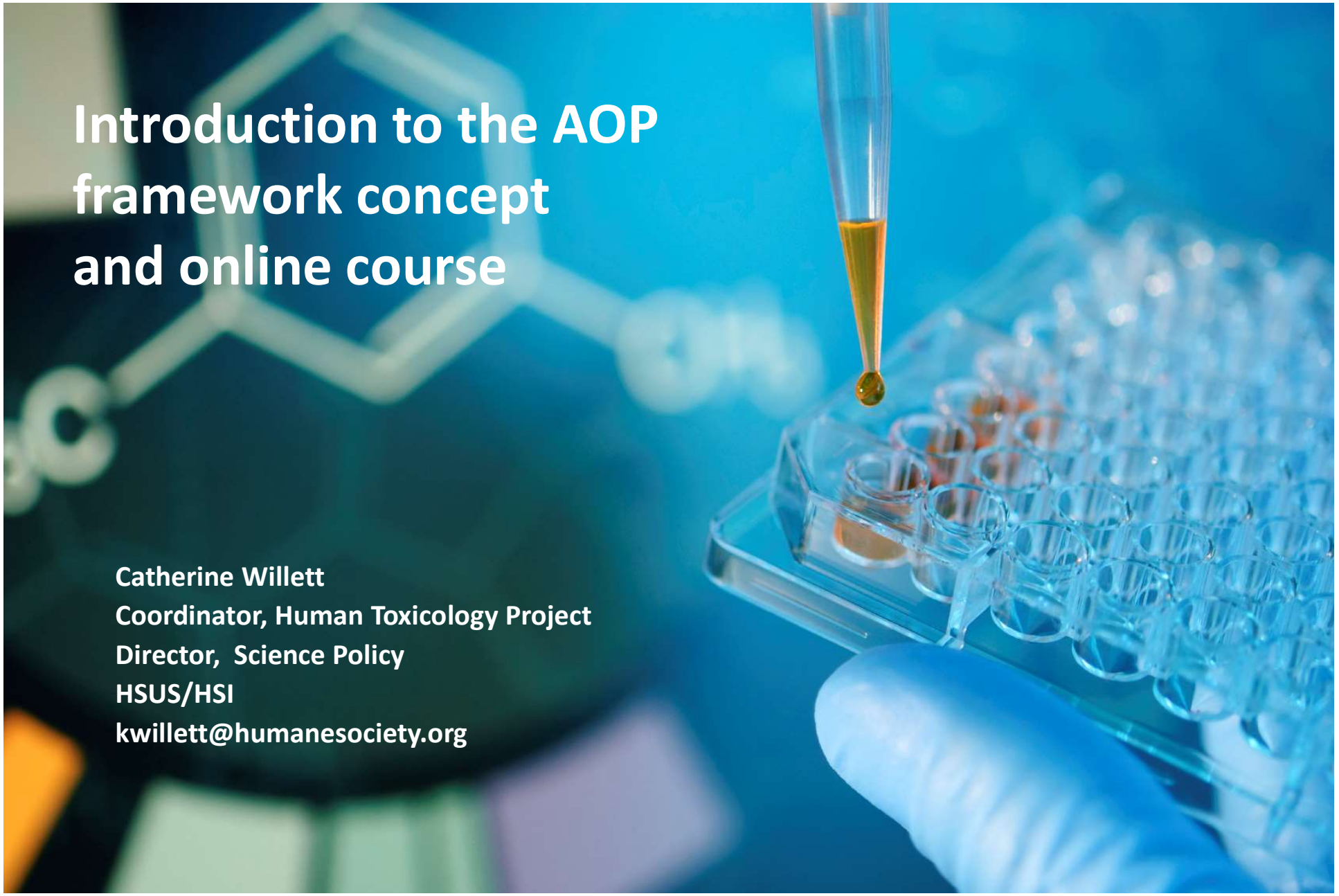
Introduction to the AOP framework concept and online course



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THE HUMANE SOCIETY OF THE UNITED STATES

HUMANE SOCIETY INTERNATIONAL

HUMAN TOXICOLOGY PROJECT

Outline

Why

- Need for more efficient tools for chemcial risk assessment
- Need to better use our existing and future data and knowledge

What

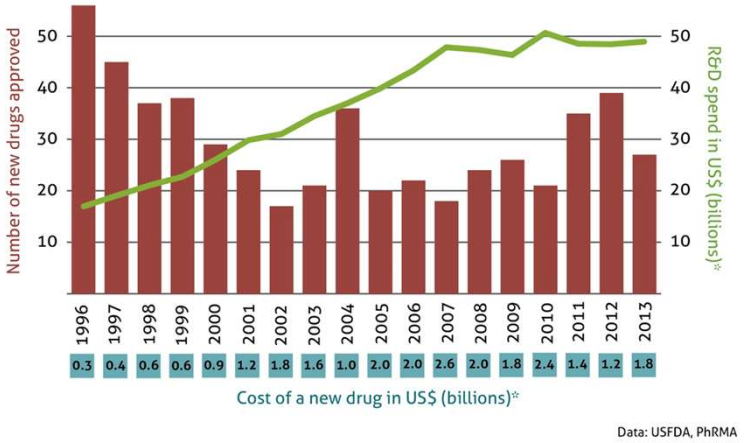
- The Adverse Outcome Pathway framework
- Purpose, definition

