

## **AOP Hands-on Training: Building the Foundation for Predictive Toxicology**

**Wednesday, March 13, 4:30 PM–6:30 PM**

Hilton Baltimore, Paca Room  
401 West Pratt St, Baltimore, MD 21201

### **Agenda:**

- 4:30 – 5:00:      **Introduction and overview of the OECD AOP framework**  
Catherine Willett, HTPC/Humane Society International
- 5:00 – 5:30:      **Approaches and tools for AOP assembly and an example of a Bayesian network approach to predicting steatosis**  
Natalia Reyero, Environmental Laboratory, Engineer Research & Development Center, US Army Corps of Engineers
- 5:30 – 5:40      **Application of the AOP framework to make regulatory decisions: Early case studies**  
Kristie Sullivan, PCRM
- 5:40 – 6:30**      **AOP Wiki demonstration and hands-on activity**
- Finding AOPs and AOP info in the Wiki
  - Entering information into the Wiki
  - Adding a diagram
- Kristie Sullivan, PCRM with support from Catherine and Natalia

# Introduction to AOPs and the OECD AOP Framework

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**THE HUMANE SOCIETY**  
OF THE UNITED STATES



**HUMANE SOCIETY**  
INTERNATIONAL



**HUMAN  
TOXICOLOGY  
PROJECT**

# Outline

## Part I: introduction to AOPs

- AOPs as the basis for predictive toxicology
- Introduction to the AOP concept
- essential elements of AOPs
- Brief on building AOPs

## Part II: the OECD AOP Framework

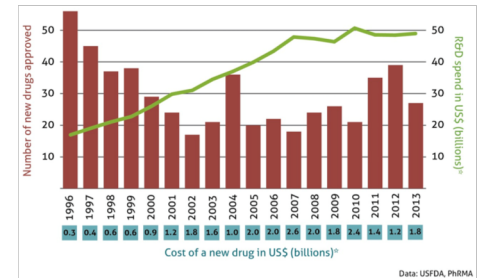
- The AOP Knowledgebase
- The OECD AOP development and evaluation process
- Available guidance, tutorials and classes

# Part I: Introduction to AOPs



# Need for predictive toxicology

- Growing need for more information on tens of thousands of chemicals
- Need for improved drug success rates and lower cost to market
- Need for faster, more relevant approaches across sectors



To increase efficiency and improve safety decisions:

- move from a system of empirically measured adverse outcomes to a predictive system based on measurement of upstream biological events coupled with an explicit biological linkage to potential adverse effects

# Need for better use of information

## Too much data!

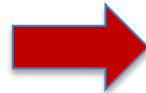
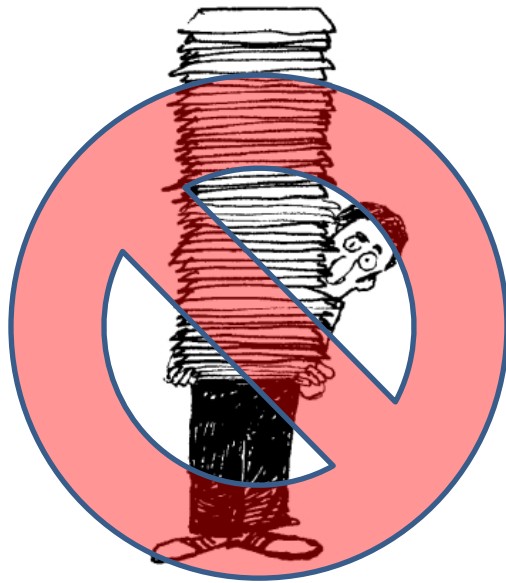
- Decades of research and testing data
- Global scientific output doubles every 9 years

## The data is largely inaccessible

- Journal articles, reports, laboratory notebooks, agency archives
- Institutional and government databases



# Issue: too much data in non-accessible formats



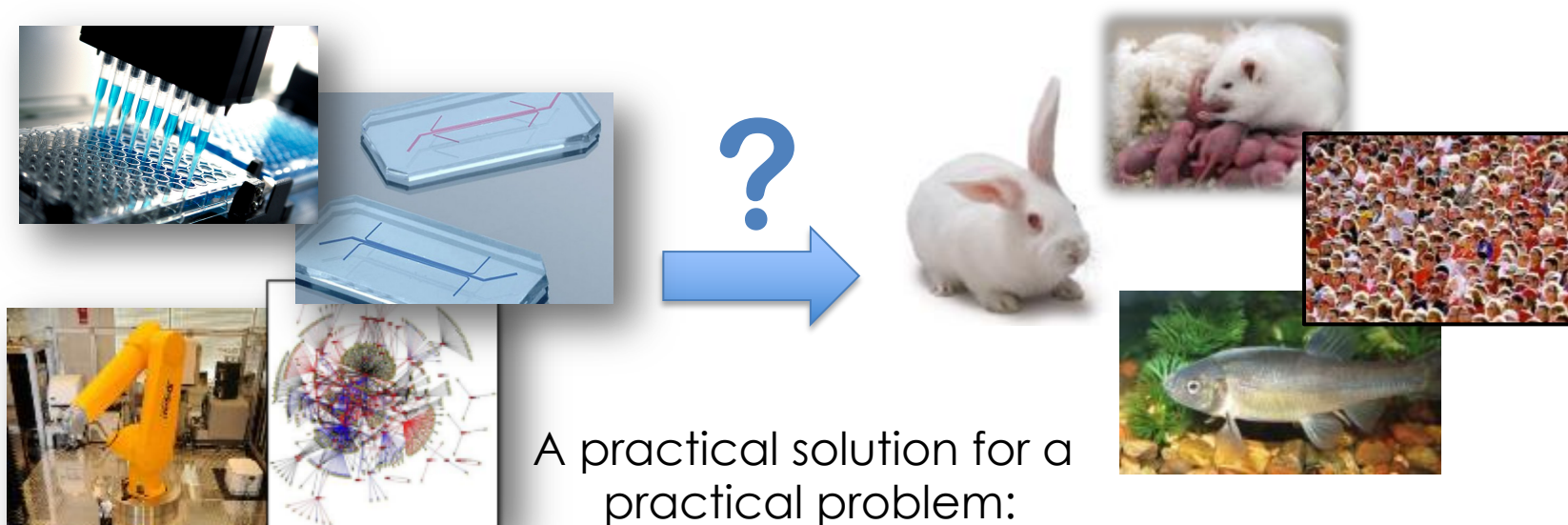
- Collaboration
- Model building
- Avoids duplication

