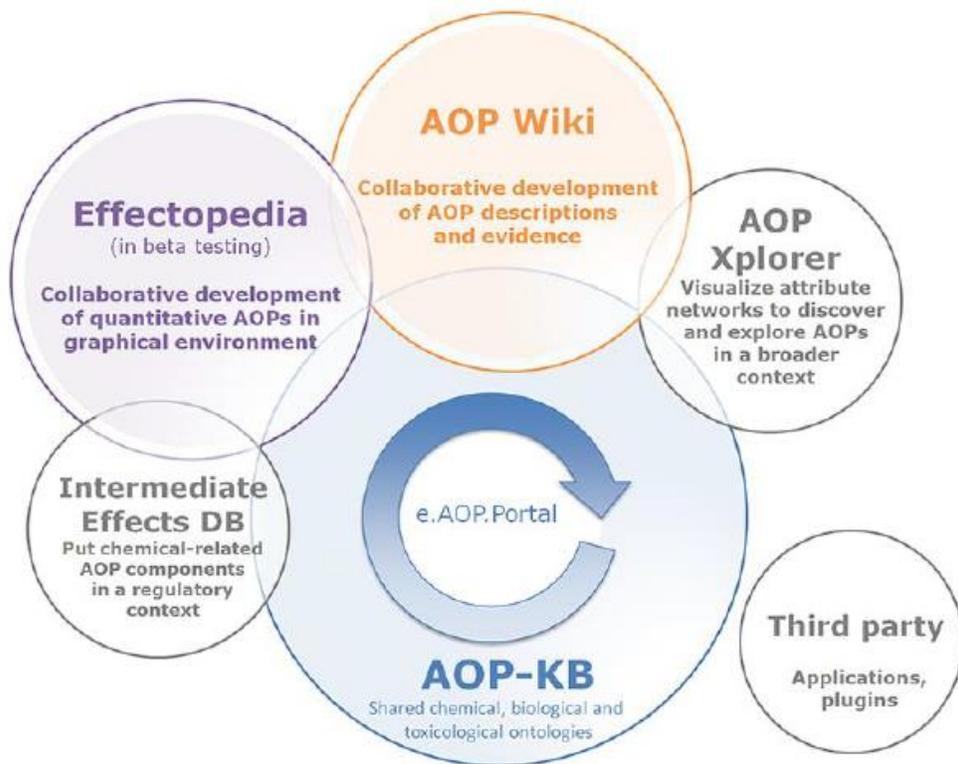


How to build an AOP

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

OECD AOP Knowledge Base



➤ 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:

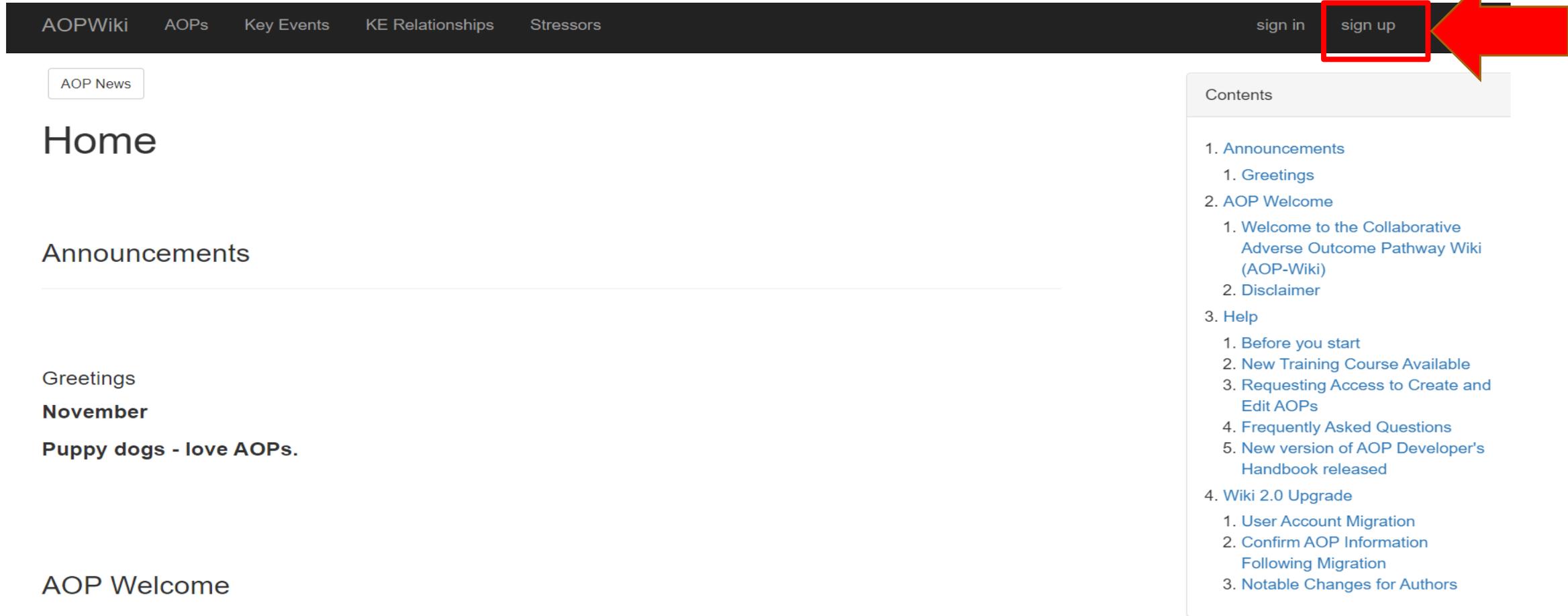
- **AOP-Wiki**
- **Effectopedia**
- **AOP Xplorer**
- **Intermediate Effect DB**