How

- Relational “knowledgebase”
- Guidance
- Evaluation
- Training and free course

Issue #1: too many chemicals, current system inadequate

- e.g. tens of thousands of chemicals await assessment
- e.g. 95% clinical failure rate for new drugs in spite of increased spending
- Faster, more relevant approaches needed across sectors



Issue #2: The need to better leverage our existing knowledge

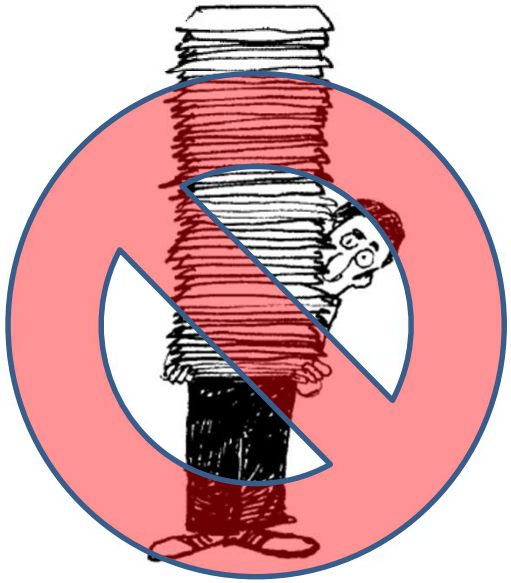
Too much data!

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

Where is the data?!

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

Better access, better organization leads to better understanding

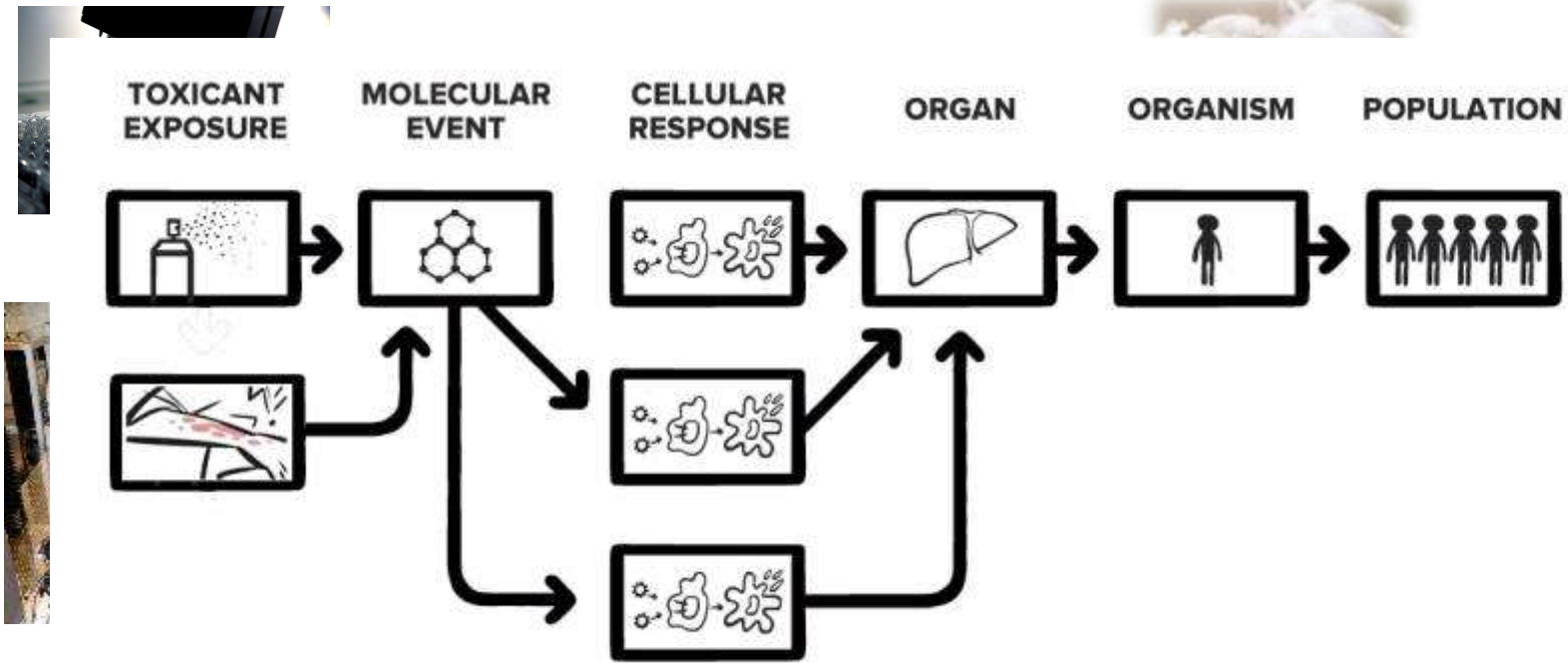


- PDFs
- Fragmented
- Siloed
- Proprietary

- Searchable
- Machine-readable
- Linked
- Facilitating collaboration
- Avoiding duplication