- PDFs
- Fragmented
- Siloed
- Proprietary
- Searchable
- Machine-readable
- Linked

(adapted from D. Villeneuve)

# The Adverse Outcome Pathway framework is the basis of predictive toxicology

AOPs: linking molecular initiation to adverse outcomes

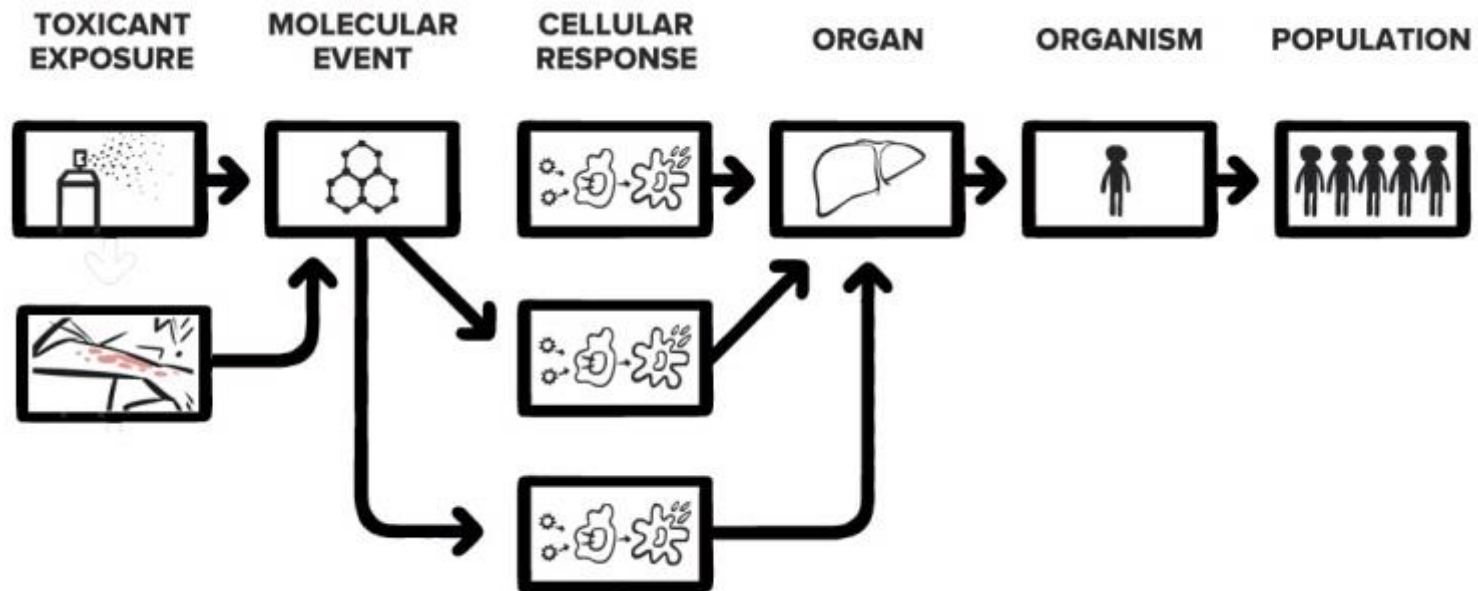


A practical solution for a practical problem:

- How to use molecular understanding to make better decisions about chemical safety

# Adverse Outcome Pathway framework: linking molecular initiation to adverse outcomes

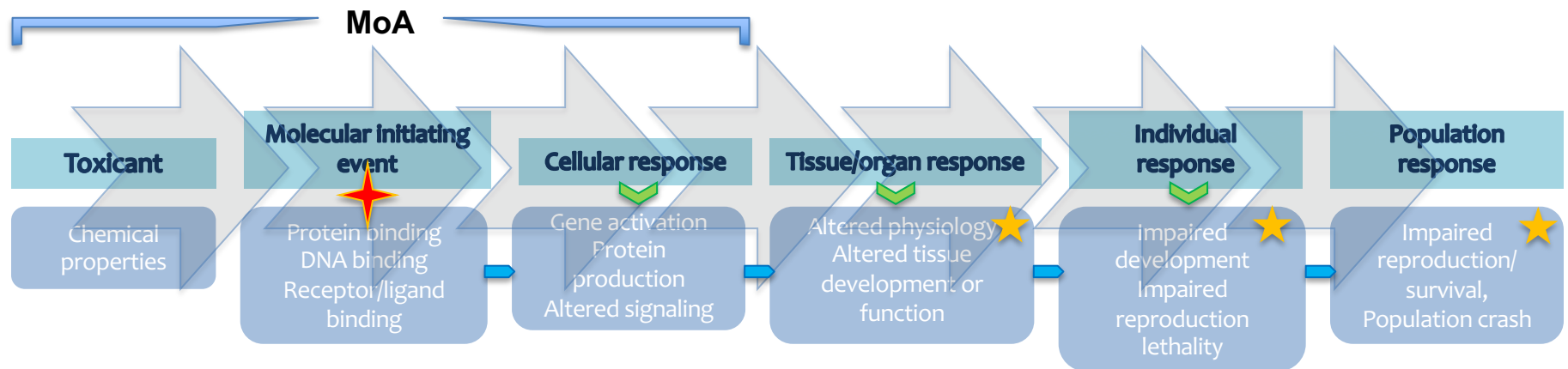
AOPs: linking molecular initiation to adverse outcomes