<https://aopkb.oecd.org>

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)



The screenshot shows the AOP Wiki website interface. At the top, there is a dark navigation bar with links for "AOPWiki", "AOPs", "Key Events", "KE Relationships", and "Stressors". On the right side of this bar, there are "sign in" and "sign up" links. The "sign up" link is highlighted with a red rectangular box, and a large red arrow points to it from the right. Below the navigation bar, there is a "Contents" sidebar on the right with a list of links: "1. Announcements", "1. Greetings", "2. AOP Welcome", "1. Welcome to the Collaborative Adverse Outcome Pathway Wiki (AOP-Wiki)", "2. Disclaimer", "3. Help", "1. Before you start", "2. New Training Course Available", "3. Requesting Access to Create and Edit AOPs", "4. Frequently Asked Questions", "5. New version of AOP Developer's Handbook released", "4. Wiki 2.0 Upgrade", "1. User Account Migration", "2. Confirm AOP Information Following Migration", and "3. Notable Changes for Authors". The main content area on the left has sections for "Home", "Announcements", "Greetings", "November", "Puppy dogs - love AOPs.", and "AOP Welcome".

- 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.

Id	Title	Point of Contact	Author Status	SAAOP Status	MIE	AO
202	Inhibitor binding to topoisomerase II leading to infant leukaemia	Andrea Terron	Open for comment. Do not cite	Included in OECD Work Plan		
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	Included in OECD Work Plan	5-HTT	incre
97	5-hydroxytryptamine transporter (5-HTT; SERT) inhibition leading to population decline	Kellie Fay	Under development: Not open for comment. Do not cite	Under Development	5-HTT	incre
195	5-hydroxytryptamine transporter (5-HTT) inhibition leading to population increase	Kellie Fay	Under development:	Under Development		

AOPWiki AOPs Key Events KE Relationships Stressors

API XML

Aop: 202

AOP Title ?

Inhibitor binding to topoisomerase II leading to infant leukaemia

Short name: ?

topoisomerase II binding, infant leukaemia

Graphical Representation ?

Click to download graphical representation template

Macromolecular Cell/Tissue Individual

Binding to topoisomerase II (Chromosomal) DNA double MLL chromosomal Infant leukaemia

Snapshots All AOPs

Watch View history Discussion 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

