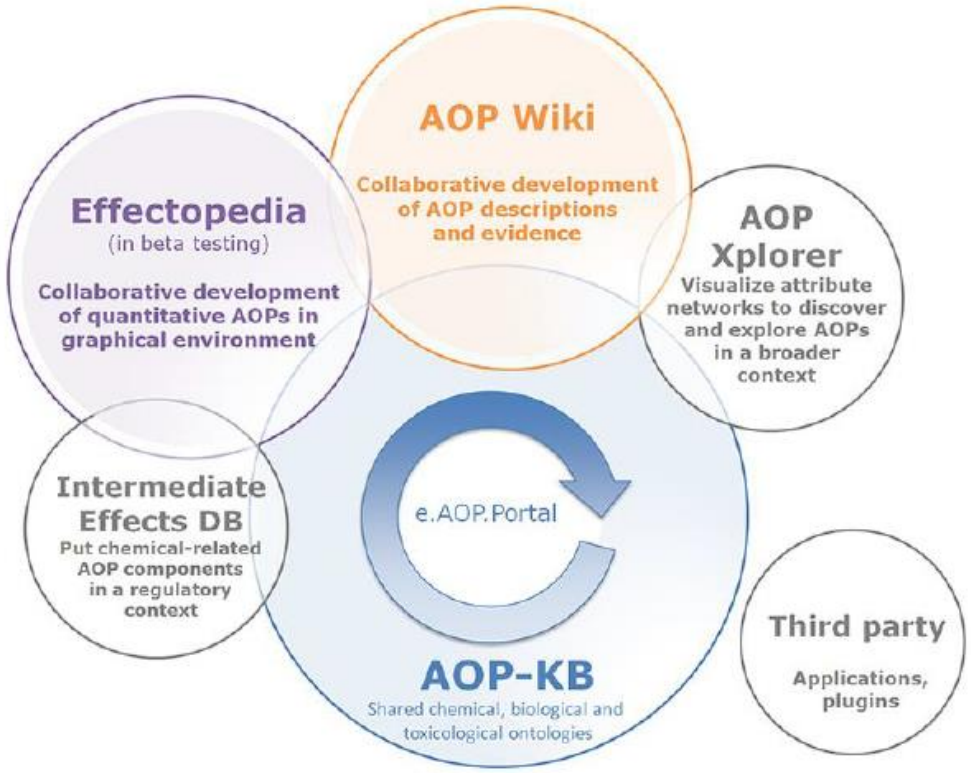
ATAL INCUBATION CENTRE
CENTRE FOR CELLULAR & MOLECULAR BIOLOGY

HUMANE SOCIETY INTERNATIONAL
INDIA

How to build an AOP

Dr. Surat Parvatam
Research Associate
Centre for Predictive Human Model Systems (CPHMS),
Atal Incubation Centre-CCMB
Humane Society International-India

OECD AOP Knowledge Base



https://aopkb.oecd.org

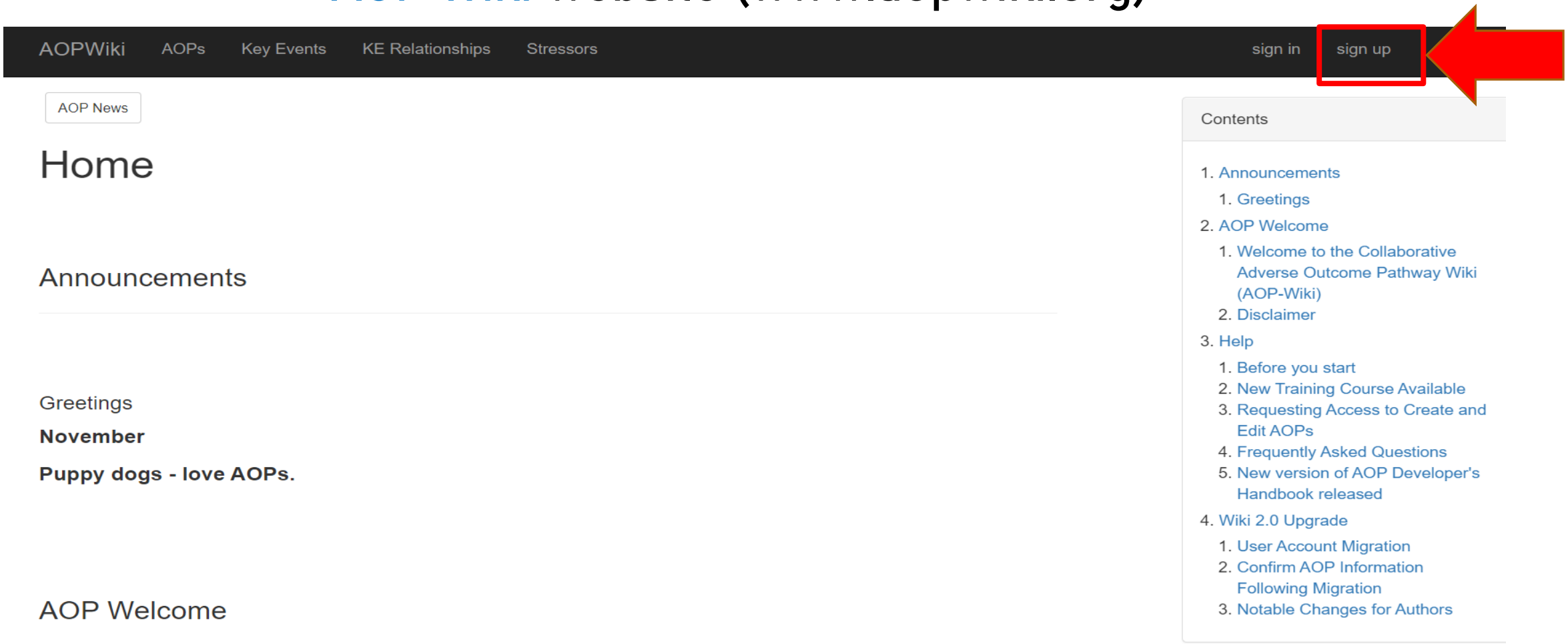
- AOP KB has been launched by OECD to help the scientific community to share, develop, and discuss AOP-related information in one place.