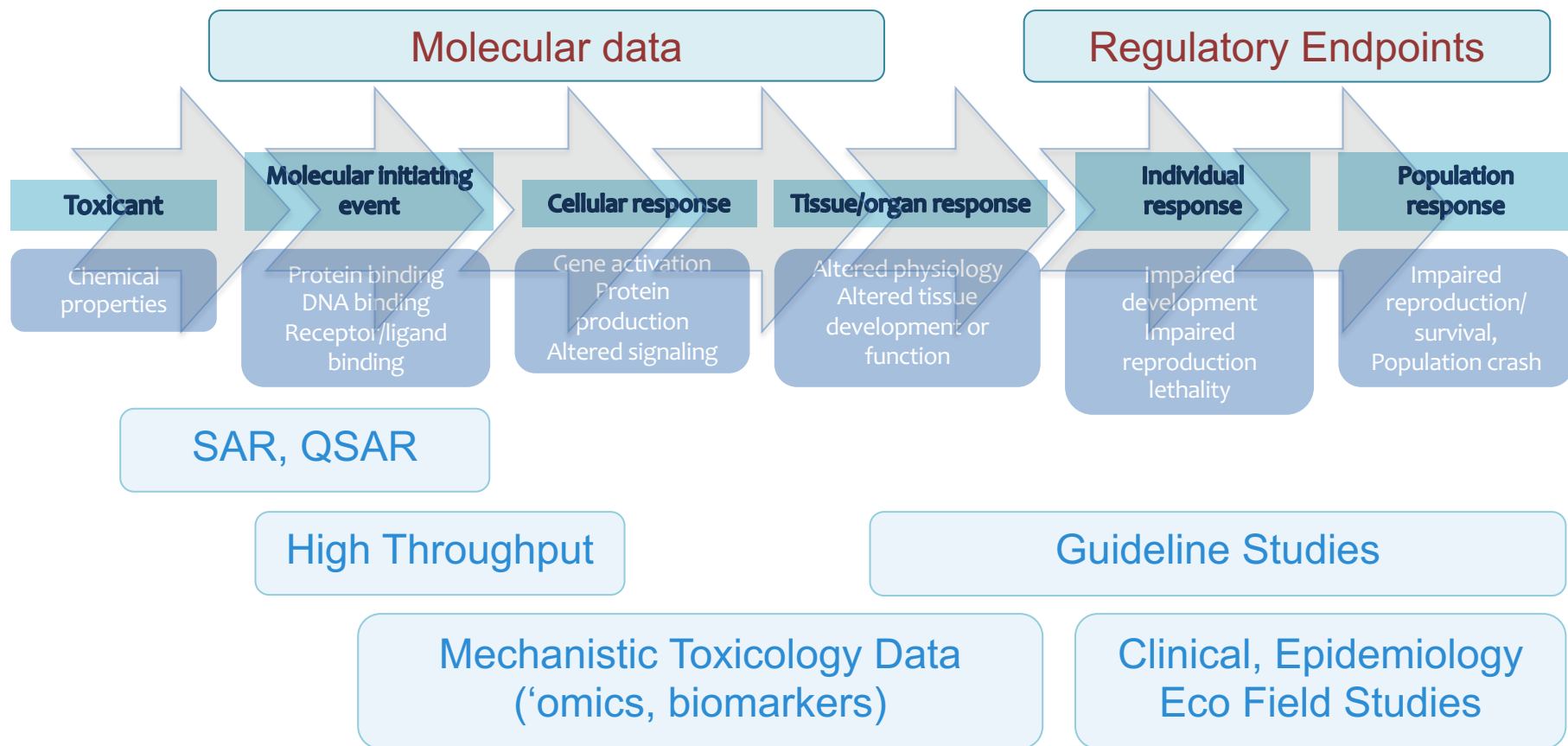
# Adverse Outcome Pathway framework: linking molecular initiation to adverse outcomes

