HUMAN TOXICOLOGY PROJECT

ASCCT
American Society for Cellular and Computational Toxicology

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

Tuesday,July 16, 4:30 PM–6:30 PM

Hilton Hawaiian Village
Waikiki Beach Resort Hibiscus 1 and 2

4:30 – 5:00: **Introduction and overview of the OECD AOP framework**
Catherine Willett, HTPC/Humane Society International

5:00 – 5:30: **Building AOPs for Neurotoxicity: Perspective from an Academic**
Prof. Dr. Ellen Fritsche, Leibniz Research Institute for Environmental Medicine

5:30 – 5:40 **Application of the AOP framework to make regulatory decisions: Early case studies**
Kristie Sullivan, PCRM

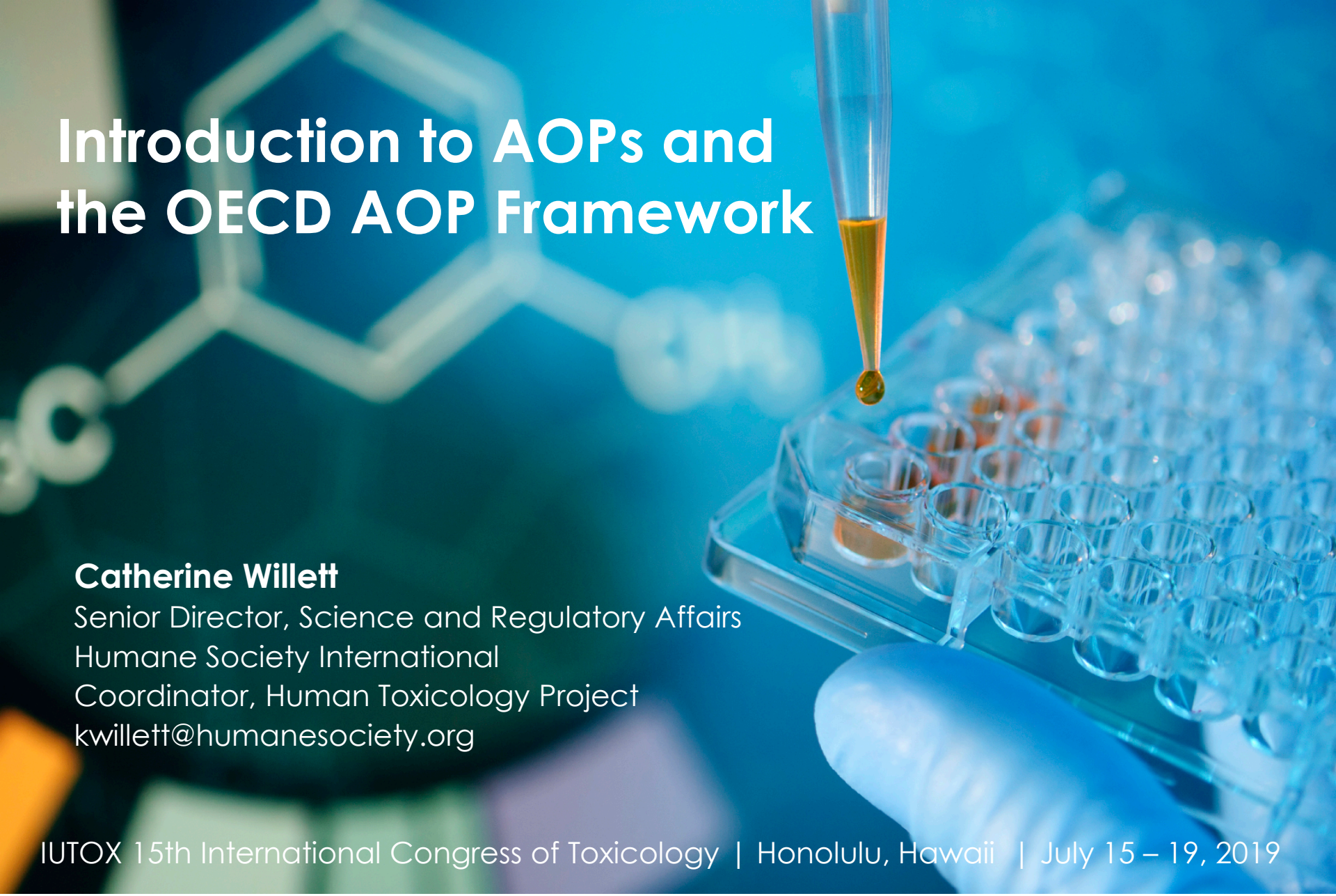
5:40 – 6:30 **AOP Wiki demonstration and hands-on activity**

- Finding AOPs and AOP info in the Wiki
- Entering information into the Wiki
- Adding a diagram

Kristie Sullivan, PCRM with support from Catherine and Ellen

WiFi: **Password:**

Introduction to AOPs and the OECD AOP Framework



Catherine Willett
Senior Director, Science and Regulatory Affairs
Humane Society International
Coordinator, Human Toxicology Project
kwillett@humanesociety.org

IUTOX 15th International Congress of Toxicology | Honolulu, Hawaii | July 15 – 19, 2019