AOPWiki AOPs Key Events KE Relationships Stressors

New Comment

Comment

Choose File No file chosen

Remove attached file

Create comment

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

Summary of the AOP

Stressors

Add stressor

Describes stressors known to trigger the MIE and provides evidence supporting that initiation. This will often be a list of prototypical compounds demonstrated to interact with the target molecule in the manner detailed in the MIE description to initiate a given pathway (e.g., 2,3,7,8-TCDD as a prototypical AhR agonist; 17 α -ethynyl estradiol as a prototypical ER agonist). However, depending on the information available, this could also refer to chemical categories (i.e., groups of chemicals with defined structural features known to trigger the MIE). It can also include non-chemical stressors such as genetic or environmental factors. The evidence supporting the stressor will typically consist of a brief description and citation of literature showing that particular stressors can trigger the MIE. Instructions To add a stressor associated with an AOP, under "Summary of the AOP" click 'Add Stressor' will bring user to the "New Aop Stressor" page. In the Name field, user can search for stressor by name. Choosing a stressor from the resulting drop down populates the field. Selection of an Evidence level from the drop down menu and add any supporting evidence in the text box. Click 'Add stressor' to add the stressor to the AOP page.

Molecular Initiating Event

Add molecular initiating event

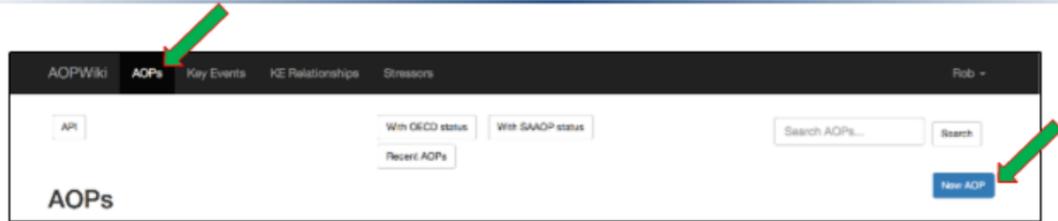
Title	Short name	
Spermatid protamine binding	protamine binding	Edit Remove

Key Events

Add key event

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”.

A screenshot of the 'New AOP' form. It has two input fields: 'Title' and 'Short name'. A red arrow points to the 'Title' field with the text 'Enter Full Title'. Another red arrow points to the 'Short name' field with the text 'Enter Short Title'. There is a 'Create Aop' button at the bottom left and a 'Back' button at the top right.

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

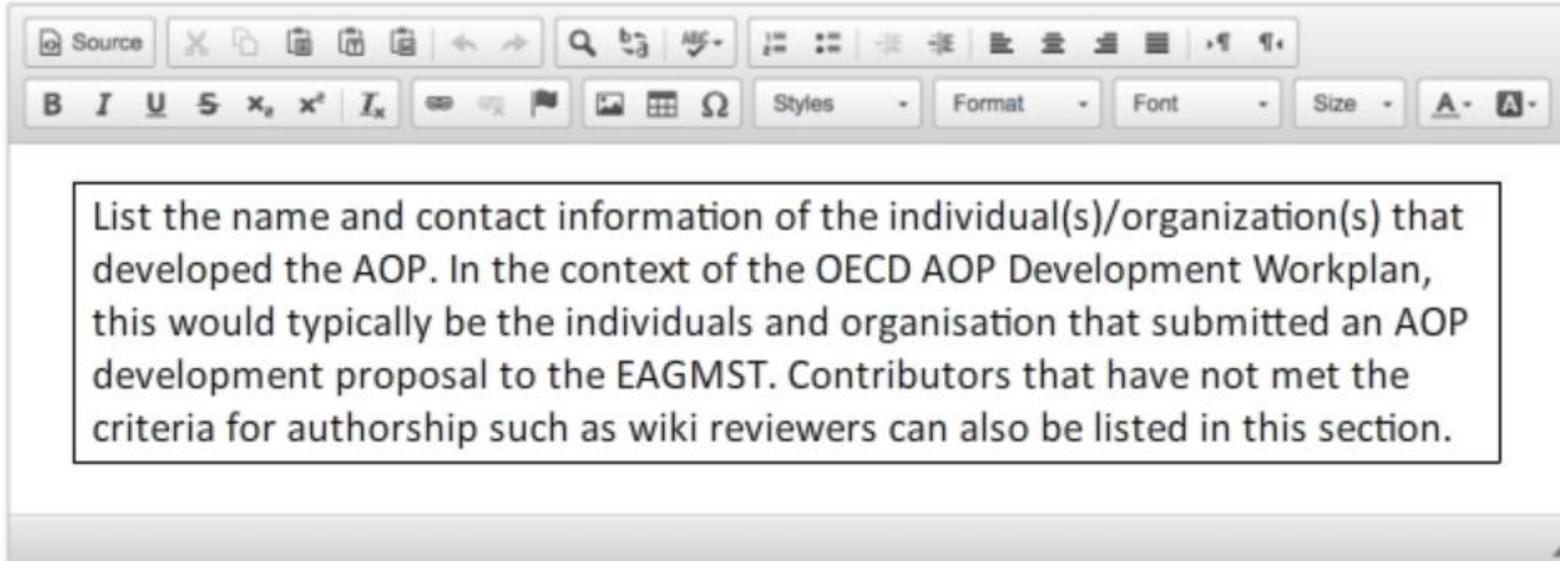
Title should be in form of “MIE leading to AO”