- AOPs: Linking molecular information to adverse outcomes

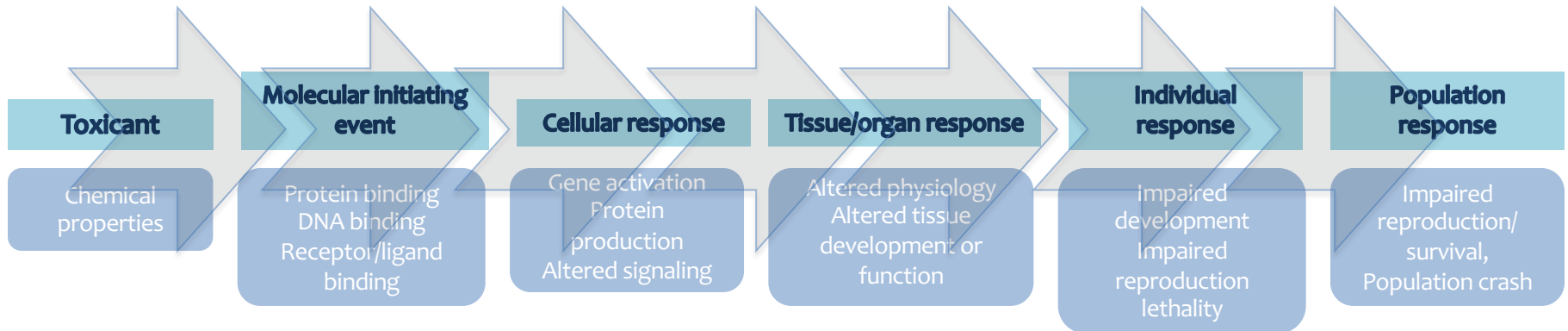


- beginning with initial interactions of a stressor with a biomolecule in a target cell or tissue (the **molecular initiating event - MIE**)
- progressing through a dependent series of intermediate events (**key events - KE**)
- Linked together through Key Event Relationships (**KER**)
- culminating with an adverse outcome (**AO**)

AOPs provide a framework for organizing, relating and evaluating biological data



# Essential elements of an AOP



- Key Events (KEs)

- Change in biological or physiological state
- Measurable and essential for progression

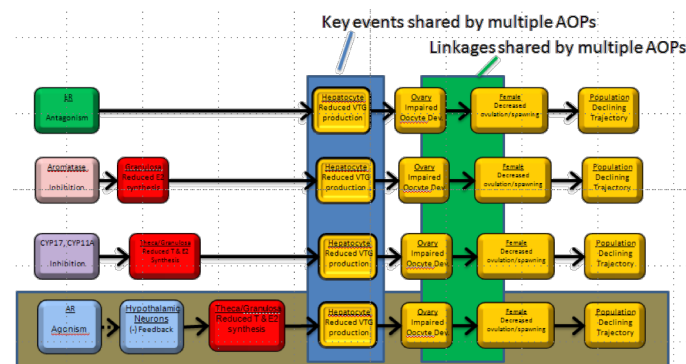
- Molecular Initiating Event (MIE): specialized KE that represents the initial point of stressor interaction with the organism

- Adverse Outcome (AO): specialized KE of regulatory significance

- Key Event Relationships (KERs)

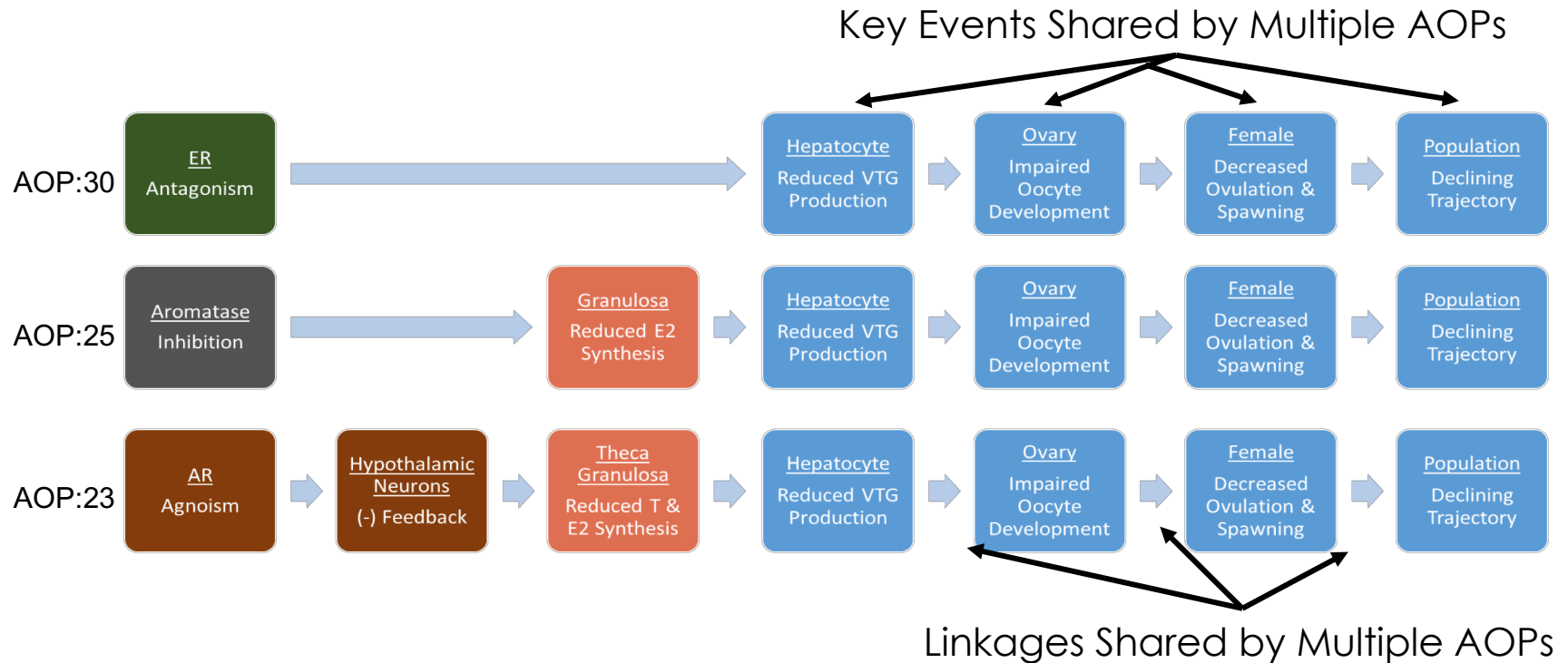
- Connection between two key events
- Critical for assembling evidence in support of the AO
- Facilitates inference or extrapolation