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

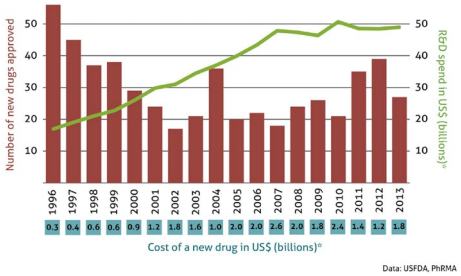
Part II: the OECD AOP Framework

- 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

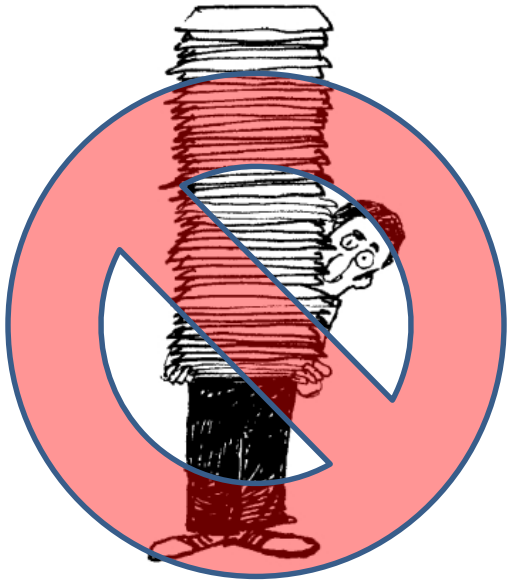
Too much data!

- 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



- PDFs
- Fragmented
- Siloed
- Proprietary

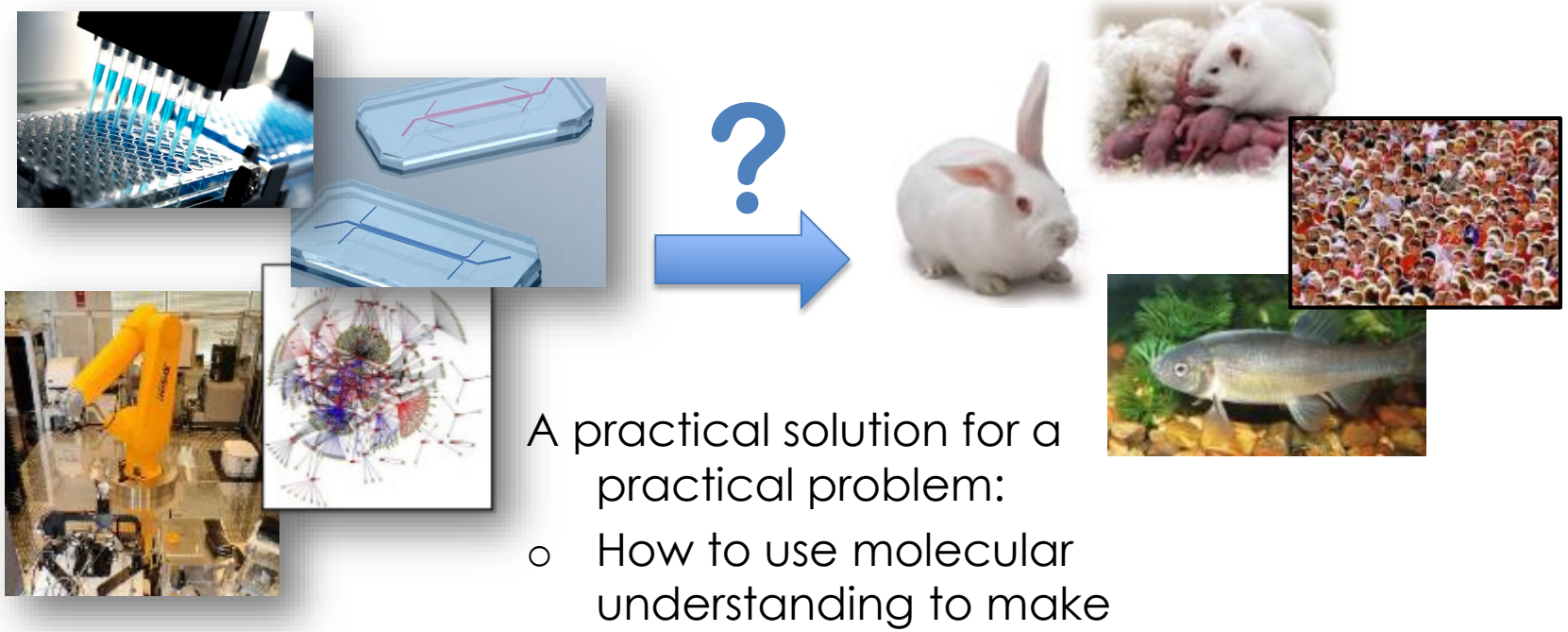
- Searchable
- Machine-readable
- Linked

- Collaboration
- Model building
- Avoids duplication

(adapted from D. Villeneuve)