- AOP-KB brings four independently developed programs:
  - AOP-Wiki
  - Effectopedia
  - AOP Xplorer
  - Intermediate Effect DB

AOP wiki

- The main element of AOP-KB is currently AOP-Wiki
- Joint effort between European Commission-DG Joint Research Centre and U.S Environmental Protection Agency (EPA).
- Provides information in a readily accessible and searchable format, promoting collaborative development of AOPs.

AOP Wiki website (www.aopwiki.org)



- After signing-up, the user can access and comment on existing AOPs.
- For editing or adding information, however, one has to request write privileges

Requesting write access on AOP Wiki

- Write access is managed by the Society for the Advancement of AOPs (SAAOP)
- Users can download and submit a completed form available on SAAOP website.

AOP-Wiki Developer Access Request Form

Requester Name: _____

Have all perspective users read and accepted the rights and responsibilities defined for contributors to the AOP-Wiki? ☐ Y ☐ N

If you are currently working on an OECD Extended Advisory Group on Molecular Screening and Toxicogenomics (EAGMST) approved AOP project please supply the project title below.

Project title or OECD assigned project number:

_____

_____

Project leader email:_____

If you are not currently working on an OECD EAGMST project, please attach a brief description of your intended contribution. This can be a proposal for a new AOP or a desire to contribute to existing AOPs. For new AOP proposals please include a graphic illustration of the AOP/partial AOP. The proposal should not exceed a page including the figure. A 1-2 paragraph summary of the contribution is sufficient. The proposal must be consistent with current OECD Guidance on AOP development, (Users' Handbook Supplement to the Guidance Document for Developing and Assessing AOPs)*.

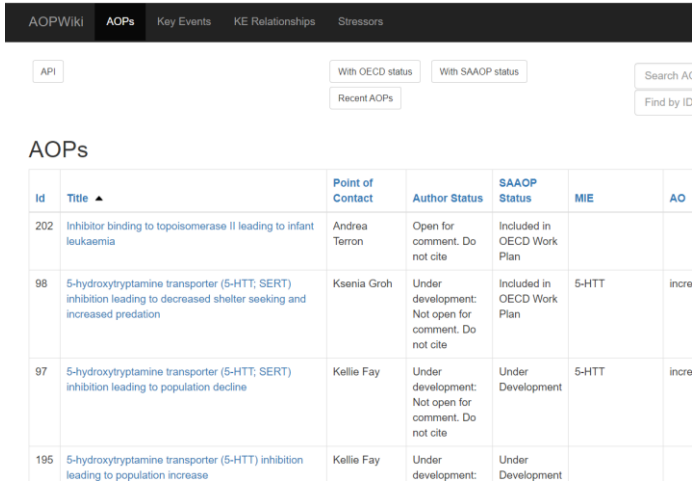
* http://aopkb.org/common/AOP_Handbook.pdf

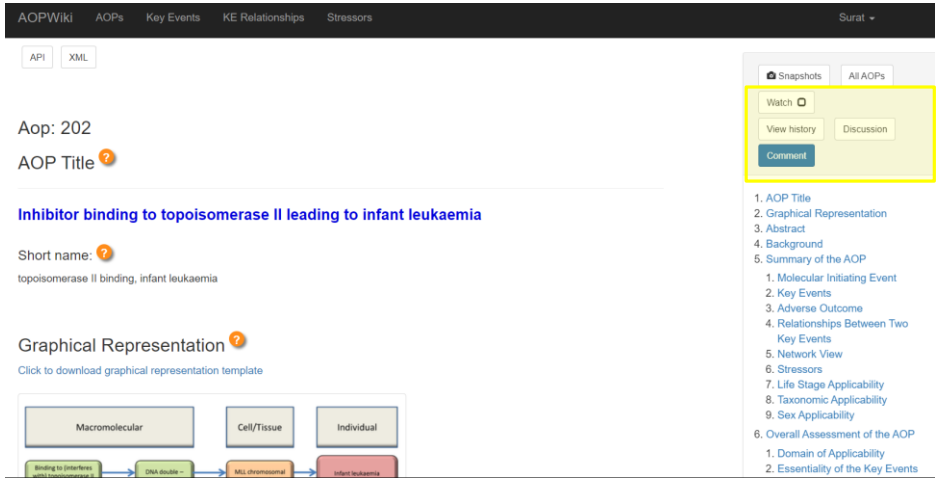
AOP-Wiki Email/Username:_____

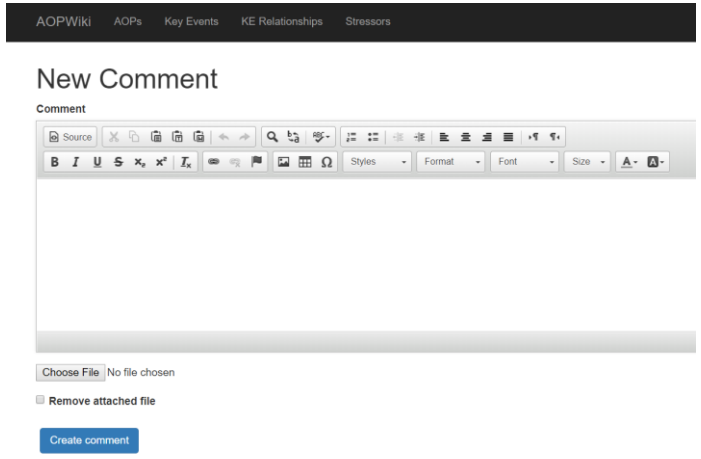
(User profile in the wiki should include the following: first name, last name, professional affiliation, professional title (position in affiliated organization), country of residence.)

Editing/commenting on AOP Wiki

- AOP Wiki does not enforce edit restrictions on AOP-related pages; however, to maintain this open structure, it is requested that people not edit, delete, add information on an AOP page unless they are a part of development team or have received permission from the lead of the team.
- To provide any comments on the page, one is encouraged to use the “Discussion” or “Comment” tab for that AOP.