# Fundamental principles of AOP development



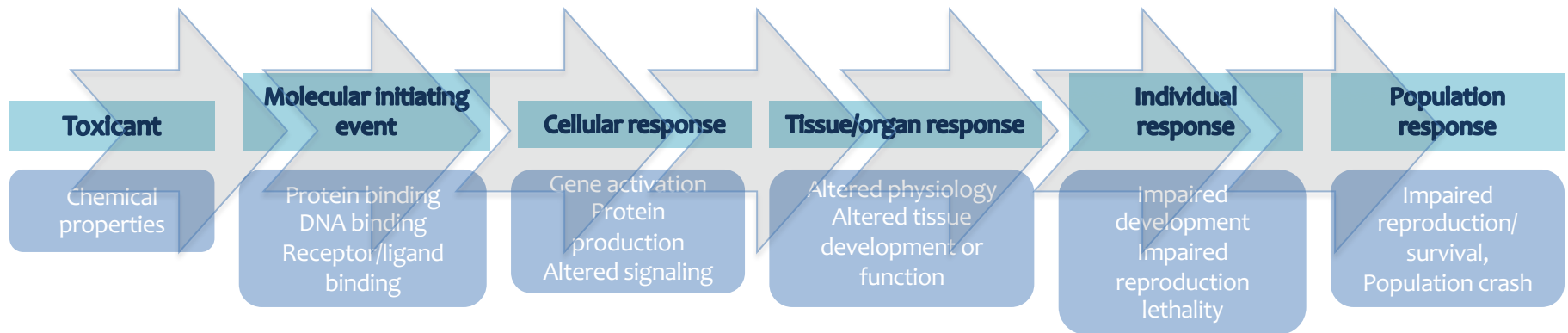
1. AOPs are not chemical specific
2. AOPs are modular
  - Key events and relationships can be shared by multiple AOPs
3. As a pragmatic construct, an individual AOP is composed of a single sequence of KEs and KERs leading to a single AO
4. AOP networks will emerge and are the basis for prediction
5. AOPs are living documents
  - AOP descriptions can be expected to evolve over time

# Networks emerge as KE and KER are shared





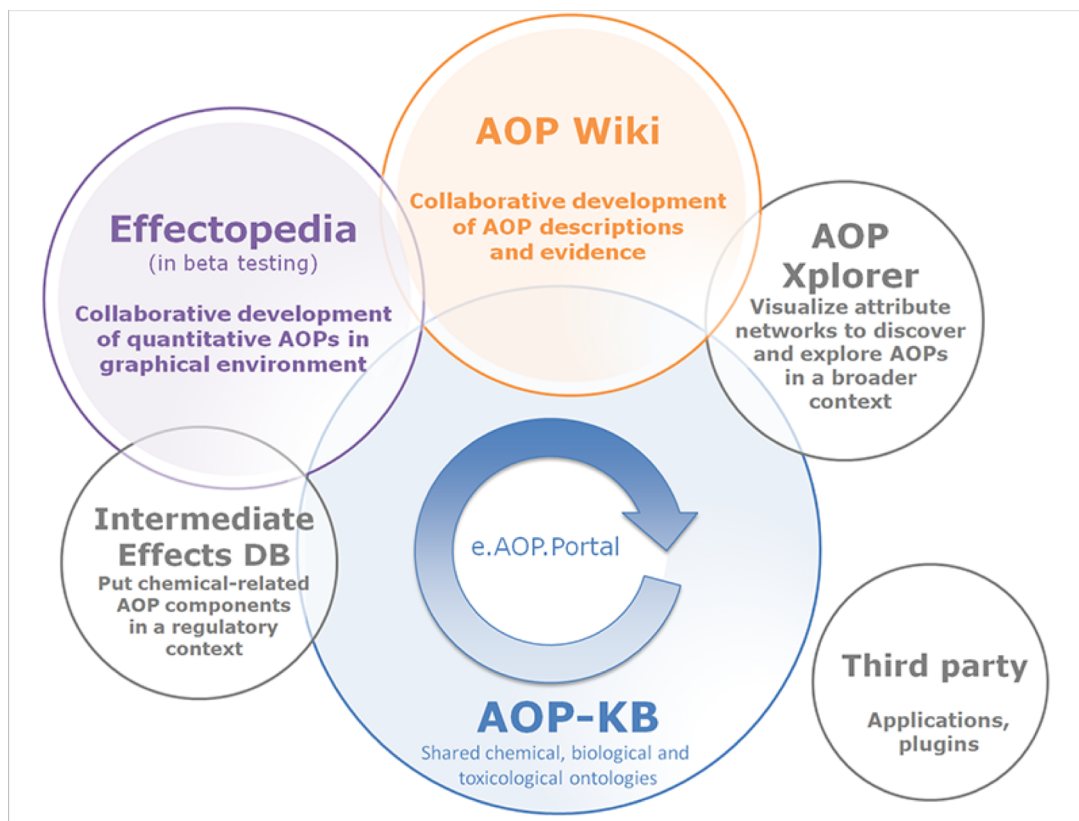
# Building an AOP



- Start anywhere
  - but one AOP = one MIE leading to one AO as a pragmatic unit
- Gather all existing knowledge
  - Not every detail, but critical steps or check-points
  - Collaboration is encouraged
- Evaluate and document the information
  - Refer to extensive OECD guidance
- Translate and capture information as a pathway in the AOP Wiki
- When you are ready, and if you so desire, you can then enter the OECD evaluation process