The Adverse Outcome Pathway framework is the basis of predictive toxicology

AOPs: linking molecular initiation to adverse outcomes

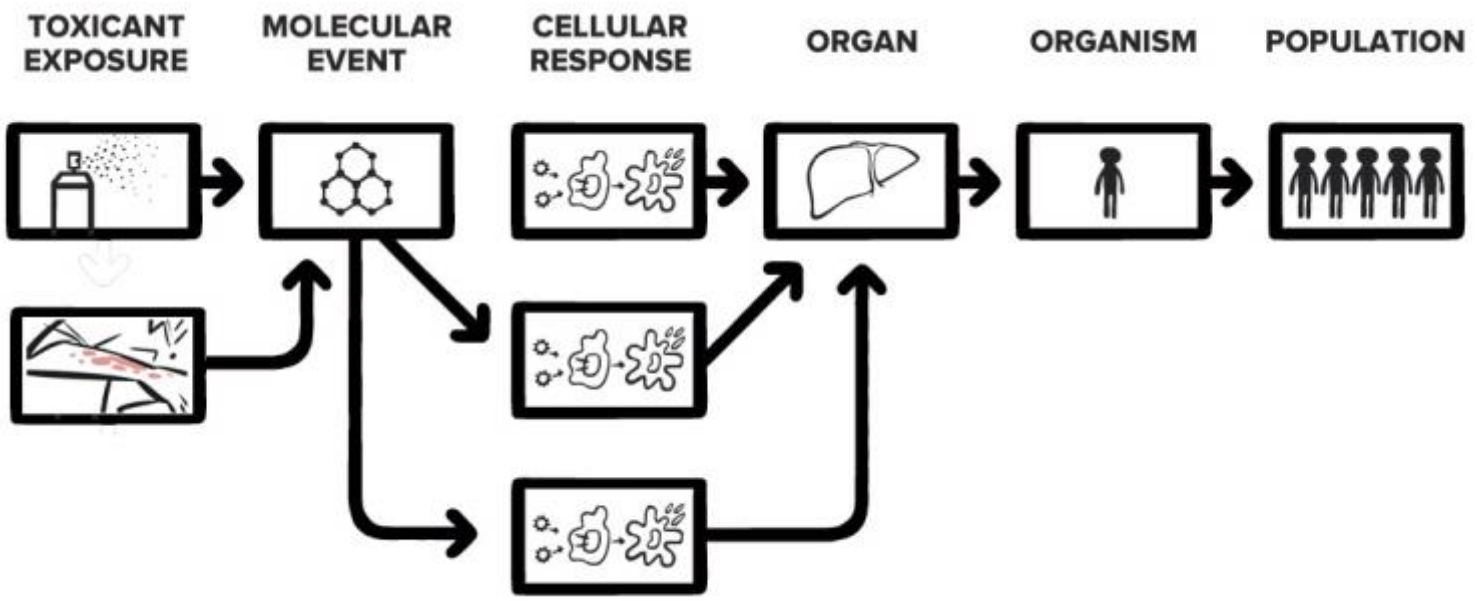


A practical solution for a practical problem:

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

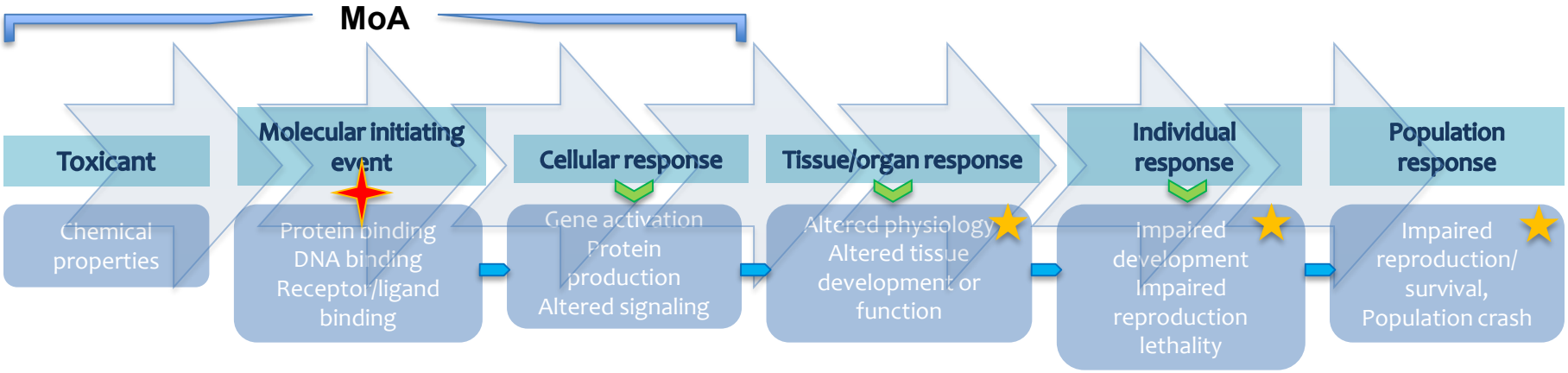
Adverse Outcome Pathway framework: linking molecular initiation to adverse outcomes