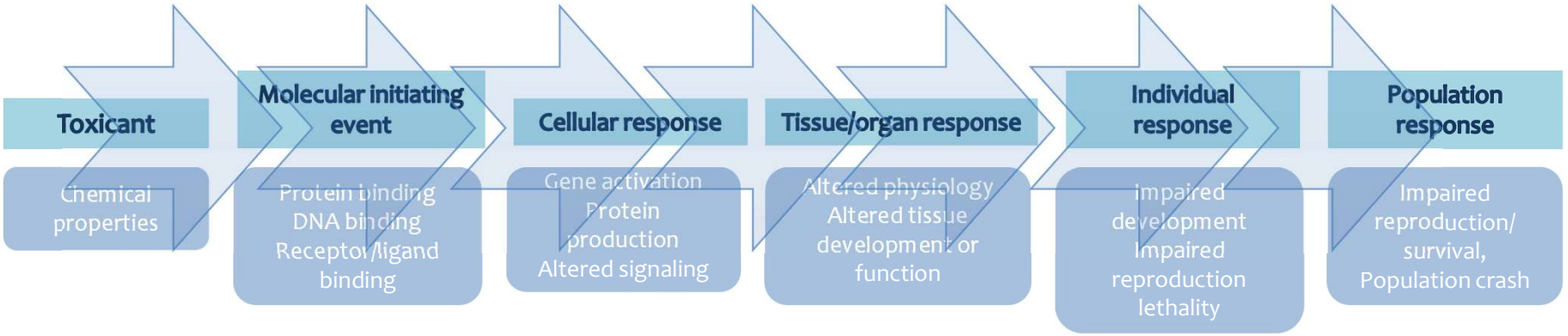
(adapted from D. Villeneuve)

Adverse Outcome Pathway framework: linking molecular initiation to adverse outcomes



- How to use molecular understanding to make better decisions about chemical safety
- Provides a framework for collecting, organizing and evaluating biological information

