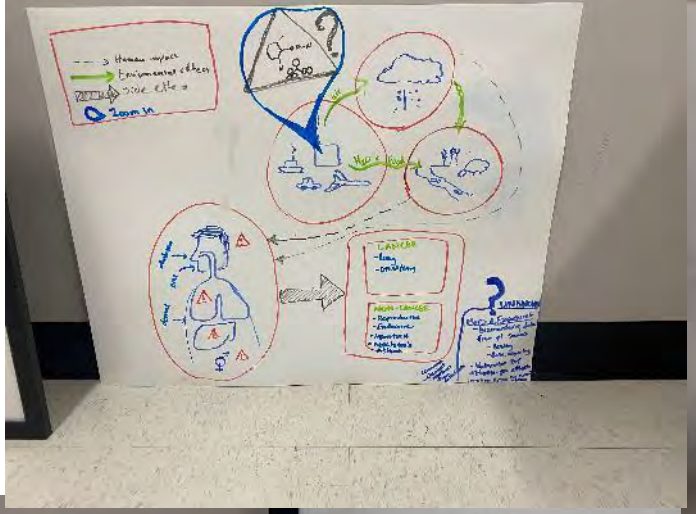
AOP Visualisation

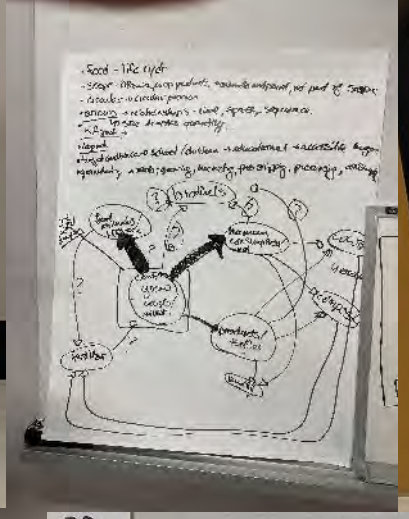
- Two focus groups: Brussels (mainly AOP developers) and Ottowa (mainly potential AOP regulatory users)
- Diagramming together: everyday examples and AOP examples