AOPs: linking molecular initiation to adverse outcomes



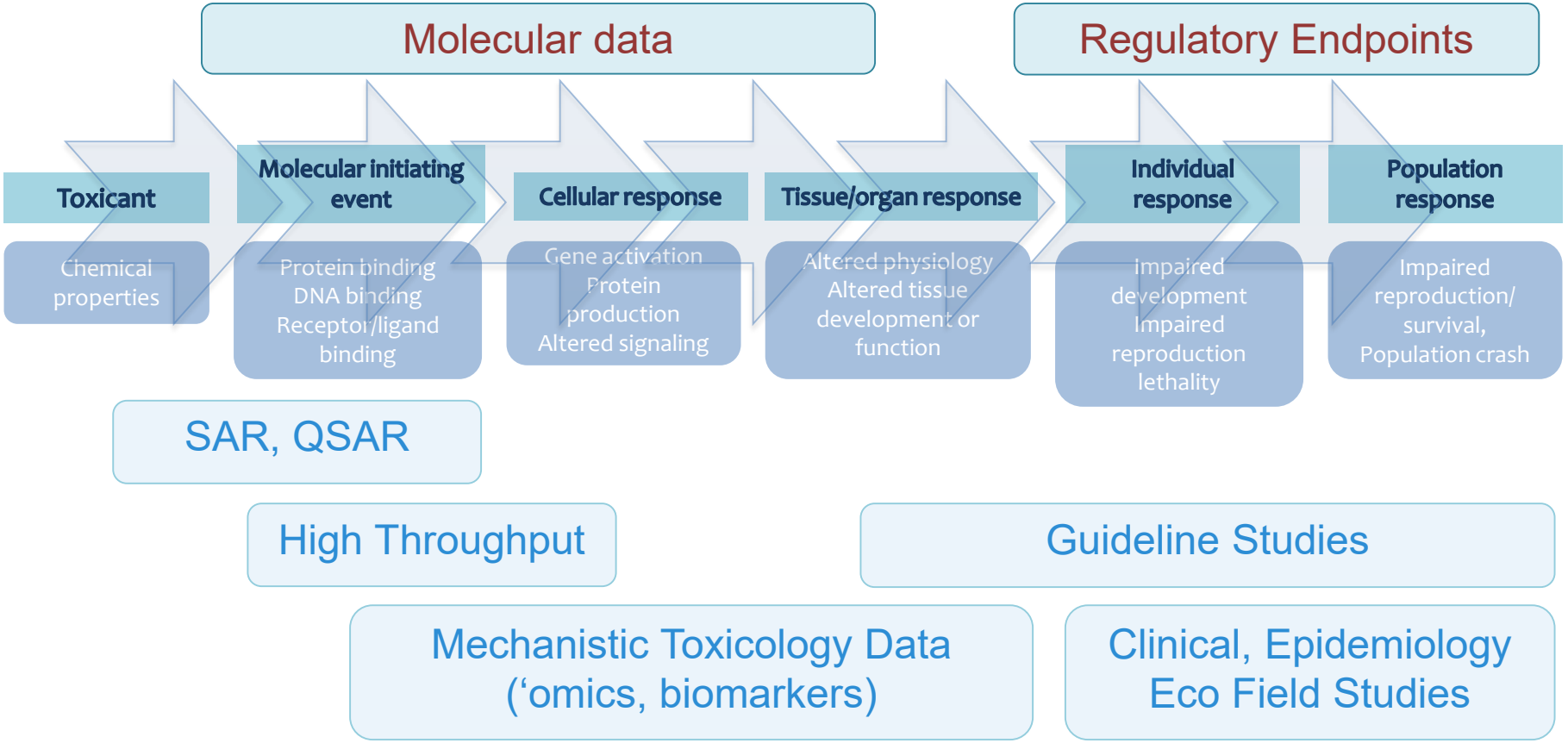
Adverse Outcome Pathway framework: linking molecular initiation to adverse outcomes

- AOPs: Linking molecular information to adverse outcomes

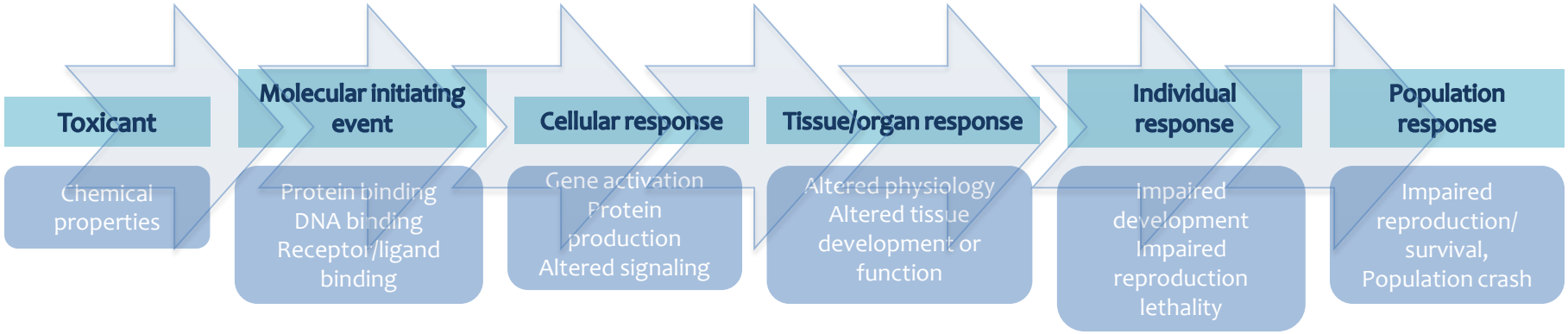


- beginning with initial interactions of a stressor with a biomolecule in a target cell or tissue (the **molecular initiating event - MIE**)
- progressing through a dependent series of intermediate events (**key events - KE**)
- Linked together through Key Event Relationships (**KER**)
- culminating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