## Part II: the OECD AOP framework

# OECD AOP Knowledgebase (AOP-KB): an international partnership

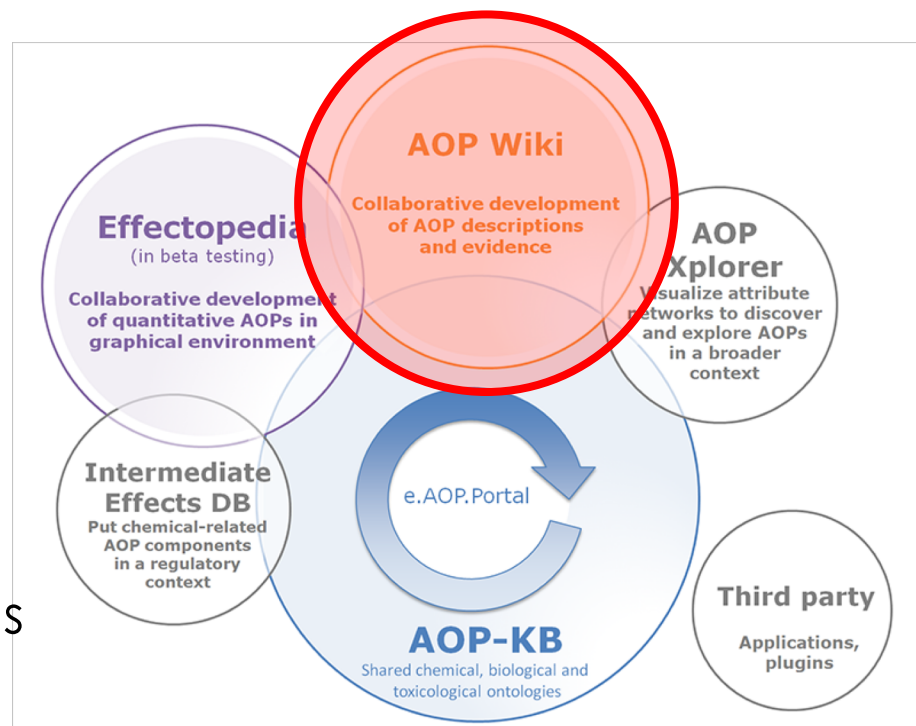


**S.A.O.P.**

<https://aopkb.oecd.org>

# AOP Wiki: information storage, linkage and evaluation

- Captures and organizes all information and supporting documentation for AOP elements
- Supported by extensive guidance, tutorials and an online course
- Is designed to enable rigorous evaluation and scientific review
- Publically available since 2014



[www.aopwiki.org](http://www.aopwiki.org)

# AOP Wiki home page

[AOPWiki](#) [AOPs](#) [Key Events](#) [KE Relationships](#) [Stressors](#)

Kate ▾

AOP News

## Home

### Announcements

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#### Greetings

**Happy Holidays from the AOP-Wiki team**

### AOP Welcome

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Welcome to the Collaborative Adverse Outcome Pathway Wiki (AOP-Wiki)



#### Contents

1. [Announcements](#)
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  5. [New version of AOP Developer's Handbook released](#)
4. [Wiki 2.0 Upgrade](#)
  1. [User Account Migration](#)
  2. [Confirm AOP Information Following Migration](#)
  3. [Notable Changes for Authors](#)



# List of AOPs

API

With OECD status

With SAAOP status

Search AOPs...

Search

Recent AOPs

Find by ID

Find by ID

## AOPs



Id ▲	Title	Point of Contact	Author Status	SAAOP Status	MIE	AO	OECD Status	OECD Project
3	Inhibition of the mitochondrial complex I of nigro-striatal neurons leads to parkinsonian motor deficits	Andrea Terron	Open for citation & comment	Included in OECD Work Plan	NADH-ubiquinone oxidoreductase (complex I), Binding of inhibitor	Motor function, impaired	EAGMST Approved	1.33
4	Ecdysone receptor agonism leading to mortality	Knut Erik Tollefsen	Open for citation & comment	Under Development	EcR	mortality		
6	Antagonist binding to PPARα leading to body-weight loss	Kurt A. Gust	Open for comment. Do not cite	Included in OECD Work Plan	PPAR	starvation-like body-weight loss	EAGMST Under Review	2.3
7	Aromatase (Cyp19a1) reduction leading to impaired fertility in adult female	Elise Grignard	Open for citation & comment	Included in OECD Work Plan	PPAR	impaired fertility	EAGMST Under Review	1.21
8	...	...	...	...	...	...	...	...

# OECD AOP Development Program

## AOP Wiki Access: three levels

Read access

- Open to anyone, no account required

Commenting

- Create account, no approvals required

Author/write access

- Create account
- Submit brief developer application for approval
- <http://www.saaop.org/AccessPage.html>.