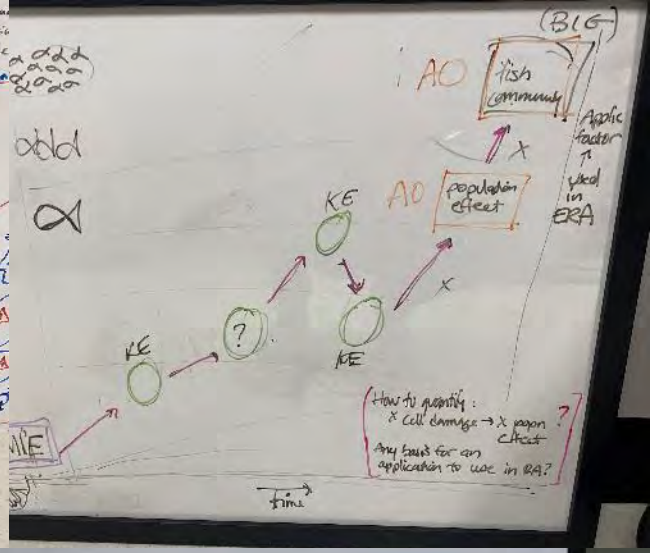


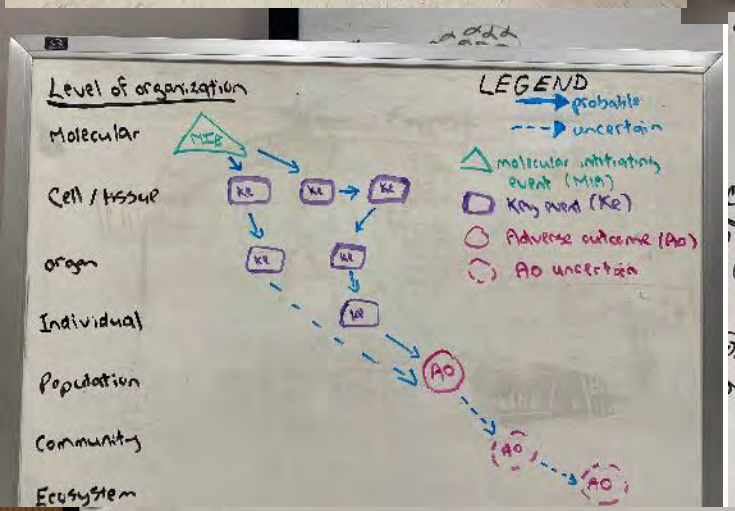


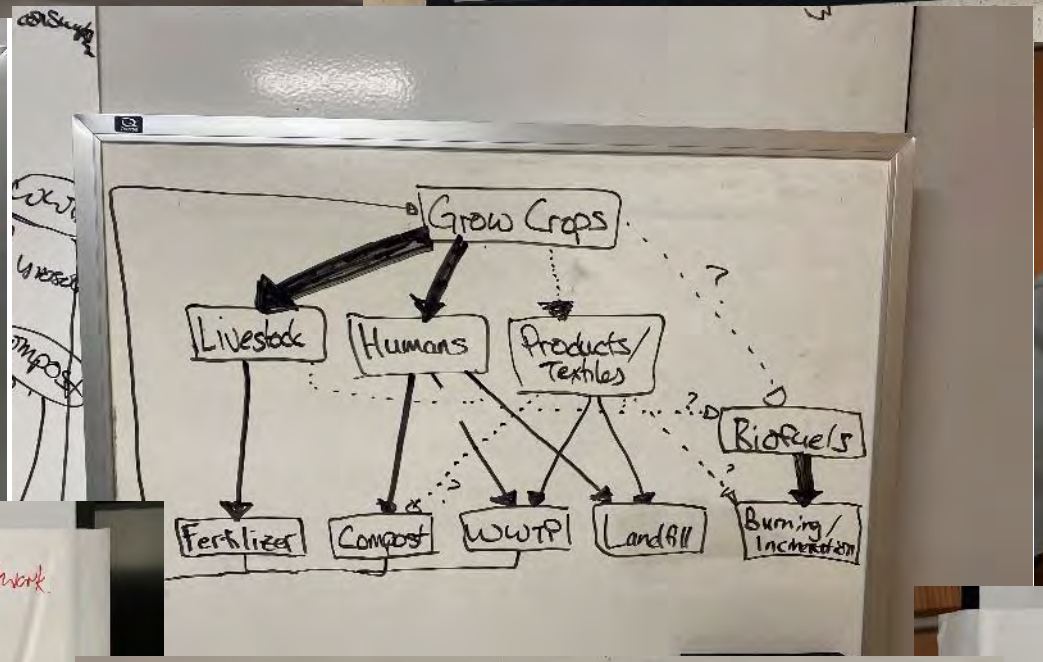

Zoom in
Cancer
Lung cancer

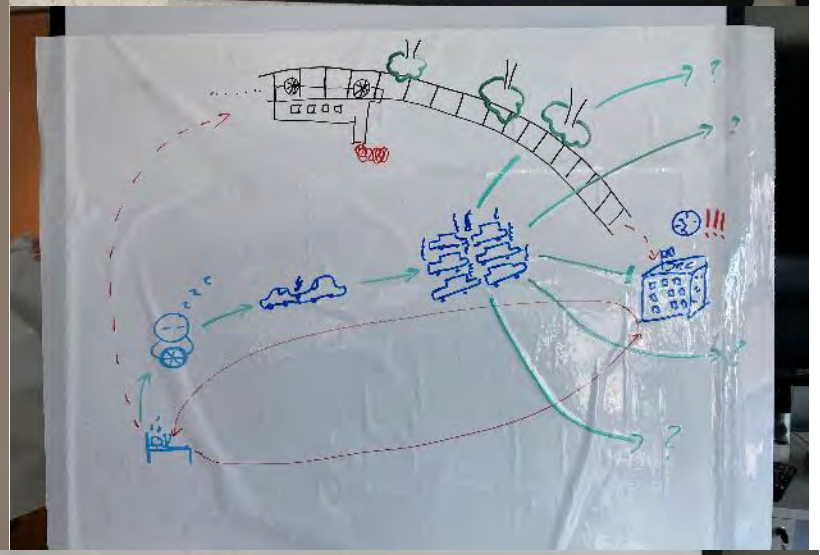


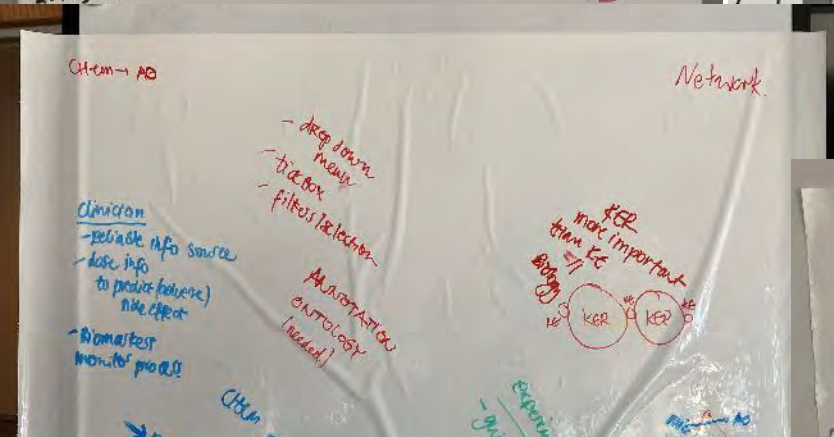

? = data gap
Li Ni Co


AO
fish community
BIG
Applic factor
population effect
KE
How to quantify:
x cell damage → x pop effect ?
Any basis for an application to use in RA?
time


Level of organization
LEGEND
probable
uncertain
molecular initiating event (MIE)
Key event (KE)
Adverse outcome (AO)
AO uncertain
Molecular
Cell / tissue
organ
Individual
Population
Community
Ecosystem
MIE
KE
AO


Grow Crops
Livestock
Humans
Products/ Textiles
Biofuels
Fertilizer
Compost
WWTP
Landfill
Burning/ Incineration




Chem → AO
Network
Clinician
reliable info source
dose info to predict adverse side effect
Biomarker monitor pool
drop down menus
tick box
filters/selection
KER
more important than KE
Biology
AOP ONTOLOGY (needed)