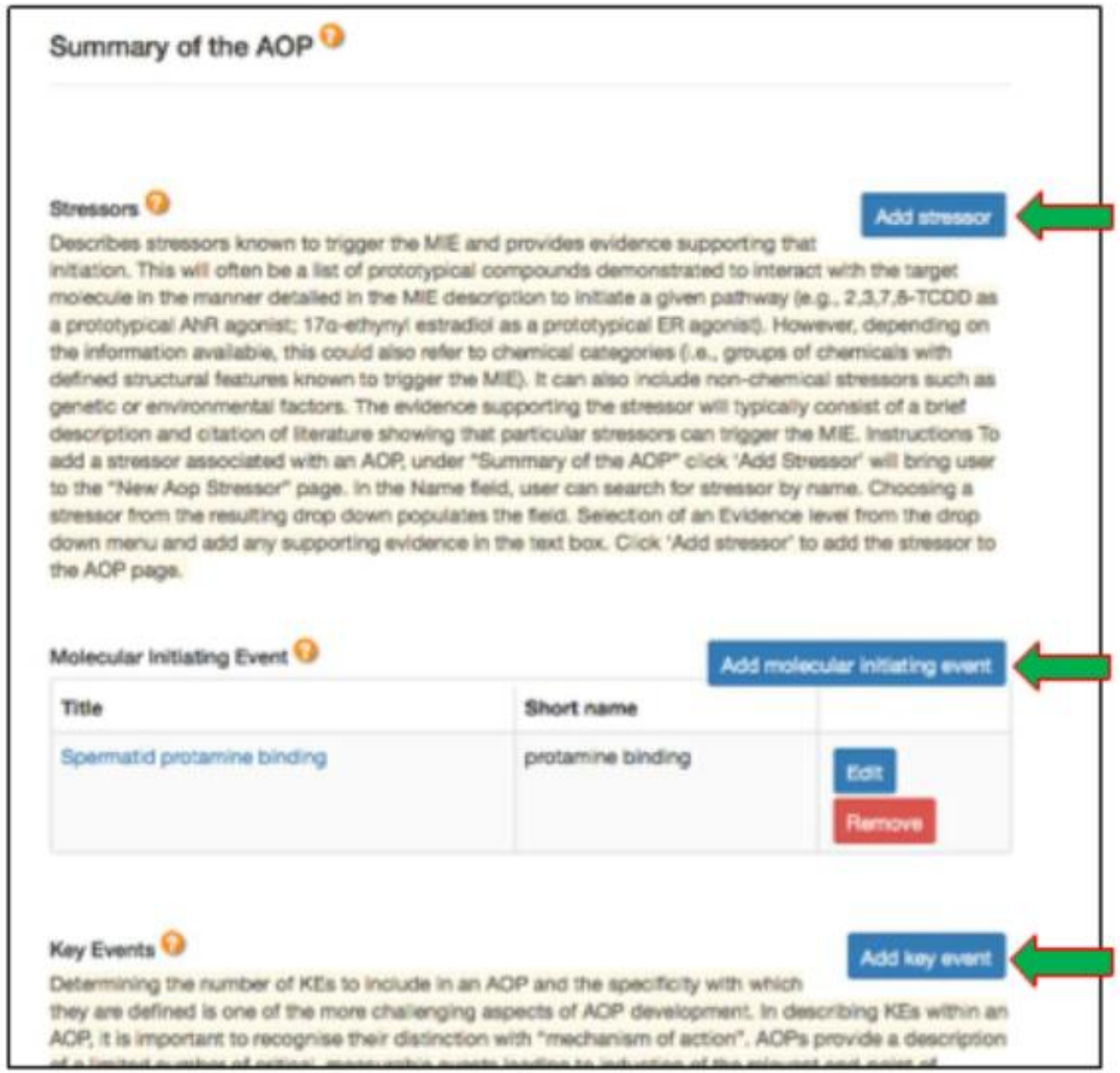




Entering information on AOP Wiki

Comment

1. AOP Title
2. Graphical Representation
3. Abstract
4. Background
5. Summary of the AOP
    1. Molecular Initiating Event
    2. Key Events
    3. Adverse Outcome
    4. Relationships Between Two Key Events
    5. Network View
    6. Stressors
    7. Life Stage Applicability
    8. Taxonomic Applicability
    9. Sex Applicability
6. Overall Assessment of the AOP
    1. Domain of Applicability
    2. Essentiality of the Key Events
    3. Evidence Assessment
    4. Quantitative Understanding
7. Considerations for Potential Applications of the AOP
8. References



For each of the categories, the user can add information by clicking on the "Add" section. This will open the entry form of that component of AOP