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

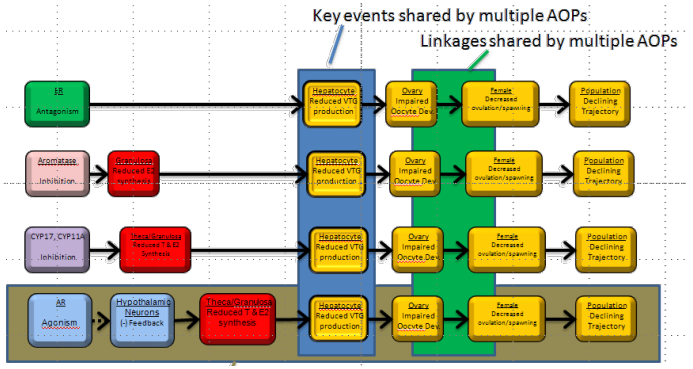


Essential elements of an AOP



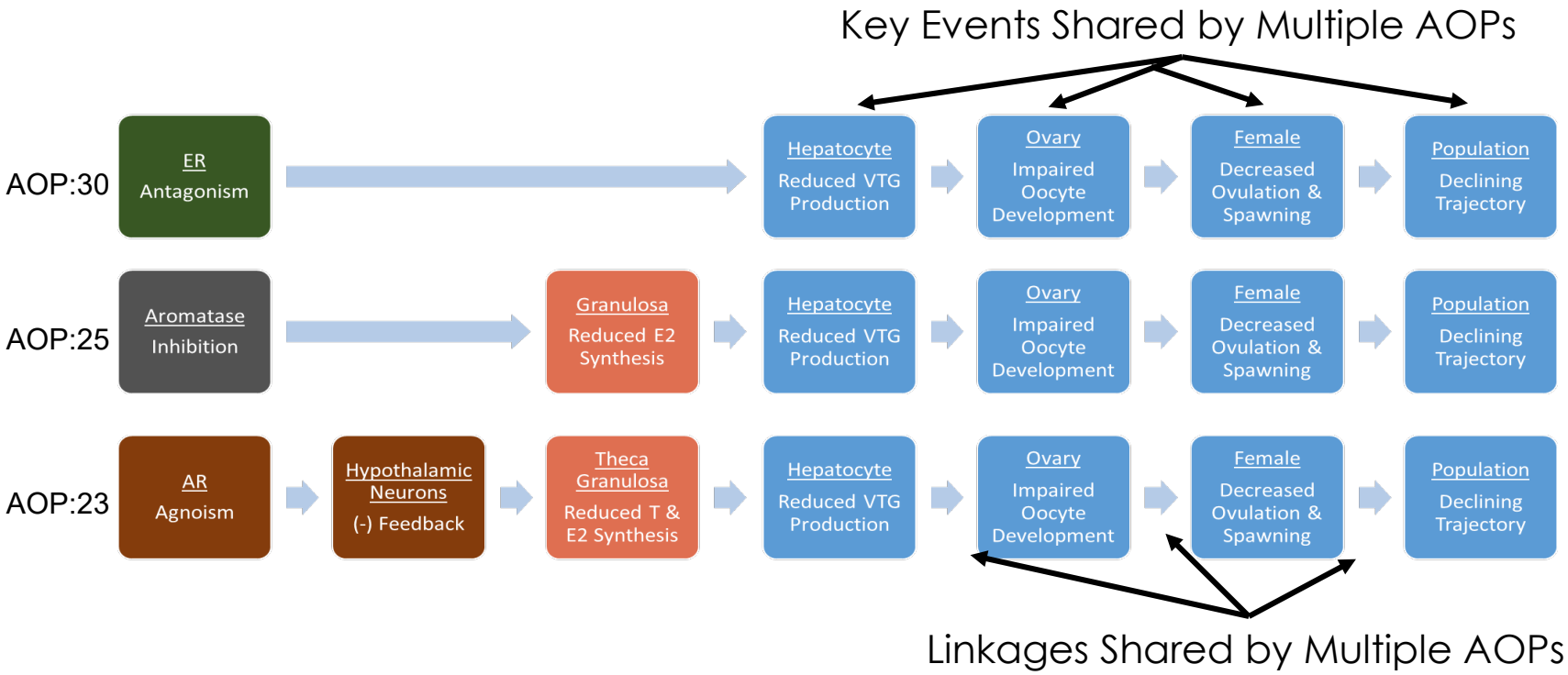
- Key Events (KEs)
  - Change in biological or physiological state
  - Measurable and essential for progression
- Molecular Initiating Event (MIE): specialized KE that represents the initial point of stressor interaction with the organism
- Adverse Outcome (AO): specialized KE of regulatory significance
- 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

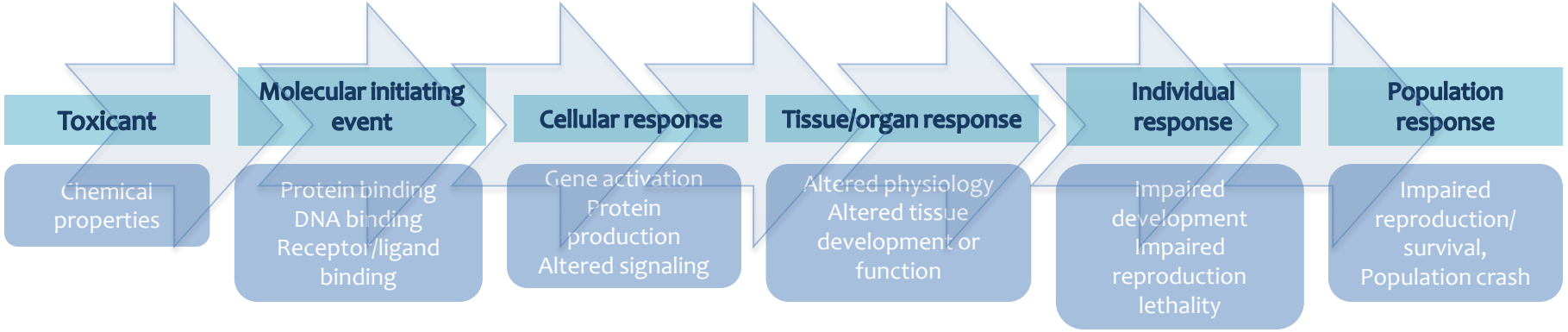


1. AOPs are not chemical specific
2. AOPs are modular
   - Key events and relationships can be shared by multiple AOPs
3. As a pragmatic construct, an individual AOP is composed of a single sequence of KEs and KERs leading to a single AO
4. AOP networks will emerge and are the basis for prediction
5.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