EYE IRRITATION
SKIN IRRITATION
RESPIRATORY
LONG TERM EFFECT

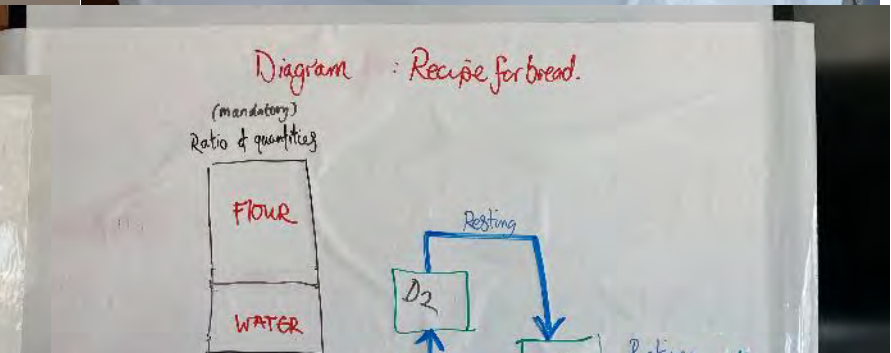
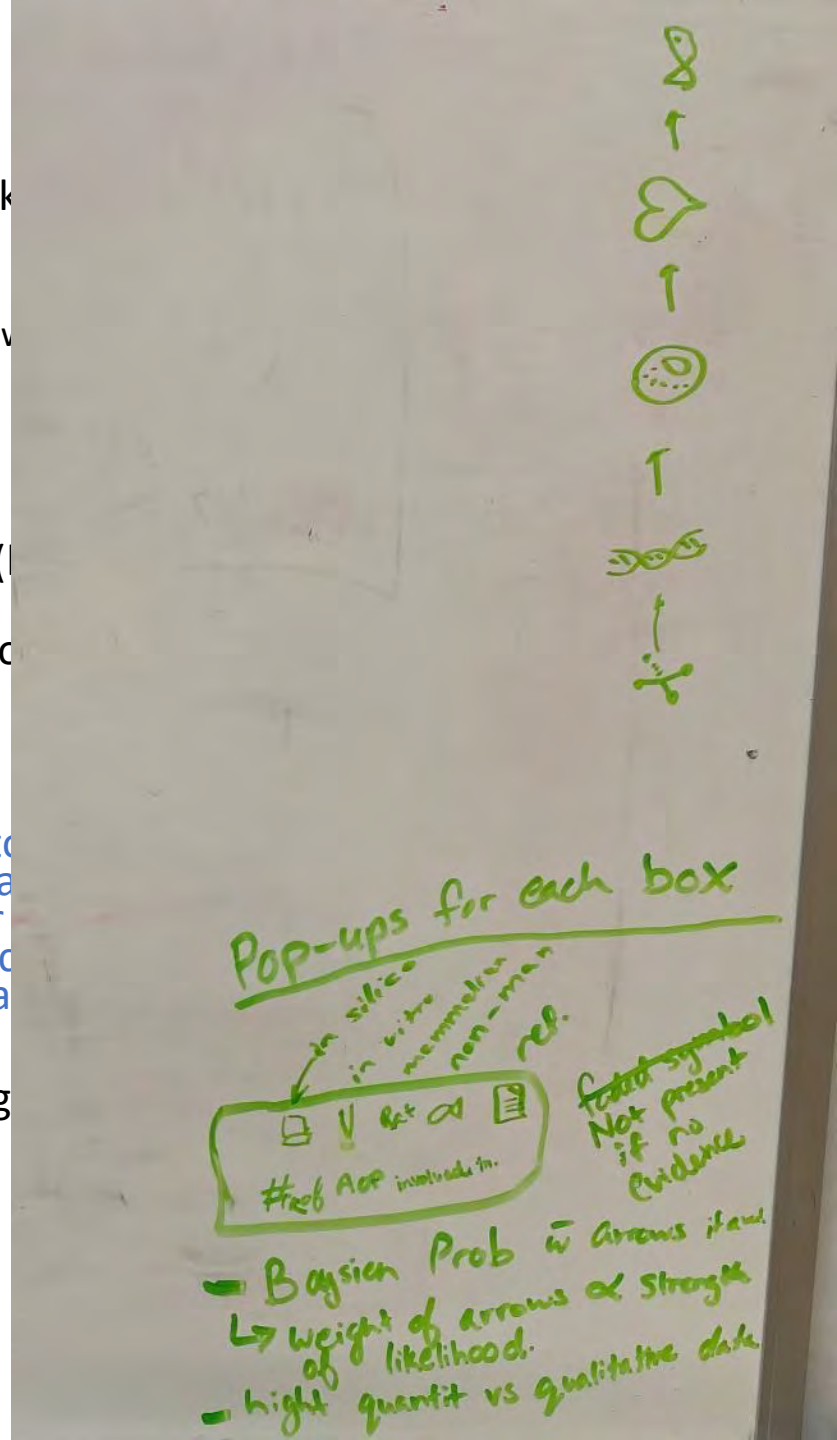


Diagram : Recipe for bread.
(mandatory)
Ratio & quantities
FLOUR
WATER
Resting
D2