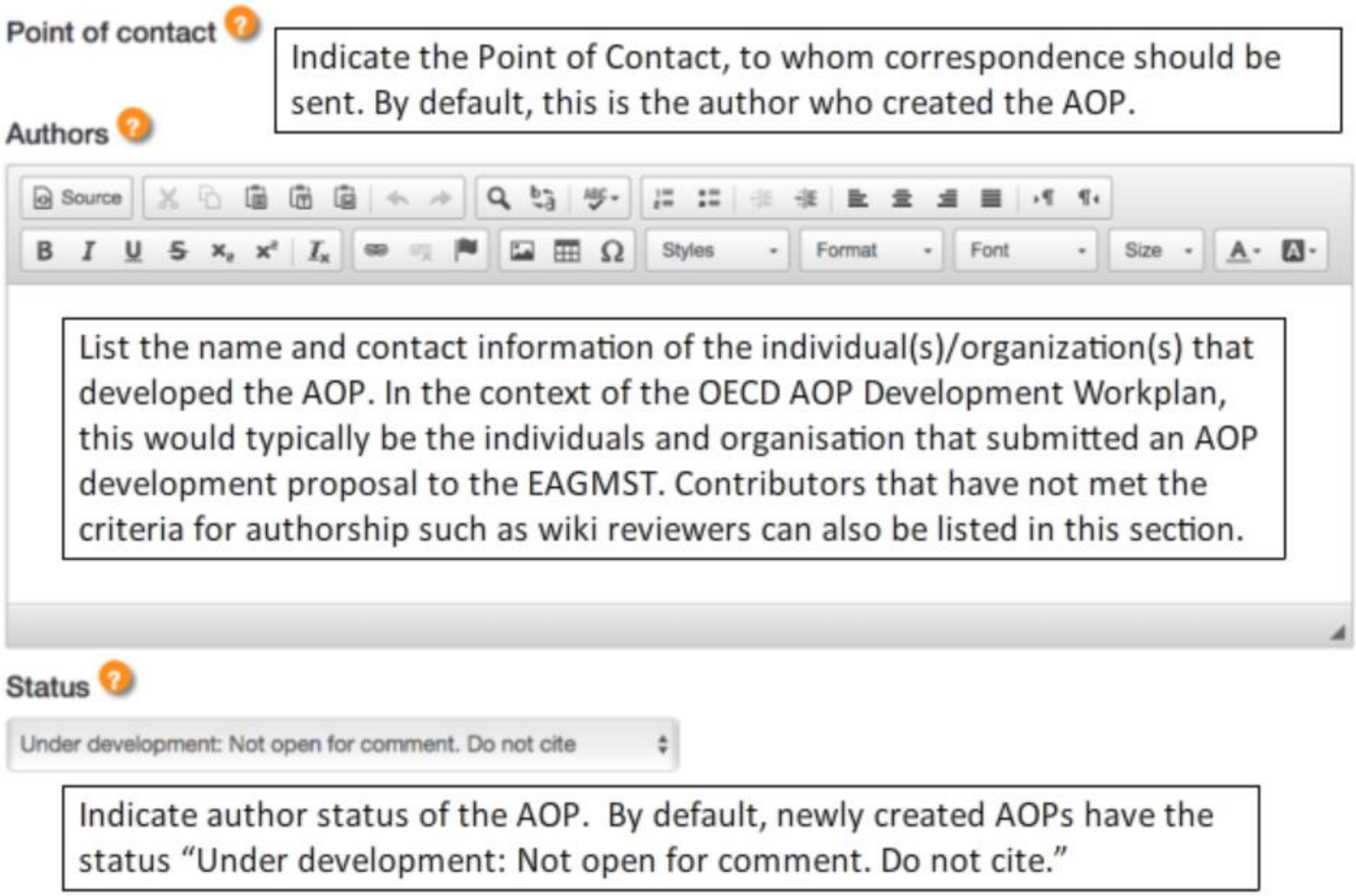
Creating new AOP on AOP Wiki

Click "**AOPs**" in the main header to go to the "AOPs" page, then select the "**New AOP**" button. This will open the 'New AOP' form open (below) with fields for entering a "Title" and a "Short name".

Id	Title ▲	Point of Contact	Author Status
202	Inhibitor binding to topoisomerase II leading to infant leukaemia	Andrea Terron	Open for comment. Do not cite
98	5-hydroxytryptamine transporter (5-HTT; SERT) inhibition leading to decreased shelter seeking and increased predation	Ksenia Groh	Under development: Not open for comment. Do not cite
97	5-hydroxytryptamine transporter (5-HTT; SERT) inhibition leading to population decline	Kellie Fay	Under development: Not open for comment. Do not cite

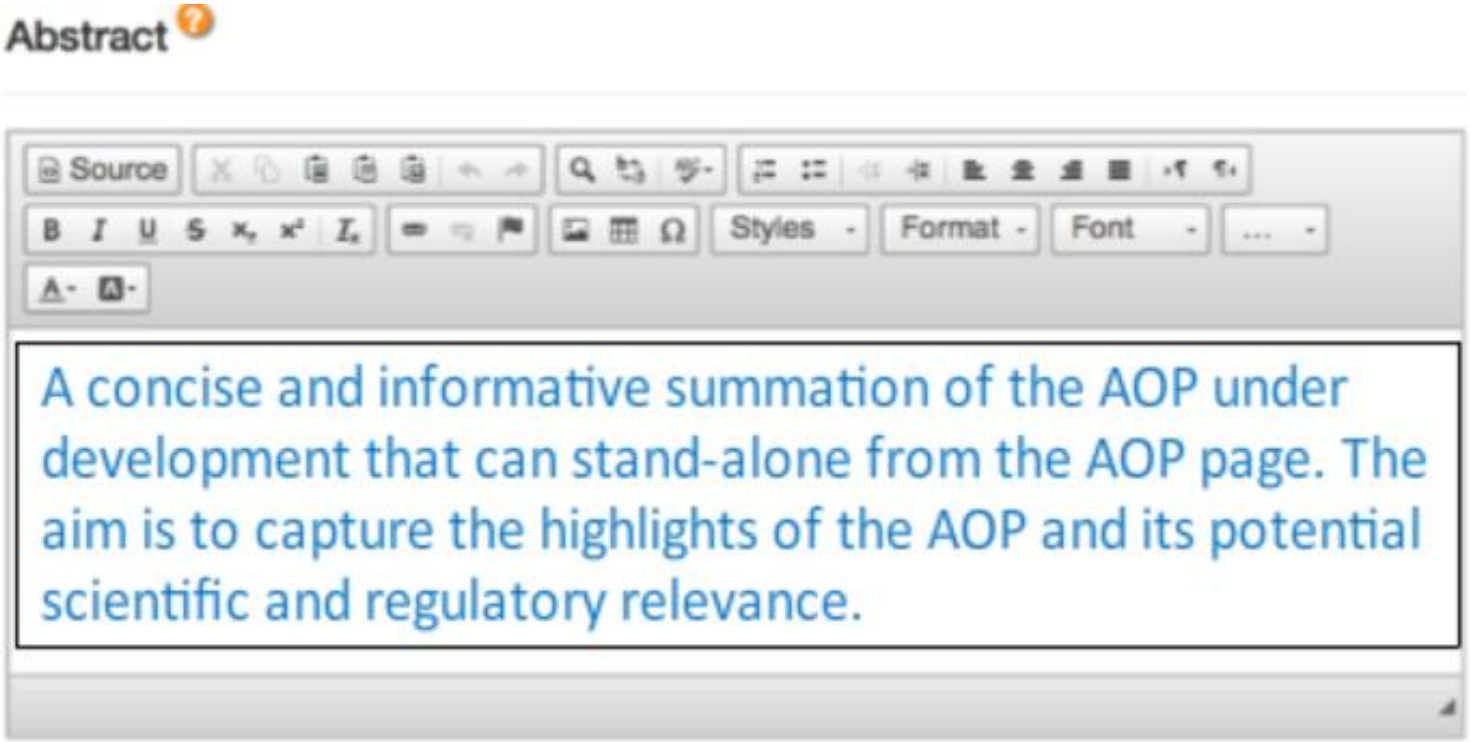
Title should be in form of "MIE leading to AO"

Author information on AOP Wiki



For each section "?" can be clicked for further information about that section.