AOPs: Linking molecular information to adverse outcomes

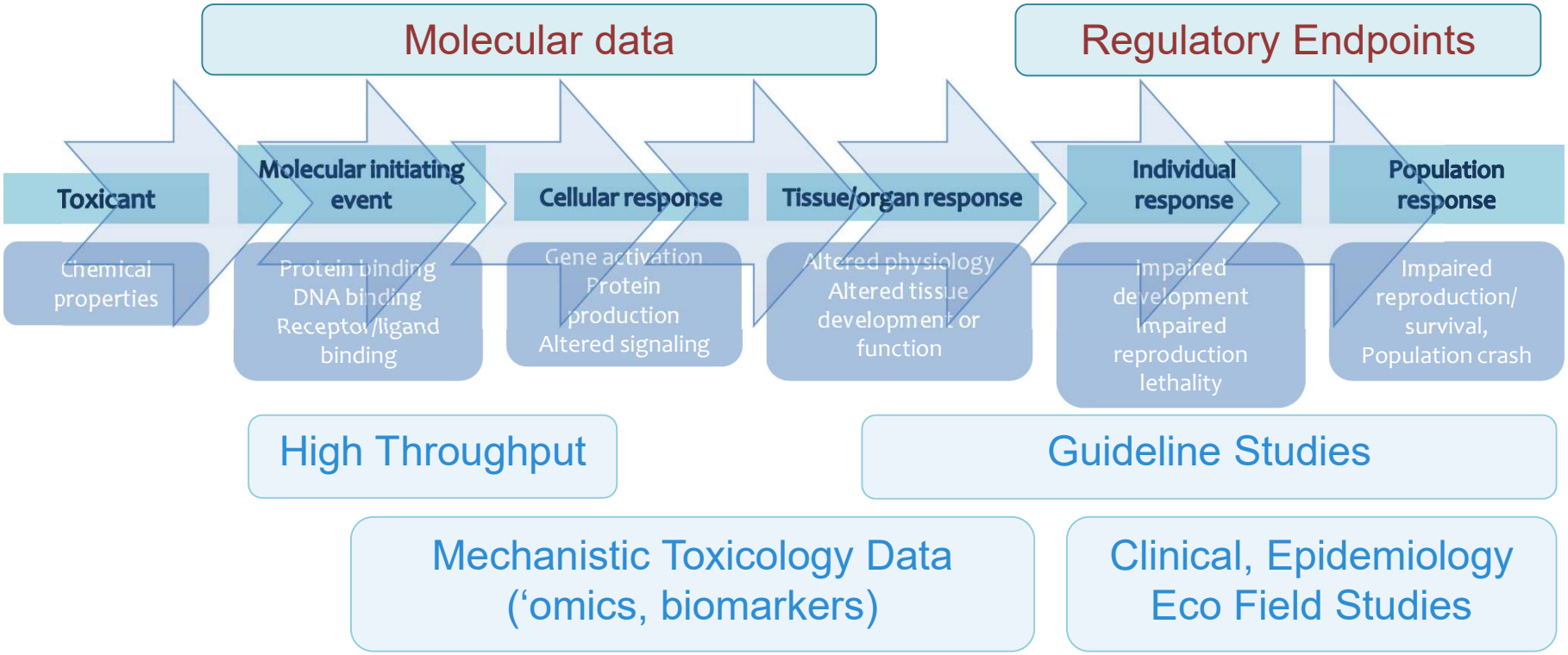


A sequence of events

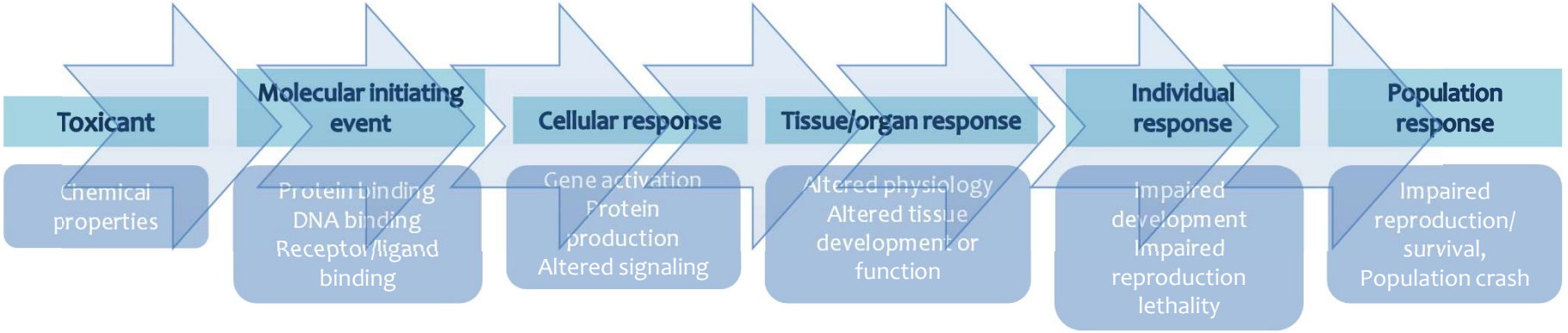
- beginning with initial interactions of a stressor with a biomolecule in a target cell or tissue **(the molecular initiating event),**
- progressing through a dependent series of intermediate events **(key events)**
- culminating with an **adverse outcome***