- Standardised spatial organisation [eg biological levels]
- Search / filter according to different purposes; supported by ontology
- Greater interactivity: eg click on boxes for more information about KE; click
  ability to control how much of AOP is seen
- More readability from the diagram itself:
  - level of organisation directly from KE box; how many other AOPs connected to a KE, v
    Table];
  - weight of evidence through weight of arrows / distinguished into types of evidence
- Better ways of showing up what is not known / uncertainty / probability
- Feedback loops through quantification
- For regulators: greater contextualisation of the AOP, extending to stressor (
  and ecosystem level [even if there is not specifically the data for them]
- Disambiguation of arrows – dotted and solid arrows currently not clear [sho
  adjacent KEs?]
- Static and dynamic for different purposes

"Because we work on finite report, final assessments, it would be important to
these. Important to have both dynamic and static. Dynamic for interactive, pla
comparisons, look at interactions between AOPs. None of these exist on their
important to have a way to look at AOPs that's very **'tactile'** – but also a static
it, and put it into a report, what was available at the time when this report wa

- Timestamping and approval also readable directly from AOP diagram / ong
  present validation in/alongside the diagram



FAIR principles

Data *and* knowledge should be

Findable

- F1: (Meta) data are assigned globally unique and persistent identifiers
- F2: Data are described with rich metadata
- F3: Metadata clearly and explicitly include the identifier of the data they describe
- F4: (Meta)data are registered or indexed in a searchable resource

Accessible

- A1: (Meta)data are retrievable by their identifier using a standardised communication protocol
- A1.1: The protocol is open, free and universally implementable
- A1.2: The protocol allows for an authentication and authorisation procedure where necessary
- A2: Metadata should be accessible even when the data is no longer available

Inter-operable

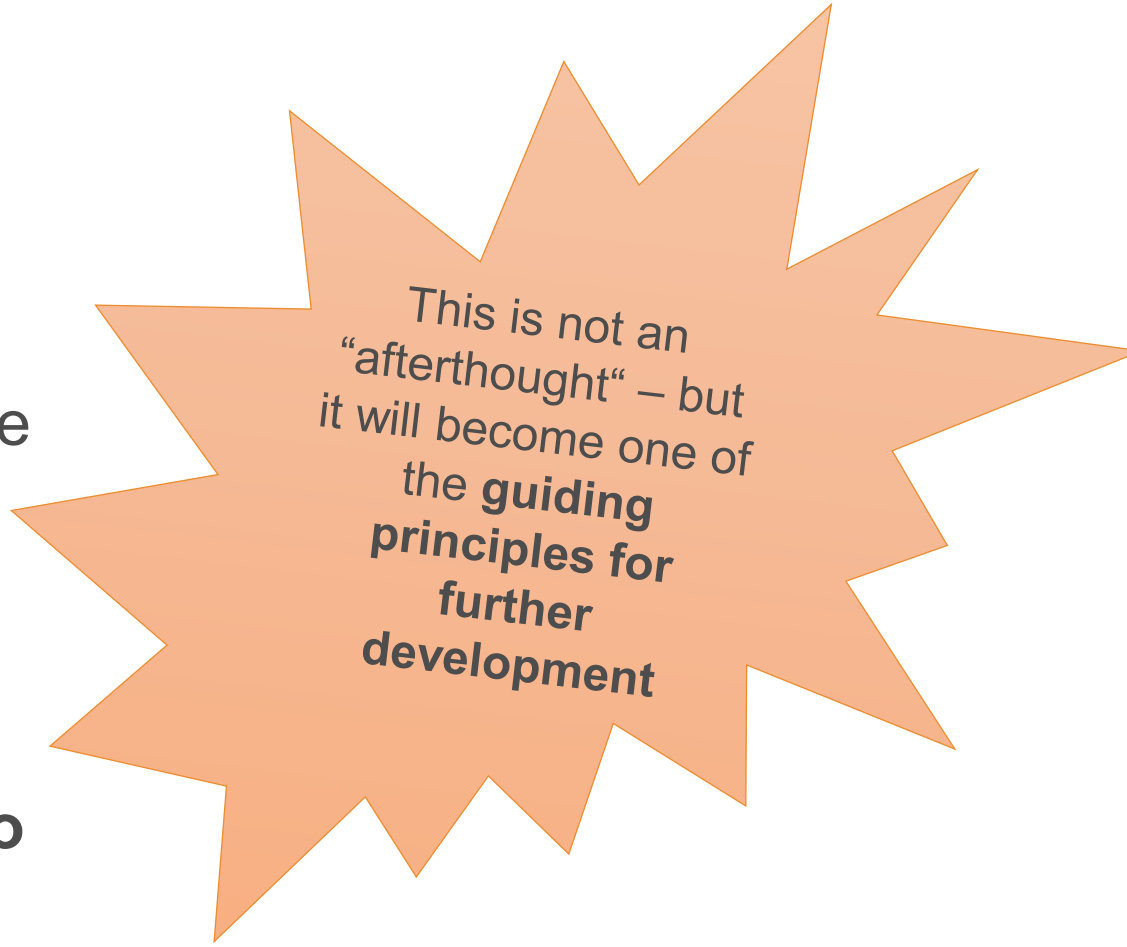
- I1: (Meta)data use a formal, accessible, shared, and broadly applicable language for knowledge representation
- I2: (Meta)data use vocabularies that follow the FAIR principles
- I3: (Meta)data include qualified references to other (meta)data

Re-useable

- R1: (Meta)data are richly described with a plurality of accurate and relevant attributes
- R1.1: (Meta)data are released with a clear and accessible data usage license
- R1.2: (Meta)data are associated with detailed provenance
- R1.3: (Meta)data meet domain-relevant community standards