Entering abstract on AOP Wiki



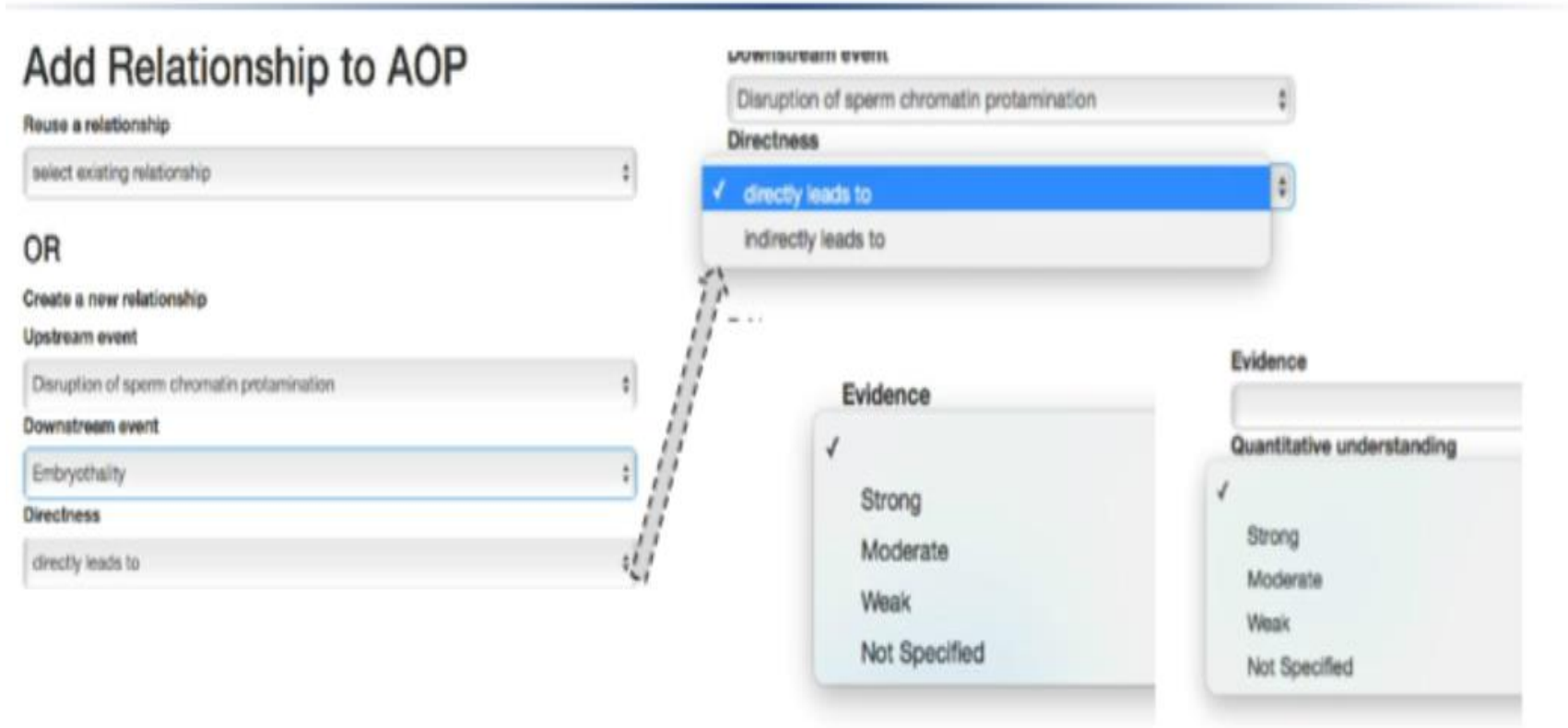
The 200-300 word abstract should include:

- Background
- Brief description of MIE, AO, major KEs
- Short summary of weight of evidence supporting AOP, applications.

Entering information on MIE, KE, AO

The user will also need to add 'biological organisation' or the level of hierarchy- molecular, cellular, tissue, organ, or population-level for the MIE, KE, and AO

Entering information about KER on AOP Wiki



Key Event Relationships describe the relationship between two Key Events, so here the user has to indicate:

- Upstream event
- Downstream event
- Direct/indirect relation
- Level of evidence

Entering supporting information on AOP Wiki: KE

1. Key Event Title
2. Key Event Components
3. Key Event Overview
    1. AOPs Including This Key Event
    2. Stressors
    3. Level of Biological Organization
    4. Cell Term
    5. Organ Term
    6. Taxonomic Applicability
    7. Life Stages
    8. Sex Applicability
4. How This Key Event Works
5. How it is Measured or Detected
6. Evidence Supporting Taxonomic Applicability
7. References

i. Table generated by AOP-Wiki that lists AOPs associated with this KE
ii. Stressor associated with KE can be added here.
iii. Apart from the section in the main page, it can also be added here.
iv. Information about the cellular and organ-level context.
v. Specific taxa, life stage, and sex where KE was measured

Entering supporting information on AOP Wiki: KER

1. KE Relationship Title
2. KE Relationship Overview
    1. AOPS Referencing Relationship
    2. Taxonomic Applicability
    3. Sex Applicability
    4. Life Stage Applicability
3. How Does This Key Event Relationship Work
4. Weight of Evidence
    1. Biological Plausibility
    2. Empirical Support for Linkage
    3. Uncertainties or Inconsistencies
5. Quantitative Understanding of the Linkage
6. Evidence Supporting Taxonomic Applicability
7. References