Author information on AOP Wiki

Point of contact 

Indicate the Point of Contact, to whom correspondence should be sent. By default, this is the author who created the AOP.

Authors 



The screenshot shows a rich text editor interface. At the top, there is a toolbar with various icons for text formatting (bold, italic, underline, strikethrough, subscript, superscript, text color, background color), list creation, indentation, and font settings. Below the toolbar is a text area containing the following instruction: "List the name and contact information of the individual(s)/organization(s) that developed the AOP. In the context of the OECD AOP Development Workplan, this would typically be the individuals and organisation that submitted an AOP development proposal to the EAGMST. Contributors that have not met the criteria for authorship such as wiki reviewers can also be listed in this section."

Status 

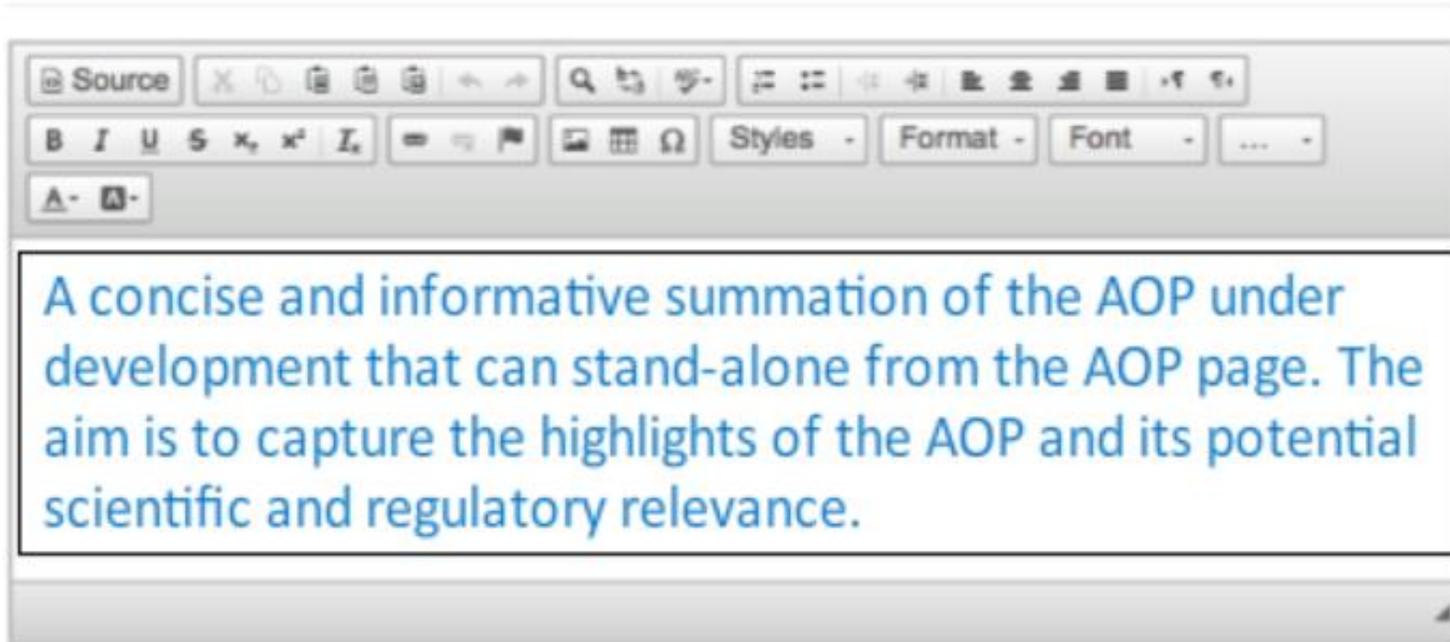
Under development: Not open for comment. Do not cite 

Indicate author status of the AOP. By default, newly created AOPs have the status "Under development: Not open for comment. Do not cite."