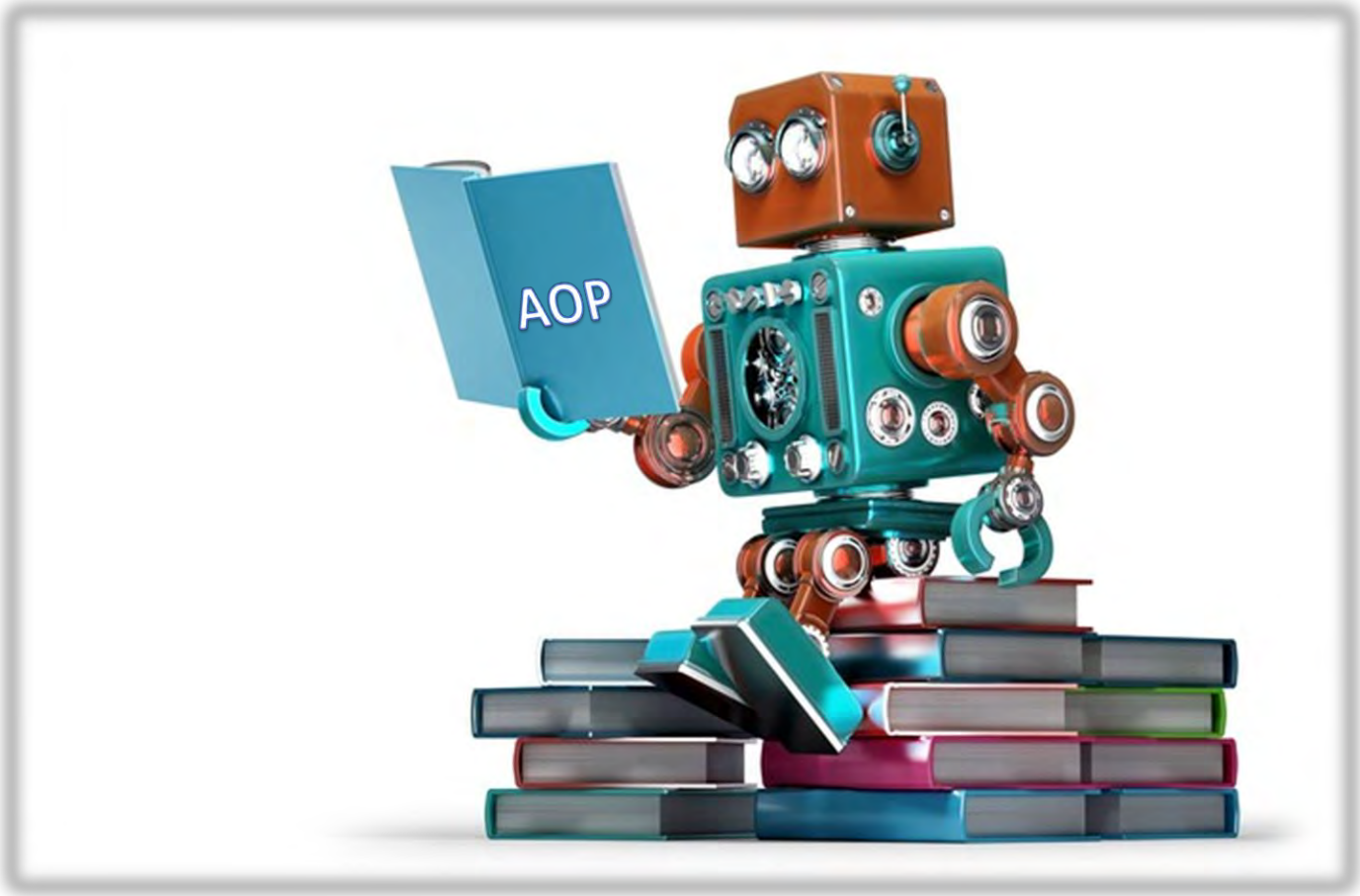
Is the AOP-Wiki FAIR?

- Upcoming initiative!
- For each of the FAIR principles we will define a **FAIR Enabling Resource** (FER), i.e. a description of how we intend to fill the various principles with life
- These FERs together are then our FIP (**FAIR Implementation Profile**)
- A gap analysis will show where we have **to become "FAIR"er**