Networks emerge as KE and KER are shared



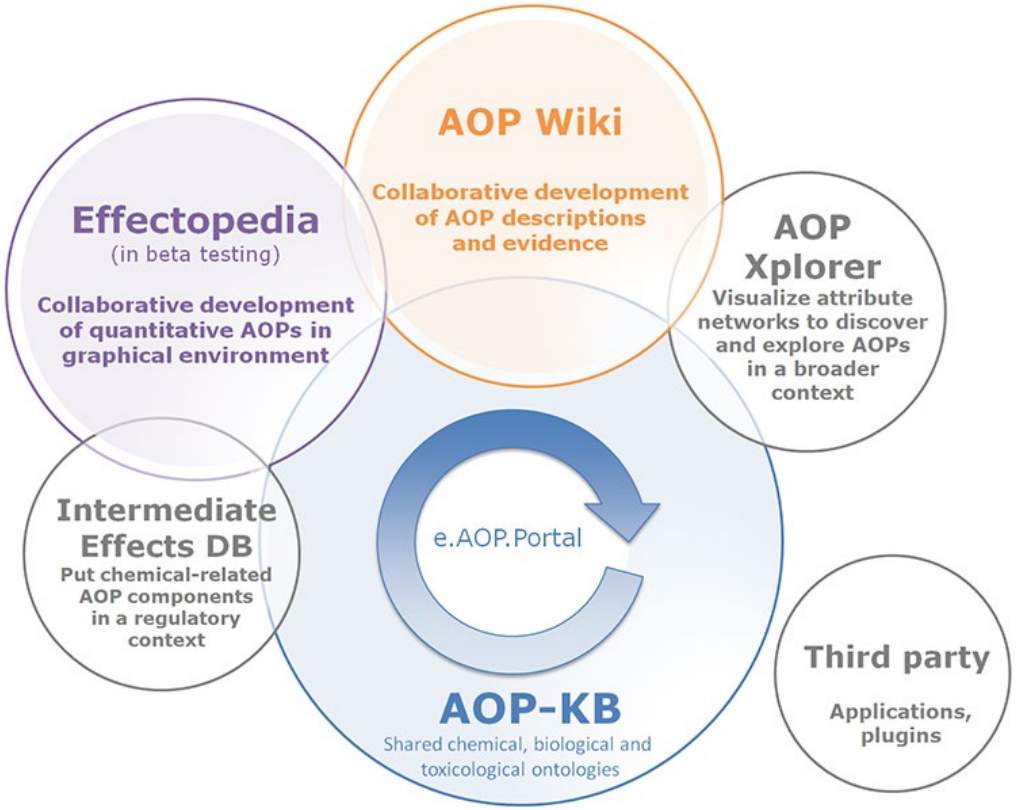
Building an AOP



- 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

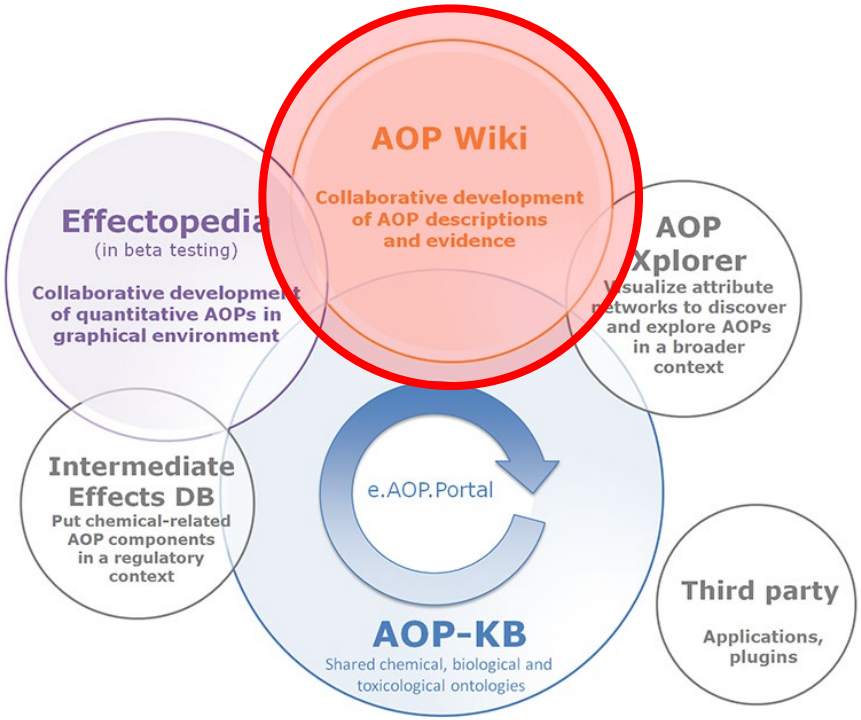
OECD AOP Knowledgebase (AOP-KB): an international partnership