*if compensatory mechanisms are overwhelmed

AOPs: Provides scaffold for organizing, evaluating and understanding data

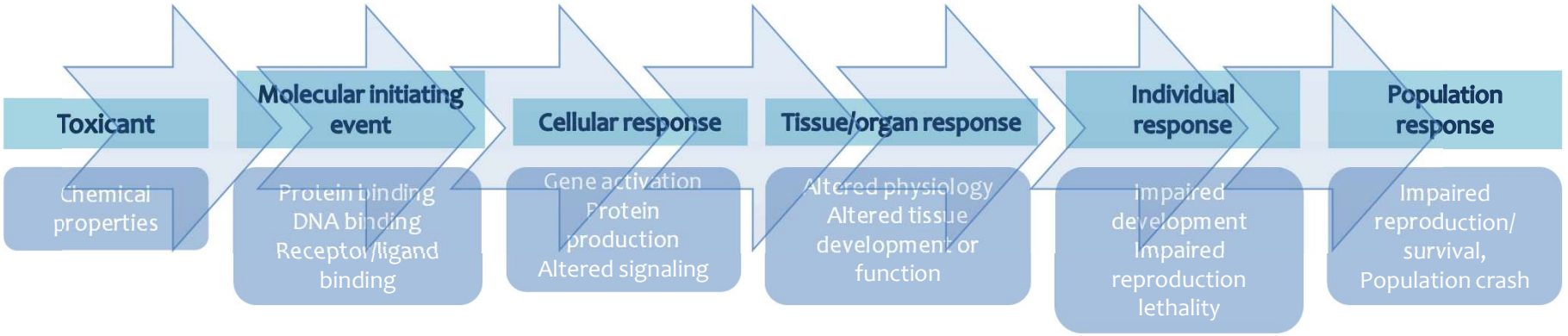


Essential elements of an AOP



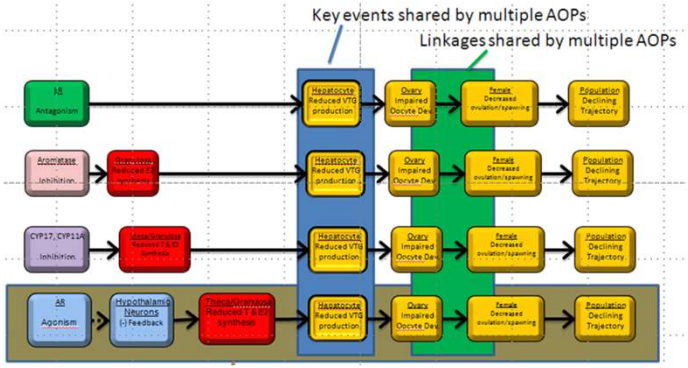
- **Key Events (KEs) – nodes**
  - Change in biological or physiological state
  - Measurable and essential for progression
- **Molecular Initiating Event (MIE):** specialized KE that represents the initial point of stressor interaction with the organism
- **Adverse Outcome (AO):** specialized KE of regulatory significance
- **Key Event Relationships (KERs)**
  - Connection between two key events
  - Critical for assembling evidence in support of the AO
  - Facilitates inference or extrapolation

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**

Fundamental principles of AOP development



AOPs are modular

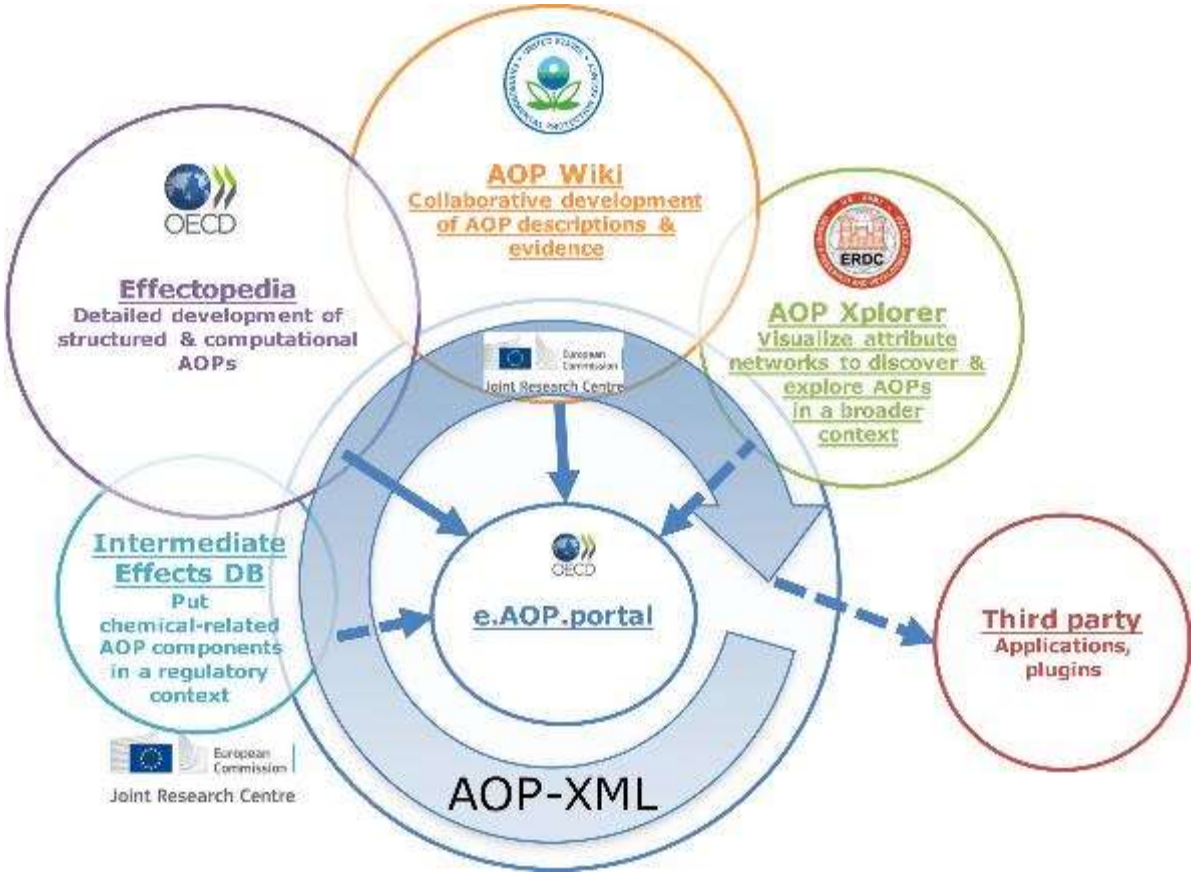
- Key events and relationships can be shared by multiple AOPs