European Commission

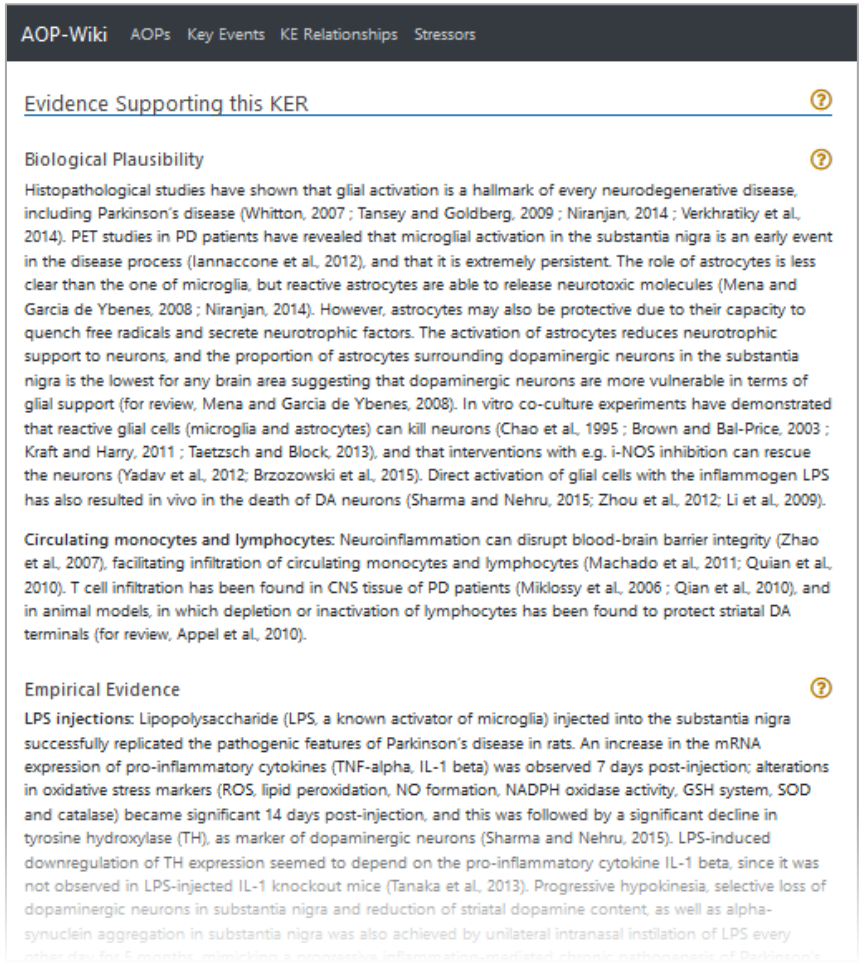
Machine Readable AOP Evidence Collection



Machine Readable AOP Evidence Collection

The Challenge:

- Causal relationships along AOPs are established currently by documenting specific kinds of evidence on Key Event Relationship (KER) and AOP pages
- Based on the Modified Bradford-Hill Considerations
  - Biological Plausibility
  - Essentiality of Key Events (Direct, Indirect data)
  - Empirical Evidence (Dose-Response and Temporal Concordance)
- Evidence collection is heavily based on **Free Text**
  - Time consuming for Authors
  - Inconsistent formatting/information
  - Hard to QUICKLY find information
  - Not easily interpreted by computers
  - IMPOSSIBLE to computationally search, aggregate, summarize, etc…


AOP-Wiki AOPs Key Events KE Relationships Stressors

Evidence Supporting this KER

Biological Plausibility

Histopathological studies have shown that glial activation is a hallmark of every neurodegenerative disease, including Parkinson's disease (Whitton, 2007 ; Tansey and Goldberg, 2009 ; Niranjan, 2014 ; Verkhratiky et al., 2014). PET studies in PD patients have revealed that microglial activation in the substantia nigra is an early event in the disease process (Iannaccone et al., 2012), and that it is extremely persistent. The role of astrocytes is less clear than the one of microglia, but reactive astrocytes are able to release neurotoxic molecules (Mena and Garcia de Ybenes, 2008 ; Niranjan, 2014). However, astrocytes may also be protective due to their capacity to quench free radicals and secrete neurotrophic factors. The activation of astrocytes reduces neurotrophic support to neurons, and the proportion of astrocytes surrounding dopaminergic neurons in the substantia nigra is the lowest for any brain area suggesting that dopaminergic neurons are more vulnerable in terms of glial support (for review, Mena and Garcia de Ybenes, 2008). In vitro co-culture experiments have demonstrated that reactive glial cells (microglia and astrocytes) can kill neurons (Chao et al., 1995 ; Brown and Bal-Price, 2003 ; Kraft and Harry, 2011 ; Taetzsch and Block, 2013), and that interventions with e.g. i-NOS inhibition can rescue the neurons (Yadav et al., 2012; Brzozowski et al., 2015). Direct activation of glial cells with the inflammogen LPS has also resulted in vivo in the death of DA neurons (Sharma and Nehru, 2015; Zhou et al., 2012; Li et al., 2009).

Circulating monocytes and lymphocytes: Neuroinflammation can disrupt blood-brain barrier integrity (Zhao et al., 2007), facilitating infiltration of circulating monocytes and lymphocytes (Machado et al., 2011; Quian et al., 2010). T cell infiltration has been found in CNS tissue of PD patients (Miklossy et al., 2006 ; Qian et al., 2010), and in animal models, in which depletion or inactivation of lymphocytes has been found to protect striatal DA terminals (for review, Appel et al., 2010).