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

AOP Wiki home page

AOP News

Home

Announcements

Greetings

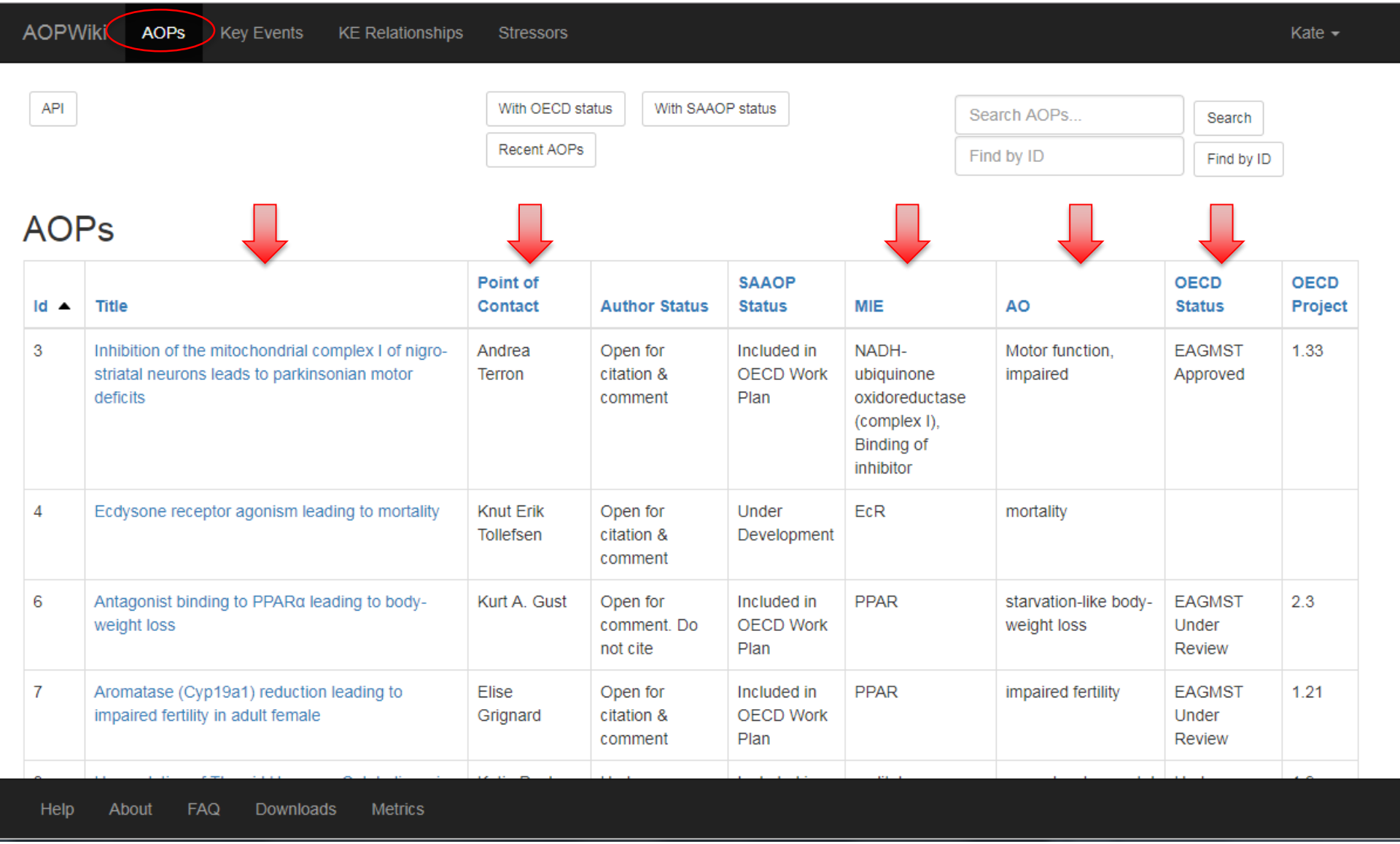
Happy Holidays from the AOP-Wiki team

AOP Welcome

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

Contents

List of 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

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

OECD AOP Development Programme

Extended Advisory Group for Molecular Screening & Toxicogenomics (EAGMST)

- Guidance, users Handbook
- Review
- Training

Working Party on Hazard Assessment (WPHA)

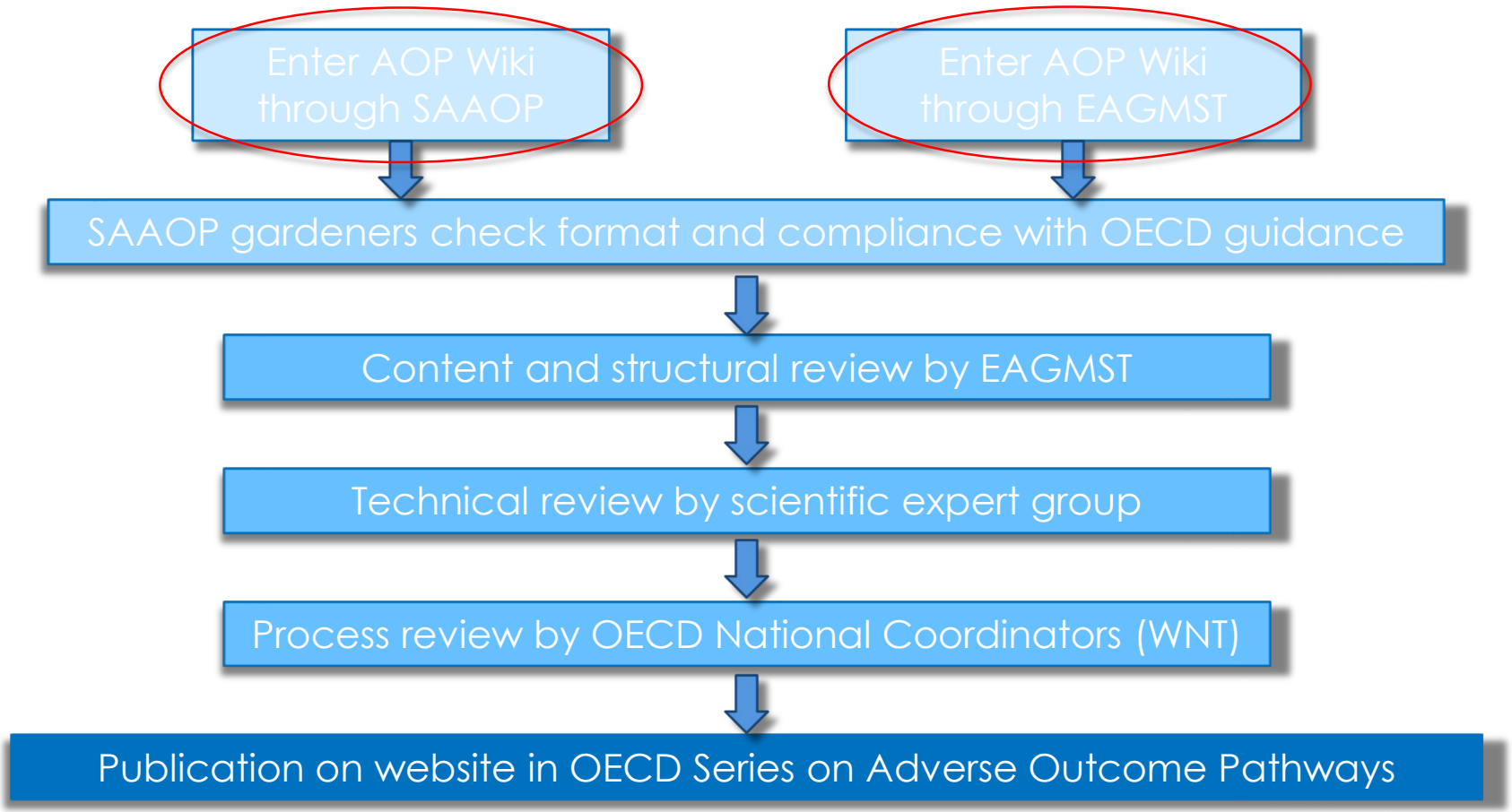
- Guidance for use of AOPs in regulatory decision making
- Integrated Approaches to Testing and Assessment (IATA)