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

Entering abstract on AOP Wiki

Abstract 



A concise and informative summation of the AOP under development that can stand-alone from the AOP page. The aim is to capture the highlights of the AOP and its potential scientific and regulatory relevance.

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

Add Event to AOP

Title

Short name

Biological organization

Molecular

Cellular

Tissue

Organ

Individual

Population

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

Add Relationship to AOP

Reuse a relationship

select existing relationship

OR

Create a new relationship

Upstream event

Disruption of sperm chromatin protamination

Downstream event

Embryothality

Directness

directly leads to

DOWNSTREAM EVENT

Disruption of sperm chromatin protamination

Directness

✓ directly leads to
indirectly leads to

Evidence

✓
Strong
Moderate
Weak
Not Specified

Evidence

Quantitative understanding

✓
Strong
Moderate
Weak
Not Specified

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

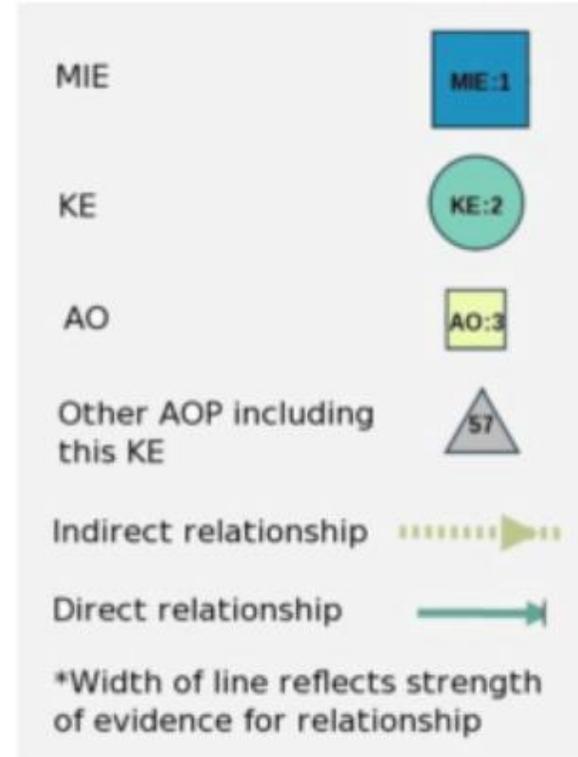
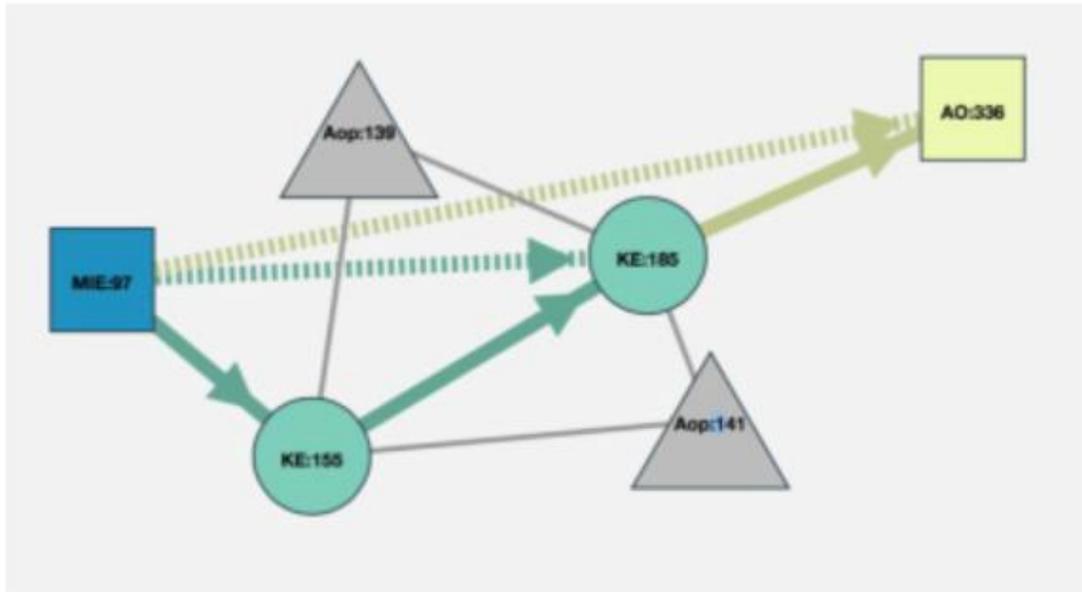
1. Support for Biological Plausibility of KERS ¹

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.