AOPs are living documents

- AOP descriptions can be expected to evolve over time
- As descriptions are updated and expanded – all AOP descriptions they link to update automatically

AOP networks will emerge and are the basis for prediction

AOP Knowledgebase: an international partnership



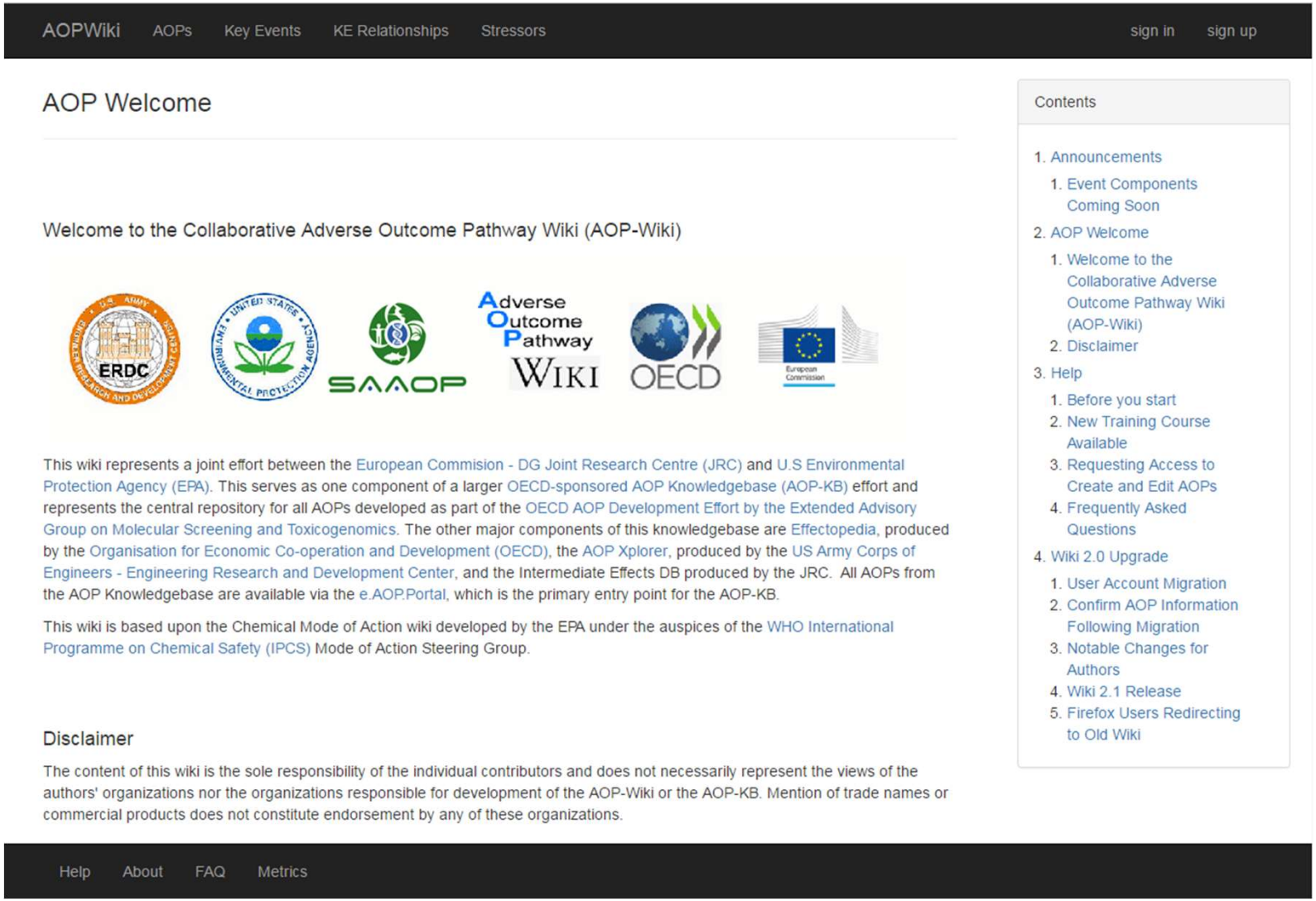
AOP Wiki: information storage, linkage and evaluation