SAAOP

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

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

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

Help | About | FAQ | Downloads | Metrics

The current state of the Wiki

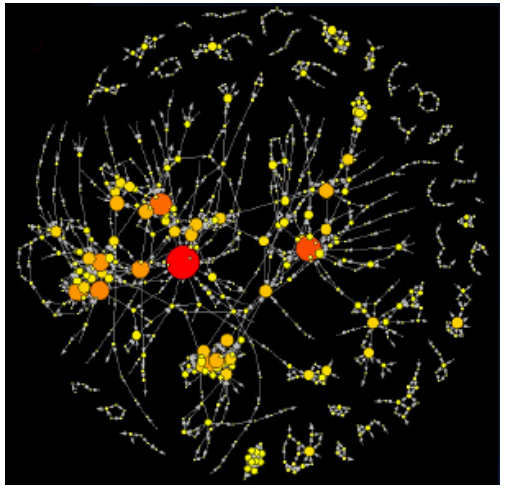
AOPWiki AOPs Key Events KE Relationships Stressors Kate

Available Reports

Summary | AOPS | Key events | KE relationships | Stressors | User contributions

Reports Summary

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



June 2017 D. Villeneuve

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

Most common endpoints addressed:

- Ecotoxicology
- Reproductive toxicity
- Neurotoxicity
- carcinogenicity
- endocrine

★Participants needed!★

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
- 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
- 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

Other training resources:*

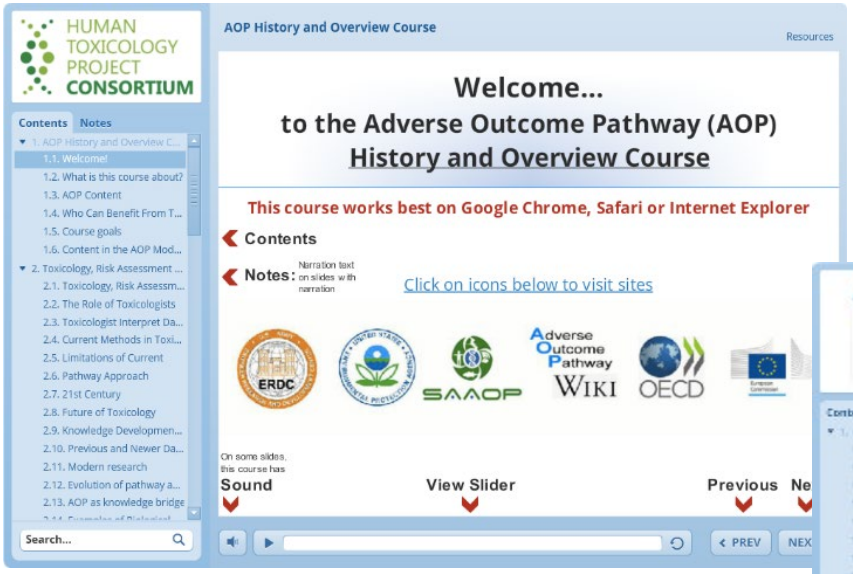
AOP Learning: https://training.effectopedia.org/

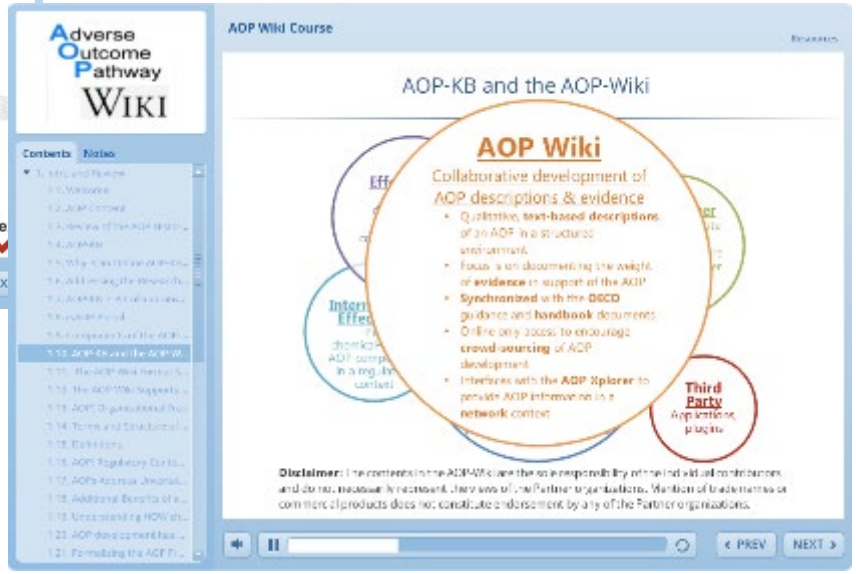
Building AOP Structure and Description

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!

Physicians Committee for Responsible Medicine

HUMAN TOXICOLOGY PROJECT

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

WiFi: Hilton Mtg **Password: PSAV2019**