Gardener  
(experienced AOP  
developers/ wiki users)

- Help ensure consistency with published principles and OECD guidelines

[https://aopwiki.org/wiki/index.php/Main\\_Page](https://aopwiki.org/wiki/index.php/Main_Page)

# OECD AOP Development Programme

## Extended Advisory Group for Molecular Screening & Toxicogenomics (EAGMST)

- Guidance, users Handbook
- Review
- Training

## Working Party on Hazard Assessment (WPHA)

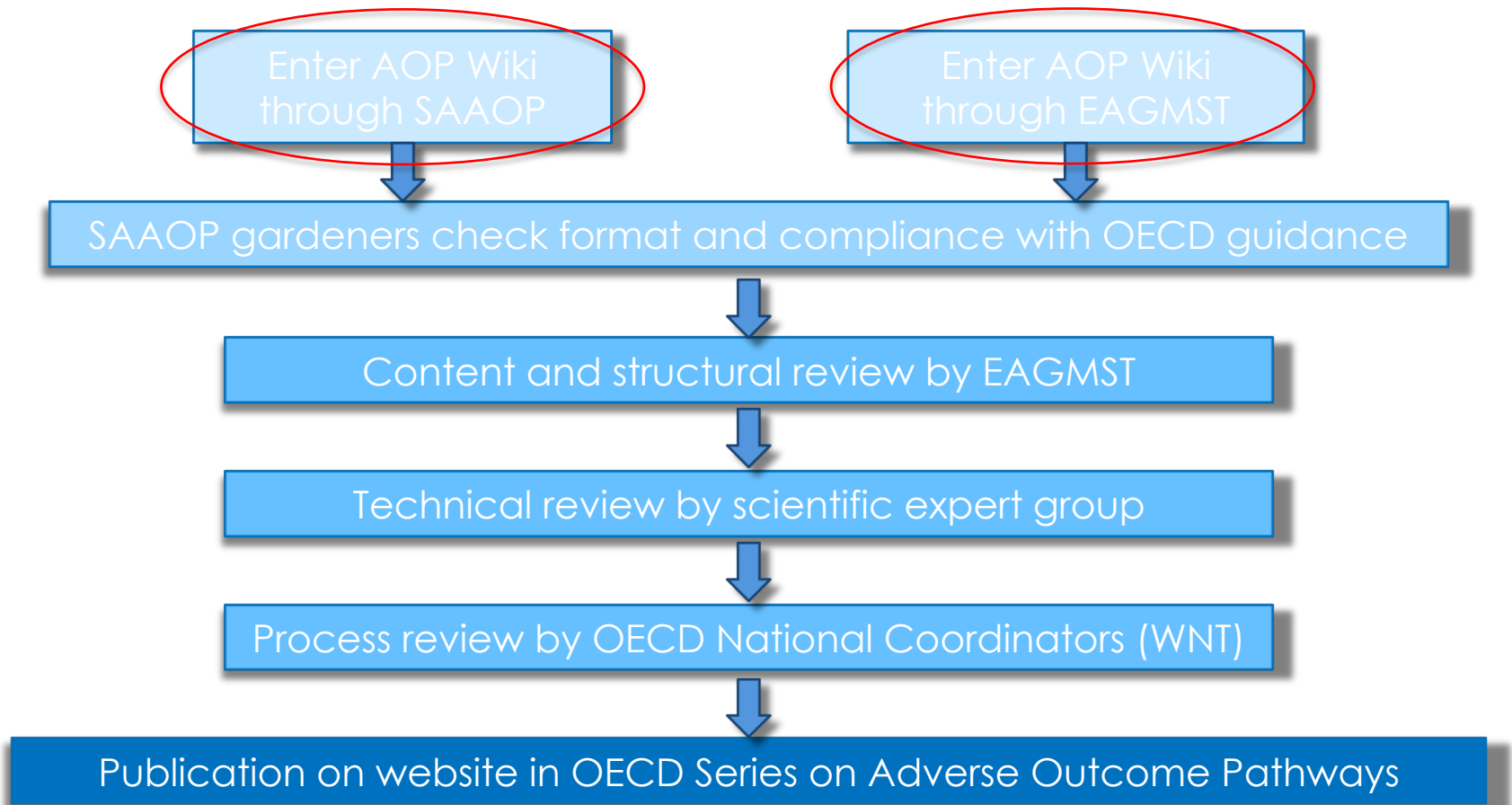
- Guidance for use of AOPs in regulatory decision making
- Integrated Approaches to Testing and Assessment (IATA)

## Society for the Advancement of AOPS



- Not officially part of the OECD program
- Any person active in developing an AOP in the wiki can join
- Is another way to enter the AOP wiki
- Provides “gardening” and other support functions
- [www.saaop.org](http://www.saaop.org)

# Work Process for Development and Review of AOPs through OECD



Explained in Wittwehr, C. (2018) **Use and acceptance of AOPs for regulatory applications**. In Garcia-Reyero & Murphy, A Systems Biology Approach to Advancing Adverse Outcome Pathways for Risk Assessment (pp. 379-390), Springer.

# List of AOPs

AOPWiki **AOPs** Key Events KE Relationships Stressors

Kate ▾

API

With OECD status

With SAAOP status

Recent AOPs

Search AOPs...