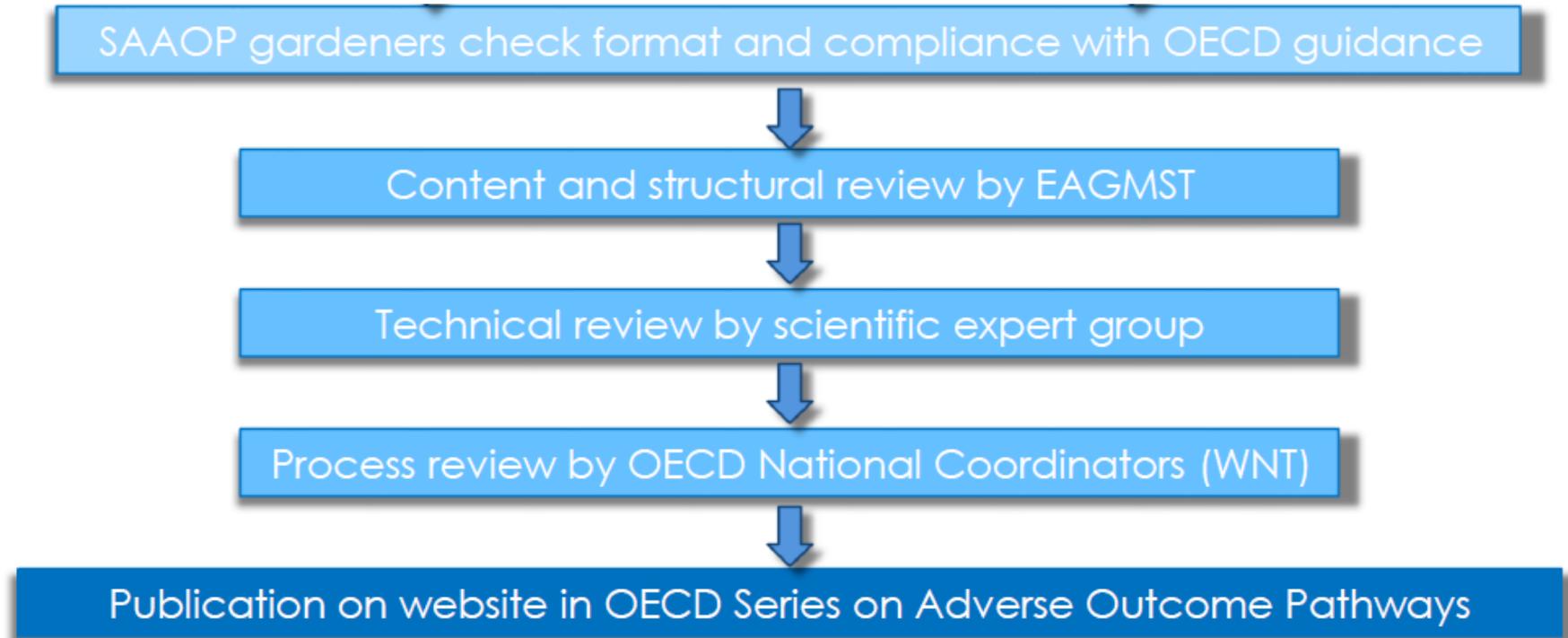
Network view

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



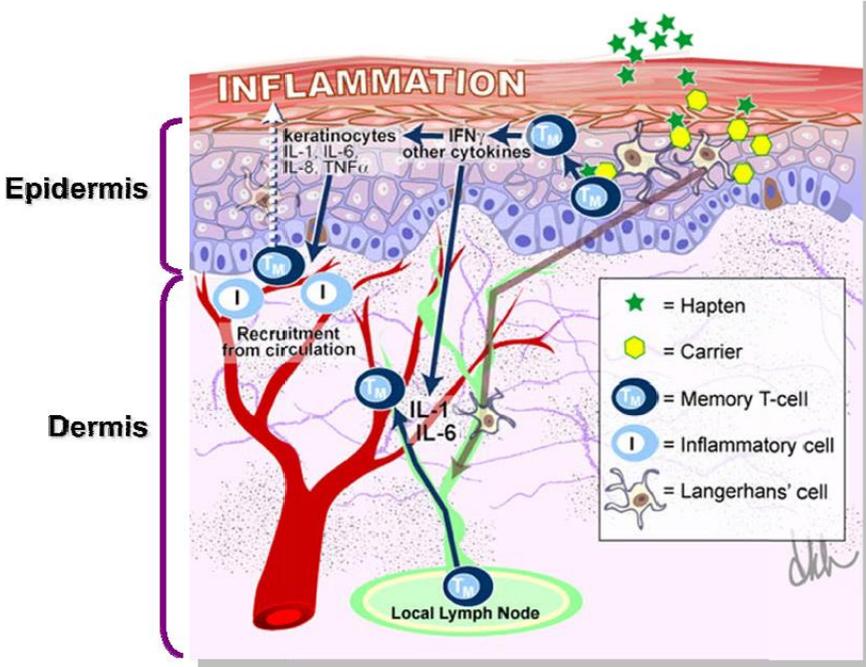
AOP on skin sensitisation

Mechanism of skin sensitisation

Skin sensitisation

Phase I: Induction

Phase II: Elicitation



AOP of skin sensitisation

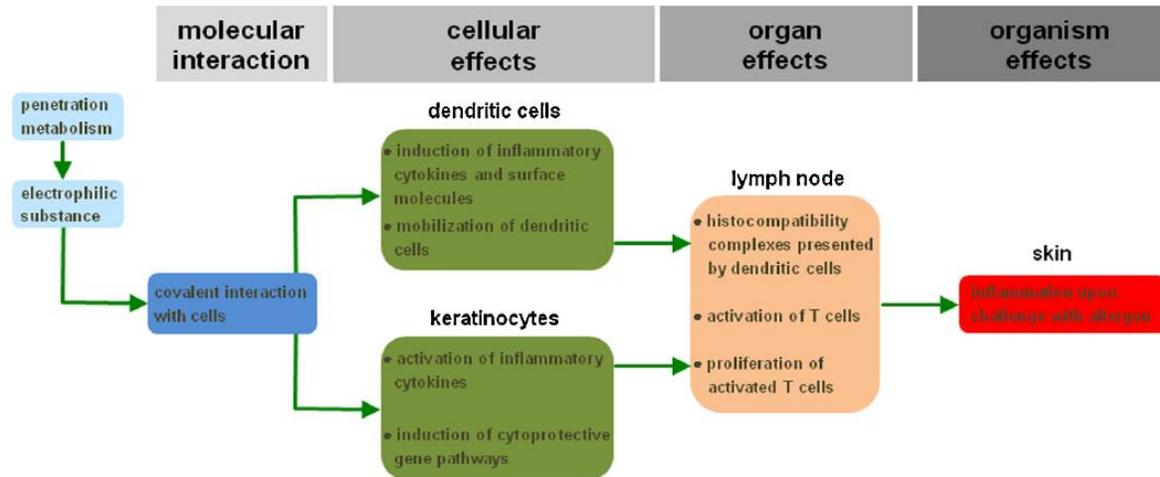