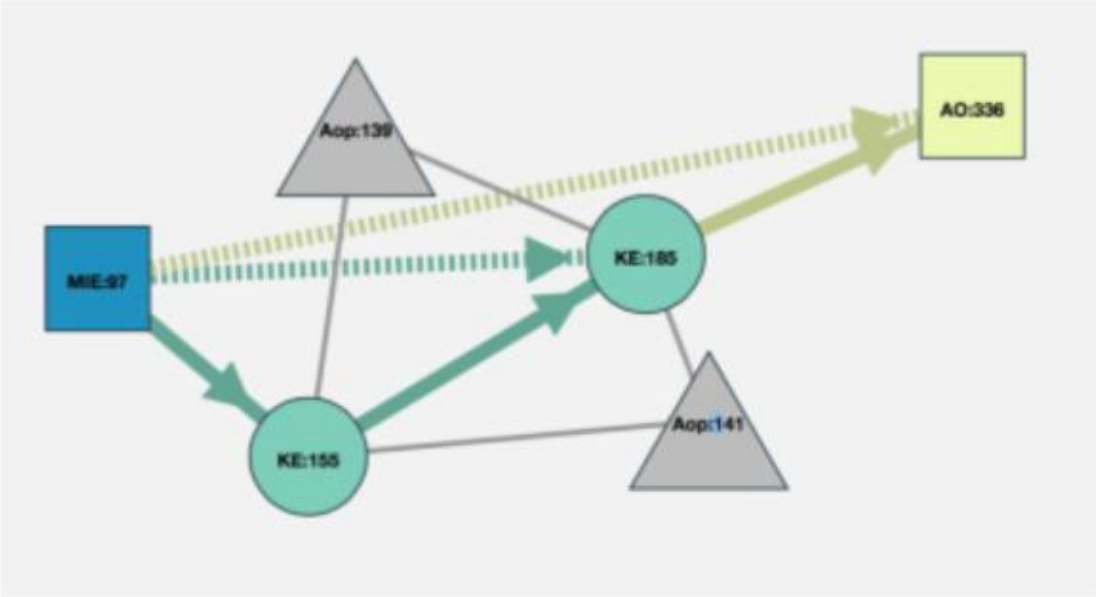
1. Support for Biological Plausibility of KERS [1]

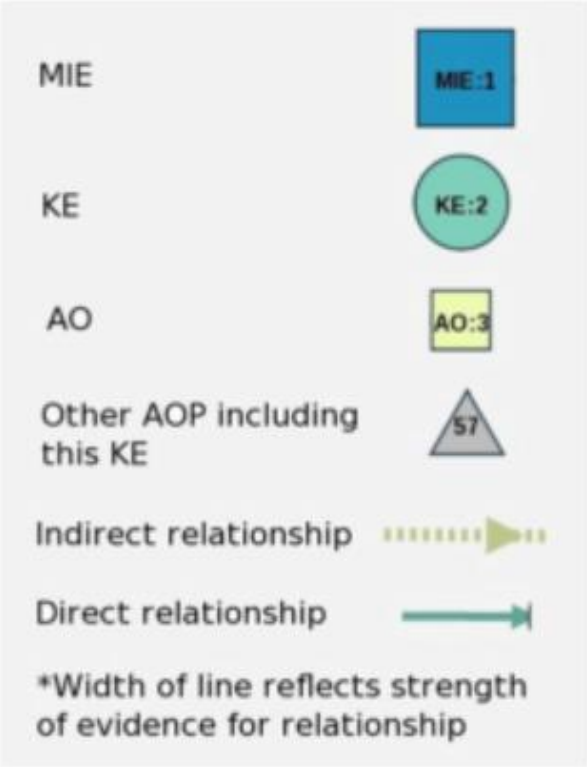
High (Strong)[2,3]	Moderate	Low (Weak)
Extensive understanding of the KER based on extensive previous documentation and broad acceptance (e.g., mutation leading to tumours) -Established mechanistic basis	The KER is plausible based on analogy to accepted biological relationships but scientific understanding is not completely established.	There is empirical support for a statistical association between KEs (See 3.), but the structural or functional relationship between them is not understood.

Consideration	Description
Dose-response concordance	Dose/concentrations needed to evoke change in Ke_{up} should be less than or equal to that needed to evoke $KE_{down.}$
Temporal concordance	Observation of KE_{up} should precede observation of KE_{down} following administration of a stressor
Incidence concordance	**KE_{up} should be observed as frequently, if not more frequently, than KE_{down} at the same dose of applied stressor.**

Network view

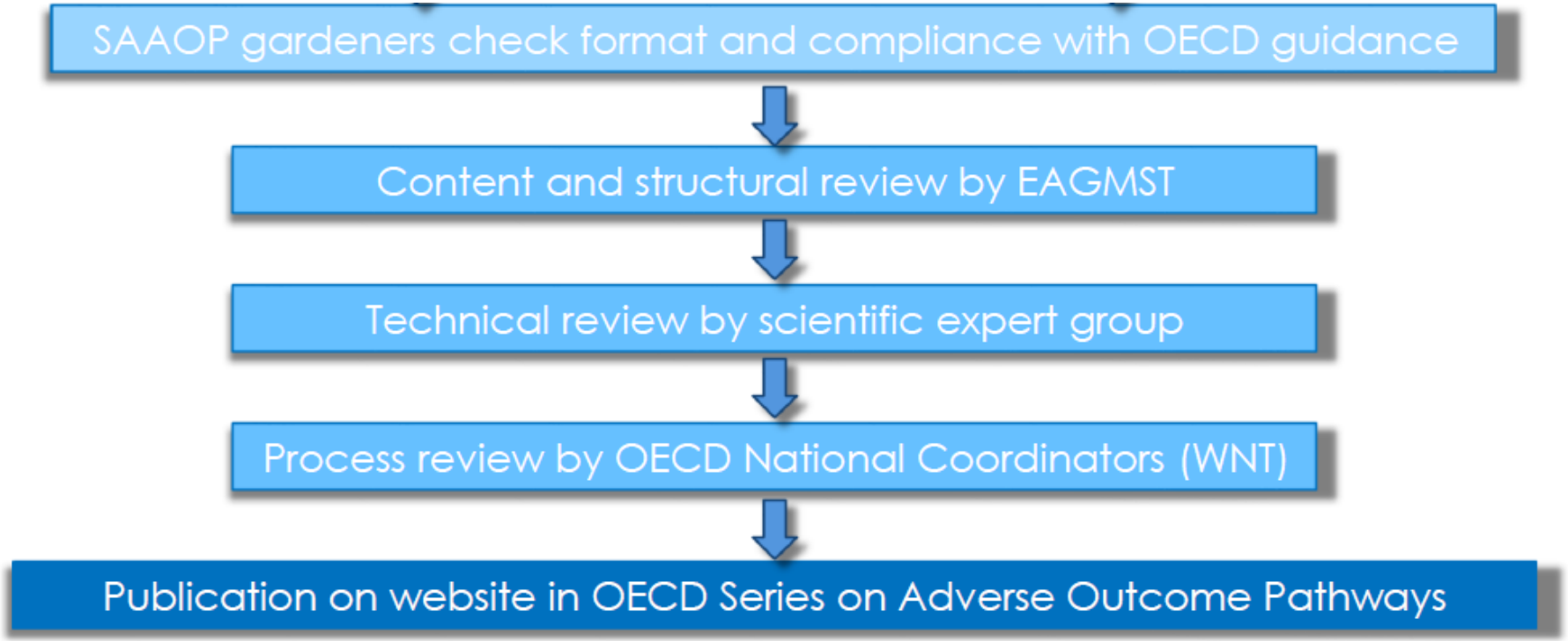
AOP for Alkylation of DNA in male pre-meiotic germ cells leading to heritable mutations.