Search

Find by ID

Find by ID

## AOPs



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Help

About

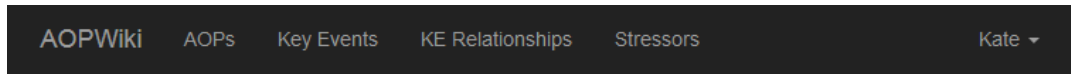
FAQ

Downloads

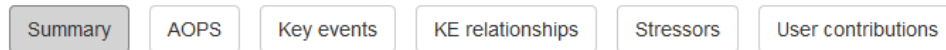
Metrics



# The current state of the Wiki



## Available Reports

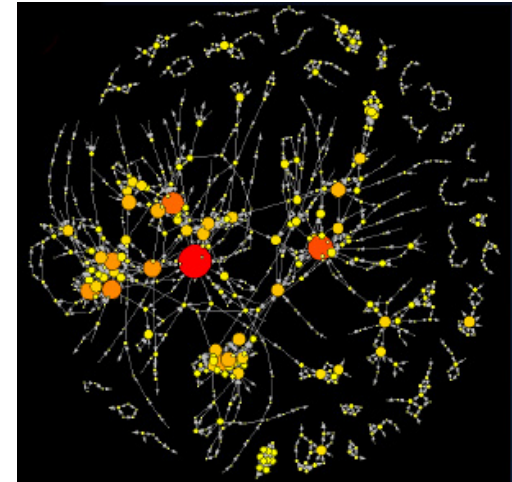


### Reports Summary

Report	Count
AOPs	243
Key events	1185
KE relationships	1479
Stressors	413

OECD endorsed and published 7  
EAGMST approved 9  
Under EAGMST review 14

★ Participants needed! ★



June 2017 D. Villeneuve

Most common endpoints addressed:

- Ecotoxicology
- Reproductive toxicity
- Neurotoxicity
- carcinogenicity
- endocrine



Guidance, tutorials, courses

# OECD Guidance for developing and assessing AOPs

- OECD User's Handbook Supplement to the Guidance Document for Developing and Assessing AOPs (2017)
  - Series on Testing & Assessment No. 233
  - Series on Adverse Outcome Pathways No. 1
  - [https://one.oecd.org/document/ENV/JM/MONO\(2016\)12/en/pdf](https://one.oecd.org/document/ENV/JM/MONO(2016)12/en/pdf)
- Guidance Document for Developing and Assessing AOPs (2017)
  - Series on Testing & Assessment No. 233
- OECD Guidance Document for the use of adverse outcome pathways in developing integrated approaches to testing and assessment (IATA), Series on Testing and assessment no. 260 (OECD 2016)
  - [http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV/JM/MONO\(2016\)67/&doclanguage=en](http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV/JM/MONO(2016)67/&doclanguage=en)
- OECD website on the AOP program:
  - <http://www.oecd.org/chemicalsafety/testing/adverse-outcome-pathways-molecular-screening-and-toxicogenomics.htm>
- OECD's website on IATA
  - <http://www.oecd.org/chemicalsafety/risk-assessment/iata-integrated-approaches-to-testing-and-assessment.htm>
- The AOP Wiki: <http://aopwiki.org/>

# AOP training videos and tutorials

**SETAC 2015 CE Course:** Developing and Applying Adverse Outcome Pathways What You Need to Know

Part 1: <http://setac.sclivelearningcenter.com/index.aspx?PID=9484&SID=215605>

Part 2: <http://setac.sclivelearningcenter.com/index.aspx?PID=9484&SID=215606>

**SOT CE Course “AOP Development and Evaluation”:**

<http://www.toxicology.org/education/ce/onlineCourses.asp>

subscription required

**Society for the Advancement of Adverse Outcome Pathways Training videos:**

[http://www.saaop.org/workshops/AOPs\\_Wiki\\_July2017.html](http://www.saaop.org/workshops/AOPs_Wiki_July2017.html)

**Other training resources:\***

AOP Learning: <https://training.effectopedia.org/>

Building AOP Structure and Description

<https://training.effectopedia.org/course/view.php?id=10#section-1>

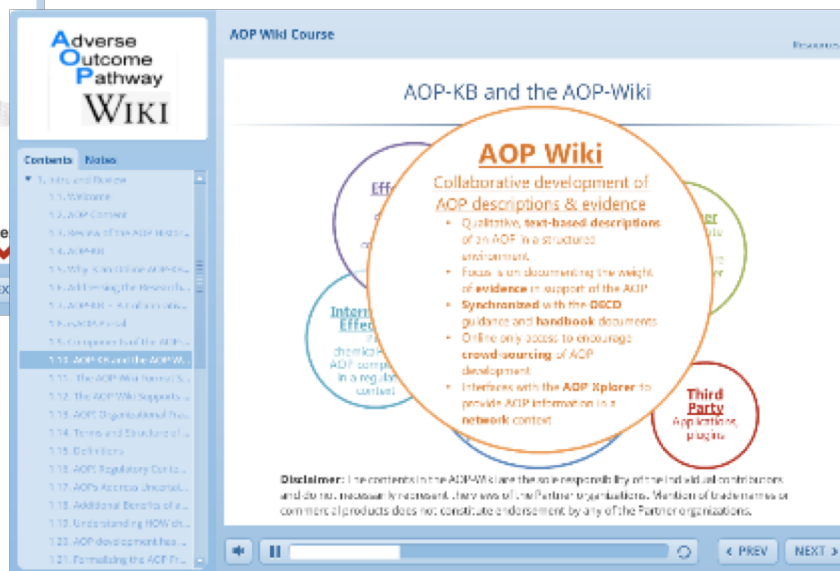
\*This course does not mention Effectopedia: this software package will be merged with the AOP Wiki in the next version of the AOP KB currently under design

# 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/>

# Summary

## 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 regulatory decisions regarding chemical safety
- A Transparent, highly curated, living document representing current knowledge
- The basis for predictive toxicology



# The AOP'' framework

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



**The AOP Framework  
Needs YOU!**

Thank you!

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