Table 3. Defined Approach (DA) performance in predicting human hazard (sensitizer/non-sensitizer).

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
<i>N</i>	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/KeratinoSensTM; D_hC: DPRA/h-CLAT.

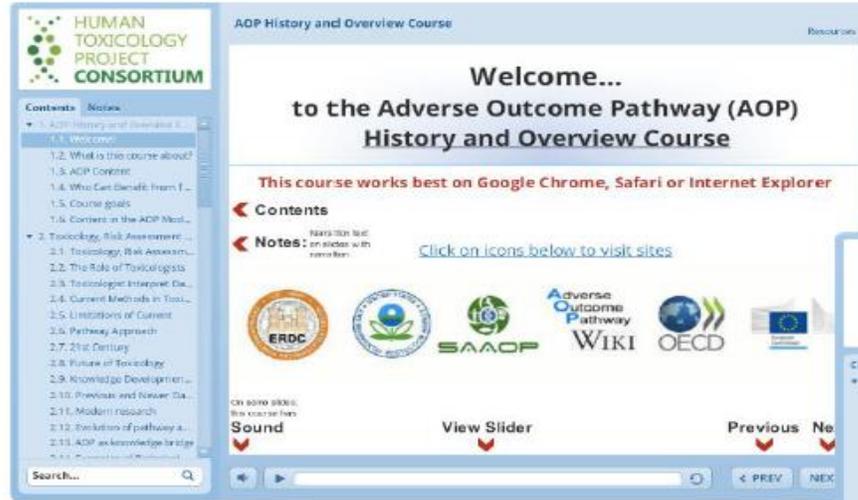
The AOP framework is:

- 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!**

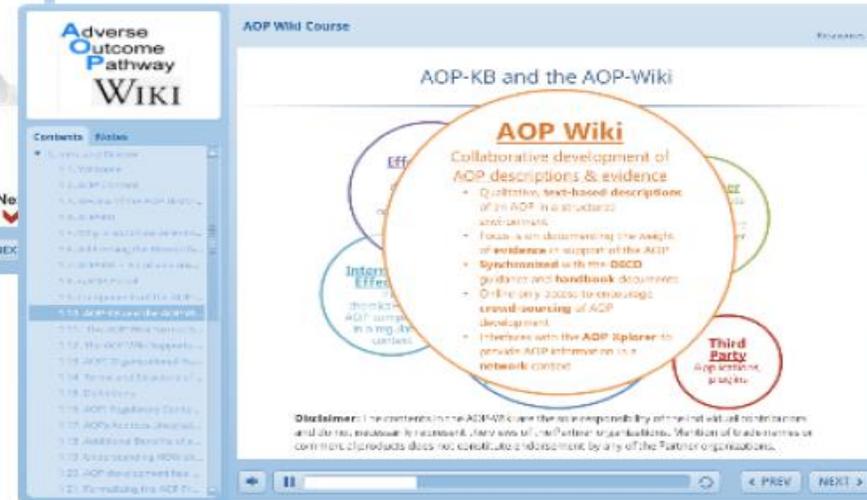
AOP Online Training Course



The screenshot shows the 'AOP History and Overview Course' welcome page. At the top left is the 'HUMAN TOXICOLOGY PROJECT CONSORTIUM' logo. The main heading reads 'Welcome... to the Adverse Outcome Pathway (AOP) History and Overview Course'. Below this, it states 'This course works best on Google Chrome, Safari or Internet Explorer'. There are sections for 'Contents' and 'Notes'. A navigation bar at the bottom includes 'View Slider', 'Previous', and 'Next' buttons. Logos for ERDC, SAACOP, AOP Wiki, and OECD are visible.

Three module course:

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



The screenshot shows the 'AOP Wiki Course' page. The main heading is 'AOP-KB and the AOP-Wiki'. The central focus is 'AOP Wiki', described as 'Collaborative development of AOP descriptions & evidence'. It lists key features: 'Qualitative, text-based descriptions of an AOP in a structured web-format', 'Focus on documenting the weight of evidence in support of the AOP', 'Synchronized with the OECD guidance and handbook documents', 'Online only access to encourage crowd-sourcing of AOP development', and 'Interviews with the AOP Explorer to provide AOP information in a network context'. A 'Third Party' logo is also present. A disclaimer at the bottom states: 'Disclaimer: The contents of the AOP-Wiki are the sole responsibility of the individual contributors and do not, without the consent, share any of the authors' organizations. Mention of trademarks or commercial products does not constitute endorsement by any of the Partner organizations.'

Download:

<https://humantoxicologyproject.org/about-pathways-2/aop-online-course/>

Run:

<https://aopwiki.org/>

Call for proposals

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!

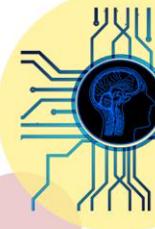
Application Deadline: 31 March 2020

Contact:

Dr Surat Parvatam (surat.parvatam@cmb.res.in)

Dr Brinda Poojary (bpoojary@hsi.org)

Science funding opportunity



HUMANE SOCIETY
INTERNATIONAL
INDIA

BIOMED²¹
COLLABORATION
Toward a human-focused paradigm in health research



Centre for
Predictive Human
Model Systems