Overall AOP can be assessed using the network view based on the information provided.

Work Process for Development and Review of AOPs through OECD



C. Willett, Humane Society International

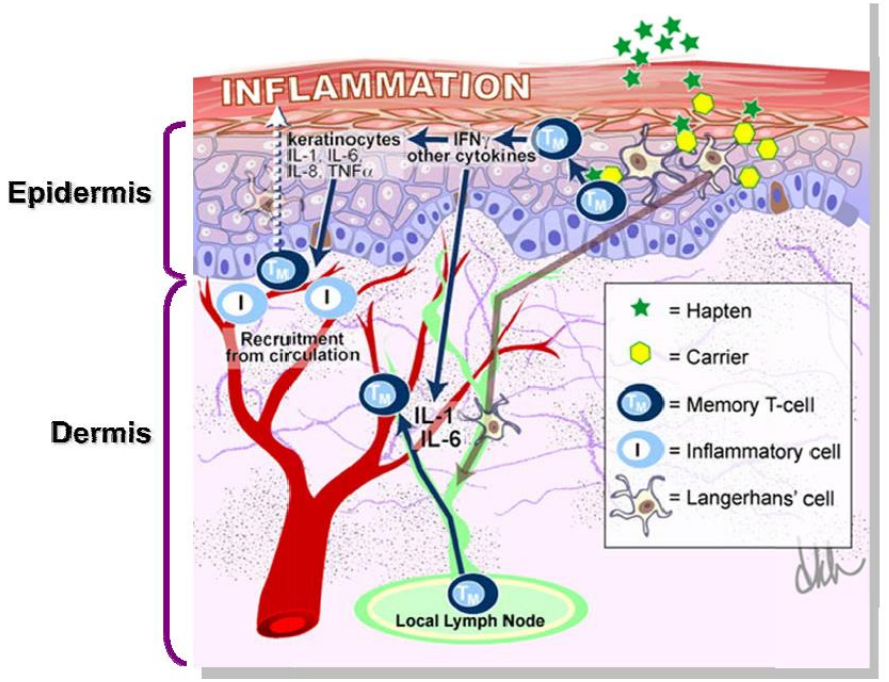
AOP on skin sensitisation

Mechanism of skin sensitisation

Skin sensitisation

Phase I: Induction

Phase II: Elicitation



AOP of skin sensitisation

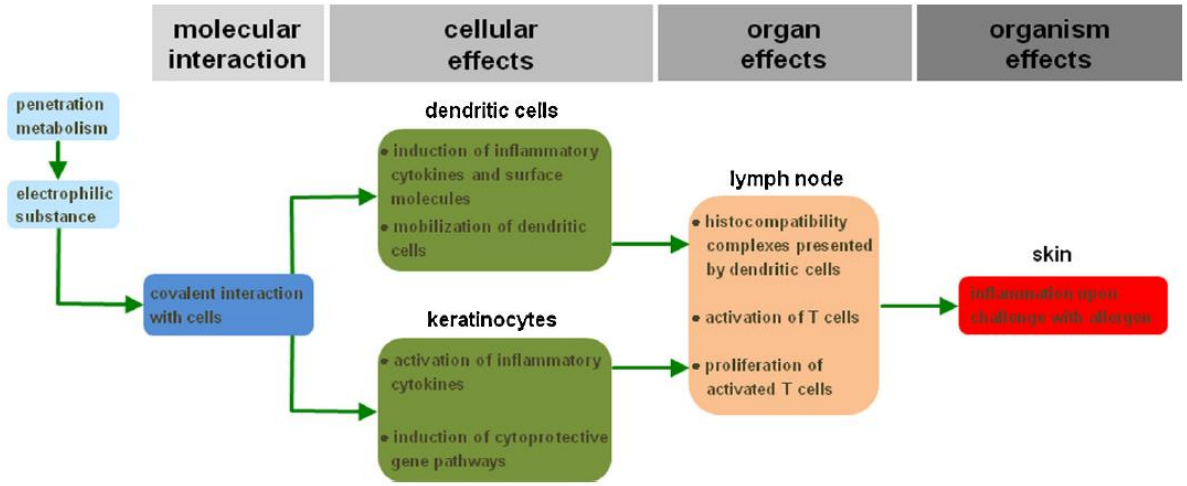


Table 3. Defined Approach (DA) performance in predicting human hazard (sensitizer/non-sensitizer).