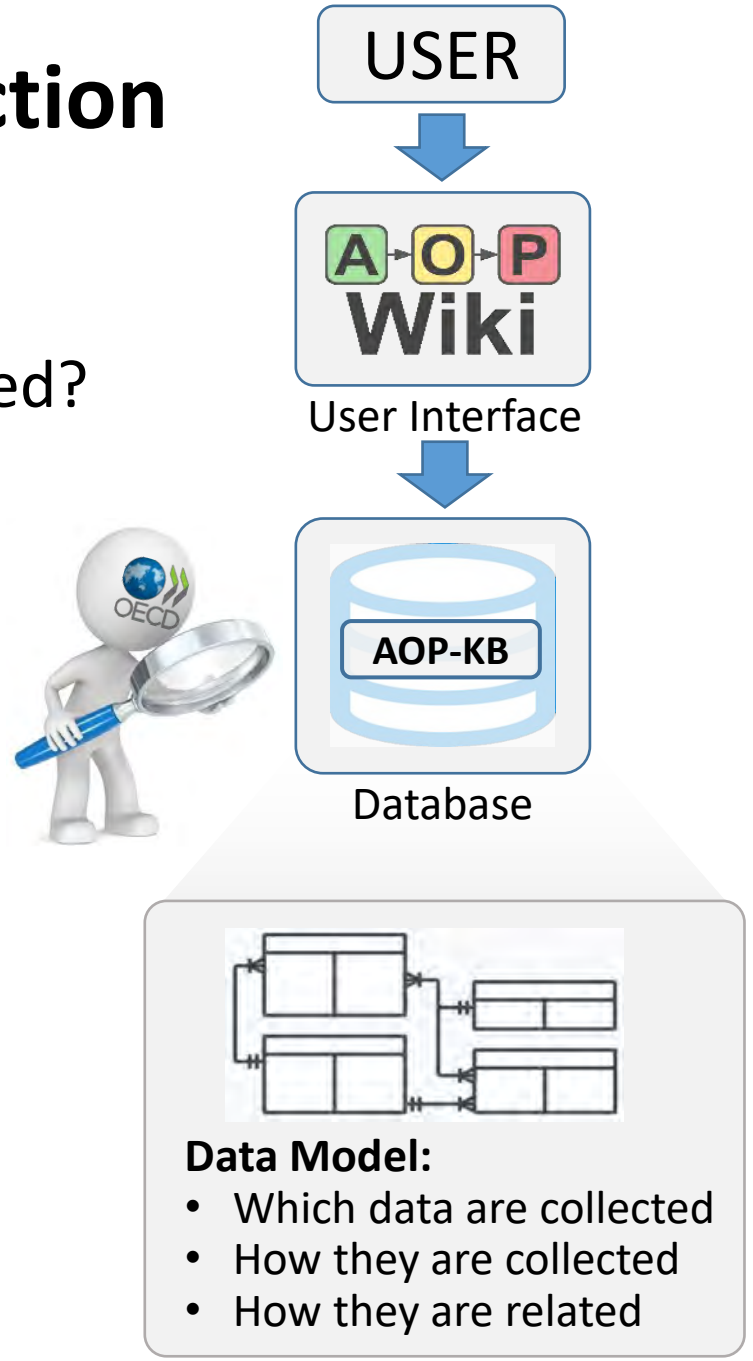
Empirical Evidence

LPS injections: Lipopolysaccharide (LPS, a known activator of microglia) injected into the substantia nigra successfully replicated the pathogenic features of Parkinson's disease in rats. An increase in the mRNA expression of pro-inflammatory cytokines (TNF-alpha, IL-1 beta) was observed 7 days post-injection; alterations in oxidative stress markers (ROS, lipid peroxidation, NO formation, NADPH oxidase activity, GSH system, SOD and catalase) became significant 14 days post-injection, and this was followed by a significant decline in tyrosine hydroxylase (TH), as marker of dopaminergic neurons (Sharma and Nehru, 2015). LPS-induced downregulation of TH expression seemed to depend on the pro-inflammatory cytokine IL-1 beta, since it was not observed in LPS-injected IL-1 knockout mice (Tanaka et al., 2013). Progressive hypokinesia, selective loss of dopaminergic neurons in substantia nigra and reduction of striatal dopamine content, as well as alpha-synuclein aggregation in substantia nigra was also achieved by unilateral intranasal instillation of LPS every

Machine Readable AOP Evidence Collection

- Update the **DATA MODEL** for how KER evidence is collected?

- Other Incentives:
  - Support of “systematic” evidence collection strategies
  - Improve FAIRness of data in the AOP-KB
    - Computationally search, aggregate and summarize information
    - Interoperability with other databases



Machine Readable AOP Evidence Collection

KER Evidence Data Model Pilot Project:

- Overall Goals:
  - Develop data model to collect KER evidence in standardized and machine readable format
  - Develop user-friendly interface with simplified data entry workflow

- Project status
  - Last year: MSAccess Pilot → This year: AOP-Wiki Clone Prototype (emod.aopwiki.org)
  - Currently testing new website