- 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 accessible since 2014

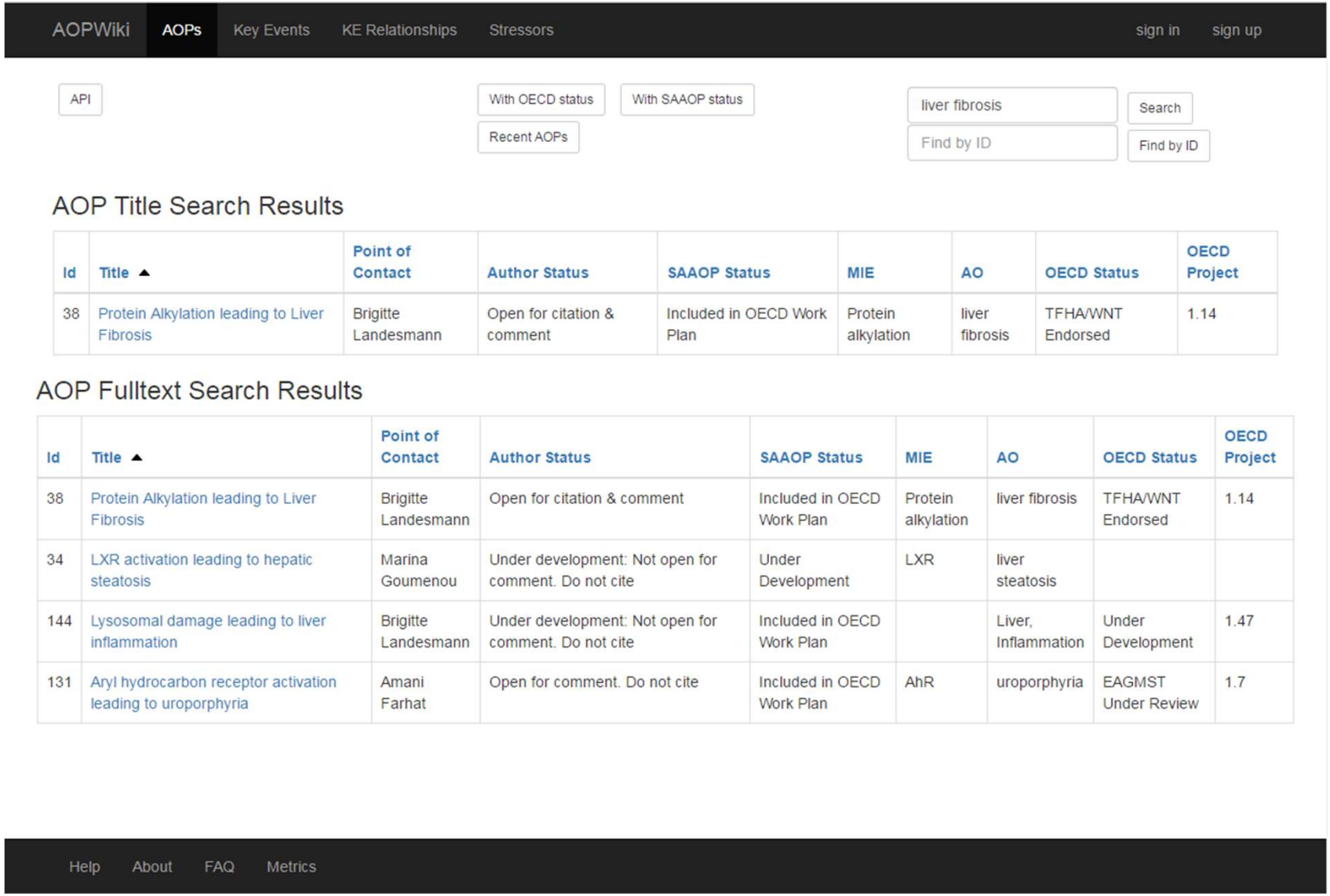
www.aopwiki.org

AOP WIKI: Home page



AOP Wiki 2.2 released Jan 28, 2018

AOP WIKI: search “liver fibrosis”



AOPWiki | AOPs | Key Events | KE Relationships | Stressors | sign in | sign up

API | With OECD status | With SAAOP status | Recent AOPs | liver fibrosis | Search | Find by ID | Find by ID

AOP Title Search Results

Id	Title ▲	Point of Contact	Author Status	SAAOP Status	MIE	AO	OECD Status	OECD Project
38	Protein Alkylation leading to Liver Fibrosis	Brigitte Landesmann	Open for citation & comment	Included in OECD Work Plan	Protein alkylation	liver fibrosis	TFHA/WNT Endorsed	1.14

AOP Fulltext Search Results

Id	Title ▲	Point of Contact	Author Status	SAAOP Status	MIE	AO	OECD Status	OECD Project
38	Protein Alkylation leading to Liver Fibrosis	Brigitte Landesmann	Open for citation & comment	Included in OECD Work Plan	Protein alkylation	liver fibrosis	TFHA/WNT Endorsed	1.14
34	LXR activation leading to hepatic steatosis	Marina Goumenou	Under development: Not open for comment. Do not cite	Under Development	LXR	liver steatosis		
144	Lysosomal damage leading to liver inflammation	Brigitte Landesmann	Under development: Not open for comment. Do not cite	Included in OECD Work Plan		Liver, Inflammation	Under Development	1.47
131	Aryl hydrocarbon receptor activation leading to uroporphyria	Amani Farhat	Open for comment. Do not cite	Included in OECD Work Plan	AhR	uroporphyria	EAGMST Under Review	1.7