Predicting Human Hazard								
Defined Approach:	BASF 2/3 (DKH)	Kao STS	Kao ITS	ICCVAM SVM (Human)	Shiseido ANN (D_hC)	Shiseido ANN (D_hC_KS)	P&G BN ITS 3	LLNA
N	127	126	120	120	126	126	119	128
Accuracy (%)*	77.2	80.2	85.0	81.7	78.6	78.6	75.6	74.2
Sensitivity (%)	79.3	97.7	93.8	86.4	95.4	100	81.3	85.2
Specificity (%)	72.5	41.0	66.7	71.8	41.0	30.8	64.1	50.0
BA (%)	75.9	69.4	80.3	79.1	68.2	65.4	72.7	67.6

*Performance is shown against the maximum subset (*N*) out of 128 substances with all necessary DA features.
BA: balanced accuracy; STS: sequential testing strategy; ITS: integrated testing strategy; SVM: support vector machine; ANN: artificial neural network; BN: Bayesian network; DKH and D_hC_KS: DPRA/h-CLAT/KeratinoSens™; D_hC: DPRA/h-CLAT.

The AOP framework is:

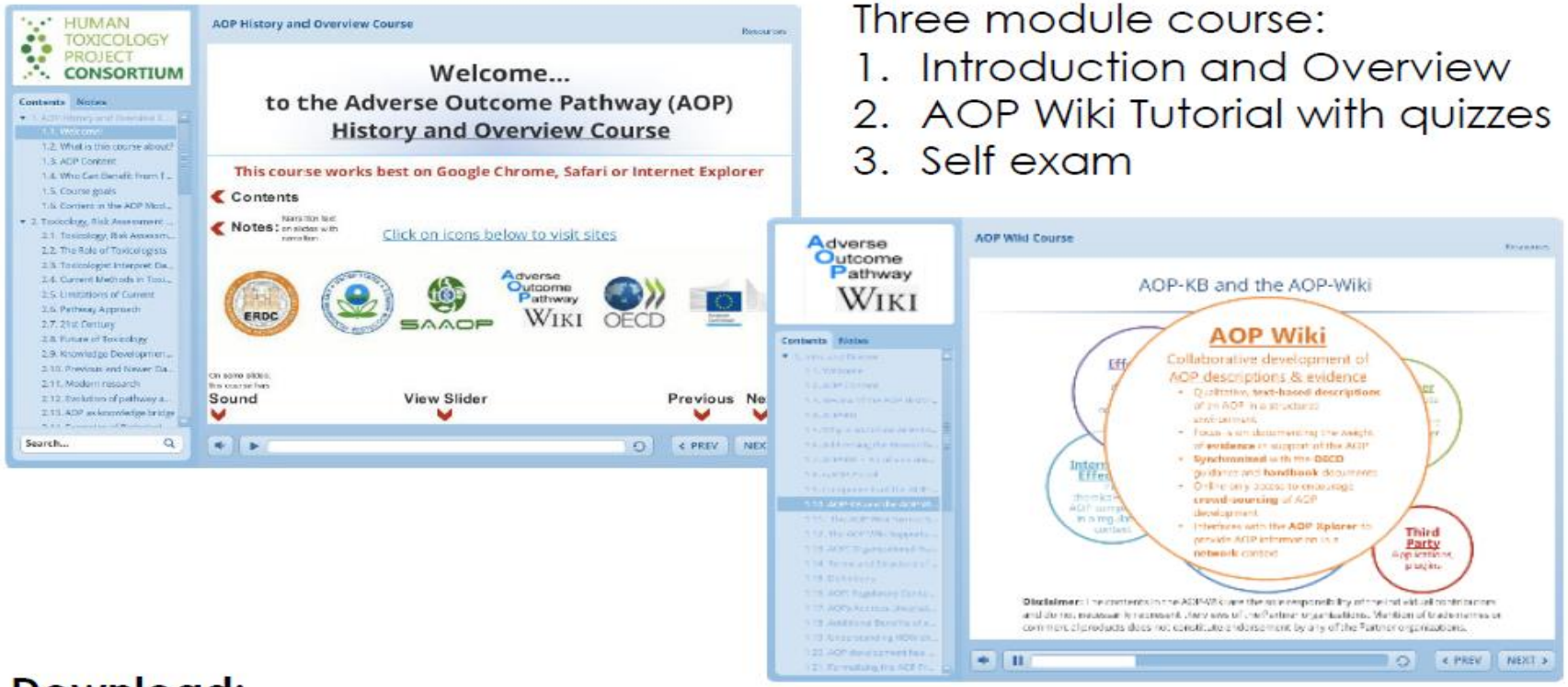
- A formal process to collect, organize, link, and evaluate biological information
- A practical solution to a practical problem – how to use mechanistic biological information to support better decisions regarding chemical safety
- A transparent, highly curated, living document representing current biological knowledge
- The basis for predictive toxicology

- is incredibly time and labor-intensive
- Its utility is dependent on wide adoption

The AOP Framework Needs YOU!

C. Willett, Humane Society International

AOP Online Training Course



Three module course:

1. Introduction and Overview
2. AOP Wiki Tutorial with quizzes
3. Self exam

Download:
https://humantoxicologyproject.org/about-pathways-2/aop-online-course/
Run:
https://aopwiki.org/

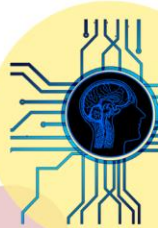
Call for proposals

Science funding opportunity

Development of Adverse Outcome Pathways

- Funding to support the development of Adverse Outcome Pathways (AOPs) in the field of cancer.
- The project will be divided into two investigations: one focusing on building links at a molecular, cellular, and tissue level, while the other focusing on organ and organism responses.
- The grant is for 7 lakhs each for two scientists, one biologist and the other with expertise in medical and allied fields, to work on these two key areas.

Help shape tomorrow's research today!



Application Deadline: 31 March 2020

Contact:

Dr Surat Parvatam (surat.parvatam@ccmb.res.in)
Dr Brinda Poojary (bpoojary@hsi.org)

CSIR-CCMB

HUMANE SOCIETY INTERNATIONAL INDIA

BIOMED21 COLLABORATION
Toward a human-focused paradigm in health research

ashraya hastha trust

Centre for Predictive Human Model Systems