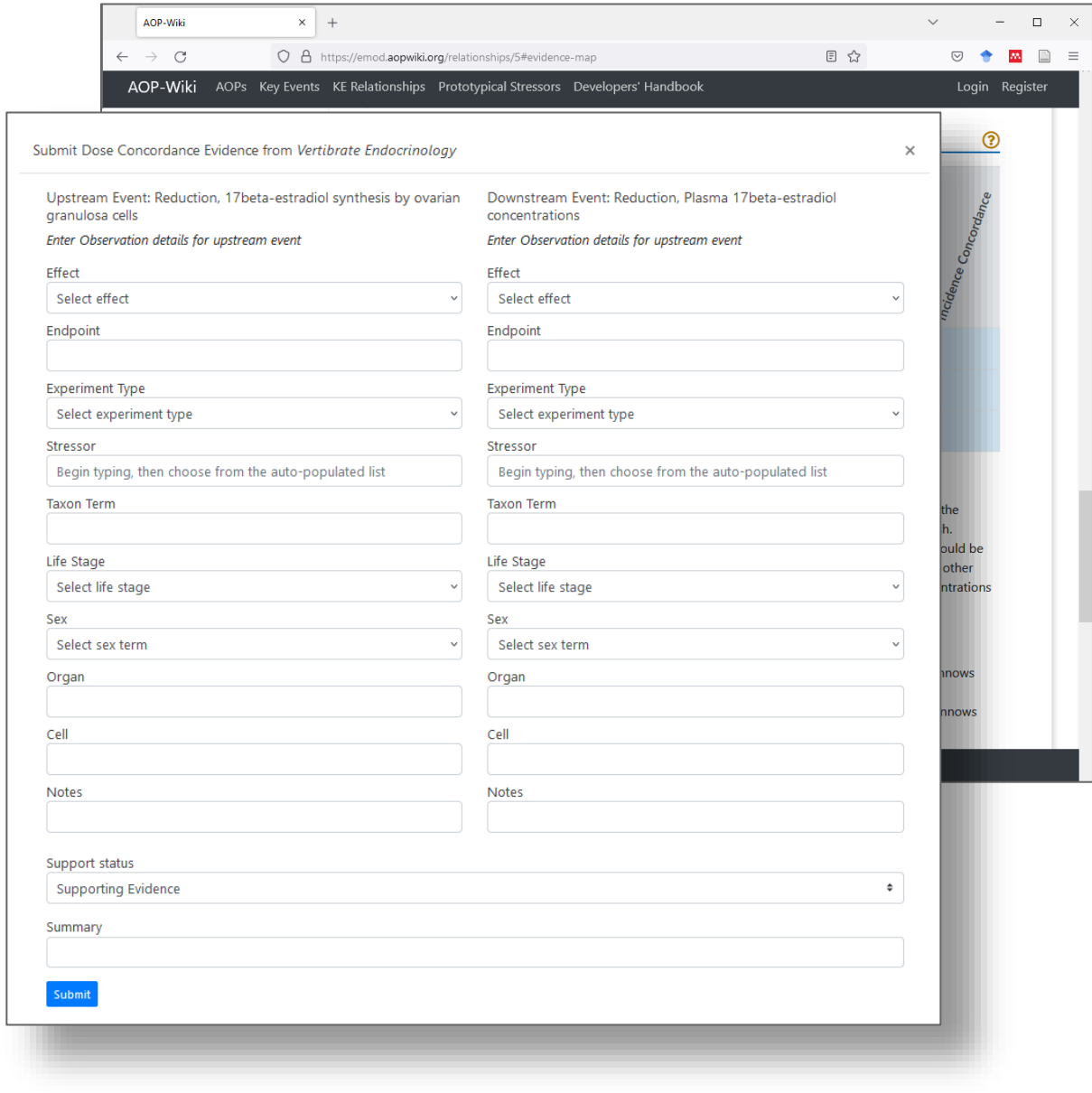
MSAccess Pilot

AOPwiki Pilot

Machine Readable AOP Evidence Collection

- Features:
  - “Evidence map” based workflow and user interface
  - Simple form for standardized data entry
  - Fixed vocabularies
    - Drop down menus, or search tools
  - Improved tracking of:
    - Citations, stressors, domain of applicability (and eventually other info such as Test Methods, Modulating Factors, etc…)
  - Summarized in bulleted text on KER main page

- Potential Benefits
  - Machine Readable → Major increase in AOP-Wiki FAIRness
  - Support systematic approaches to evidence collection
  - Improved and transparent tracking of information
  - Consistent evidence documentation across AOPs
  - Individual contributions highly compartmentalized
    - Easier to distinguish and attribute authors contributions
    - Improves crowd-based collaboration



Machine Readable AOP Evidence Collection

Next Steps

- CONSULT, TEST, CONSULT, and TEST!!!!
- Future Priorities:
  - Expand data model (test methods, modulating factors, other?)
  - Further “ontologize” the data
  - Test interoperability with other databases
    - Publication databases
    - Data repositories (e.g. ECOTOX, ToxCast, CTD, etc…)
  - Summarizing/presenting evidence to end users (e.g. on AOP page)

FEEDBACK REQUIRED!!!

A-O-P FORUM

https://aopwiki.org/forums/showthread.php?tid=171

Agenda

- Introduction
- AOP-Wiki 2.5 and 2.6:
  Rationale behind added features, hands-on technical implementation
- Beyond AOP-Wiki 2.6:
  Challenges ahead and how to address them
- Q&A and discussion
- Outlook and next steps

Q&A and discussion

- Future of the AOP-Wiki and the AOP Framework
- How to increase uptake of AOPs in regulatory environments

Agenda

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How can  get involved?

- Your ideas are welcome - they will help us shape the AOP framework of the future
- Your participation is key
  - Join the AOP community of practice and reach out to the Society for the Advancement of AOPs (SAAOP, aopwiki@googlegroups.com)
  - Get in touch with your OECD Heads of Delegation to Working Parties and with the future Advisory Group on Emerging Science in Chemical Assessment
    - Ask the coordinates of your respective Working Party Head of Delegation to the OECD Secretariat: EHS.Contact@oecd.org
  - Use the AOP Forum to share your ideas on AOP development, AOP use and the AOP Knowledge Base:
    - *either contribute to the* https://aopwiki.org/forums/showthread.php?tid=171 *thread*
    - *Or start your own discussion thread*

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