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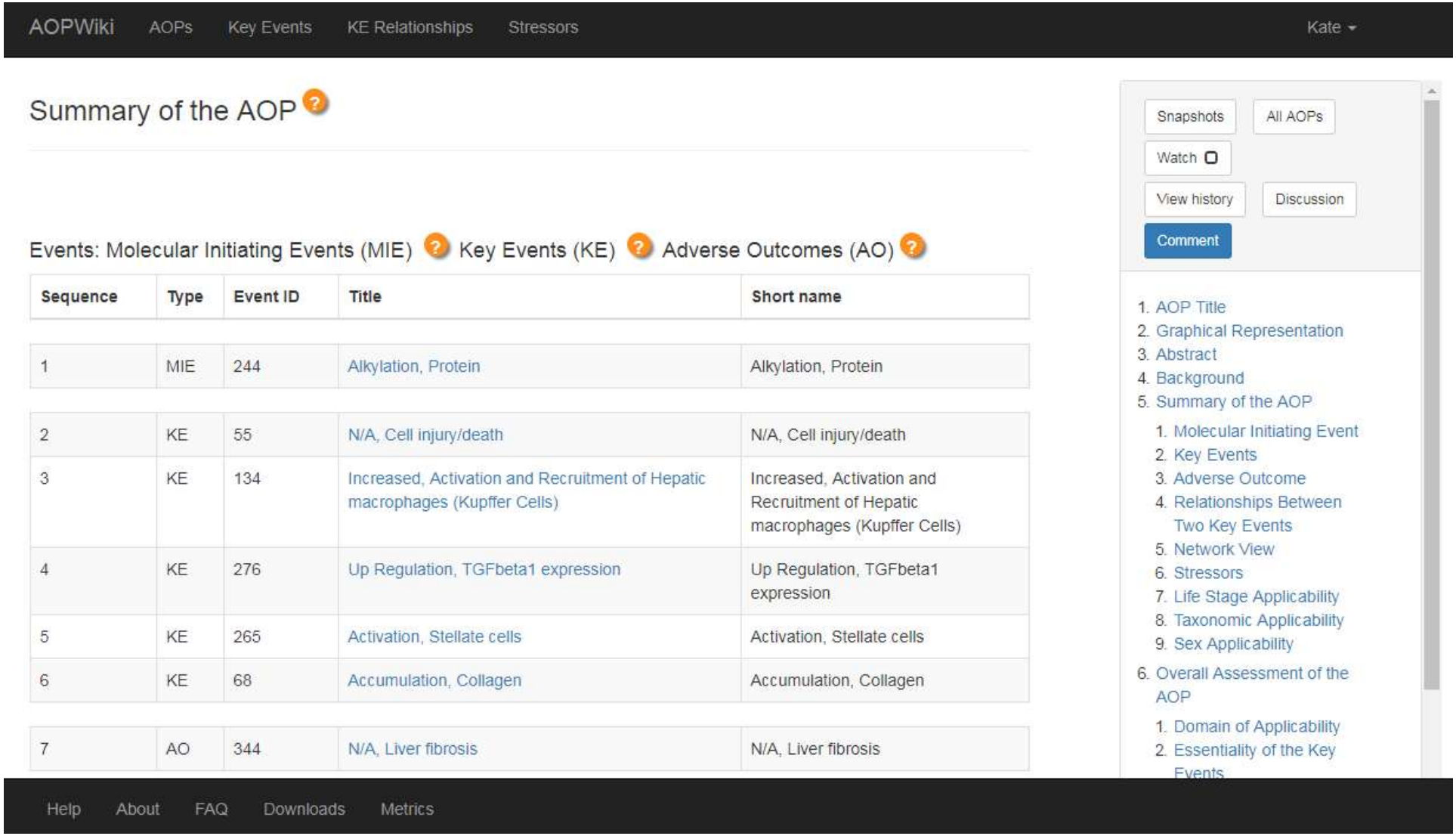
AOP 38 Summary



AOP WIKI: KER and AOP confidence evaluation

Biological Plausibility: between KE upstream and KE downstream?		
High (strong): Extensive understanding of KER	Moderate: KER is plausible	Low (weak): some empirical support
Essentiality: are downstream KEs prevented if upstream KE's blocked?		
High (strong): direct evidence from experimental studies	Moderate: indirect evidence	Low (weak) No or contradictory evidence
Empirical Evidence: amount, quality, consistent, inconsistent?		
High (strong): extensive evidence for temporal, dose-response	Moderate: multiple reports of consistent evidence, some inconsistent	Low (weak): limited or no studies and/or significant inconsistencies

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

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OECD AOP Development Programme

Extended Advisory Group for Molecular Screening & Toxicogenomics (EAGMST)

- Guidance, users Handbook
- Review
- Training

Task force on Hazard Assessment (TFHA)

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

Society for the Advancement of AOPS

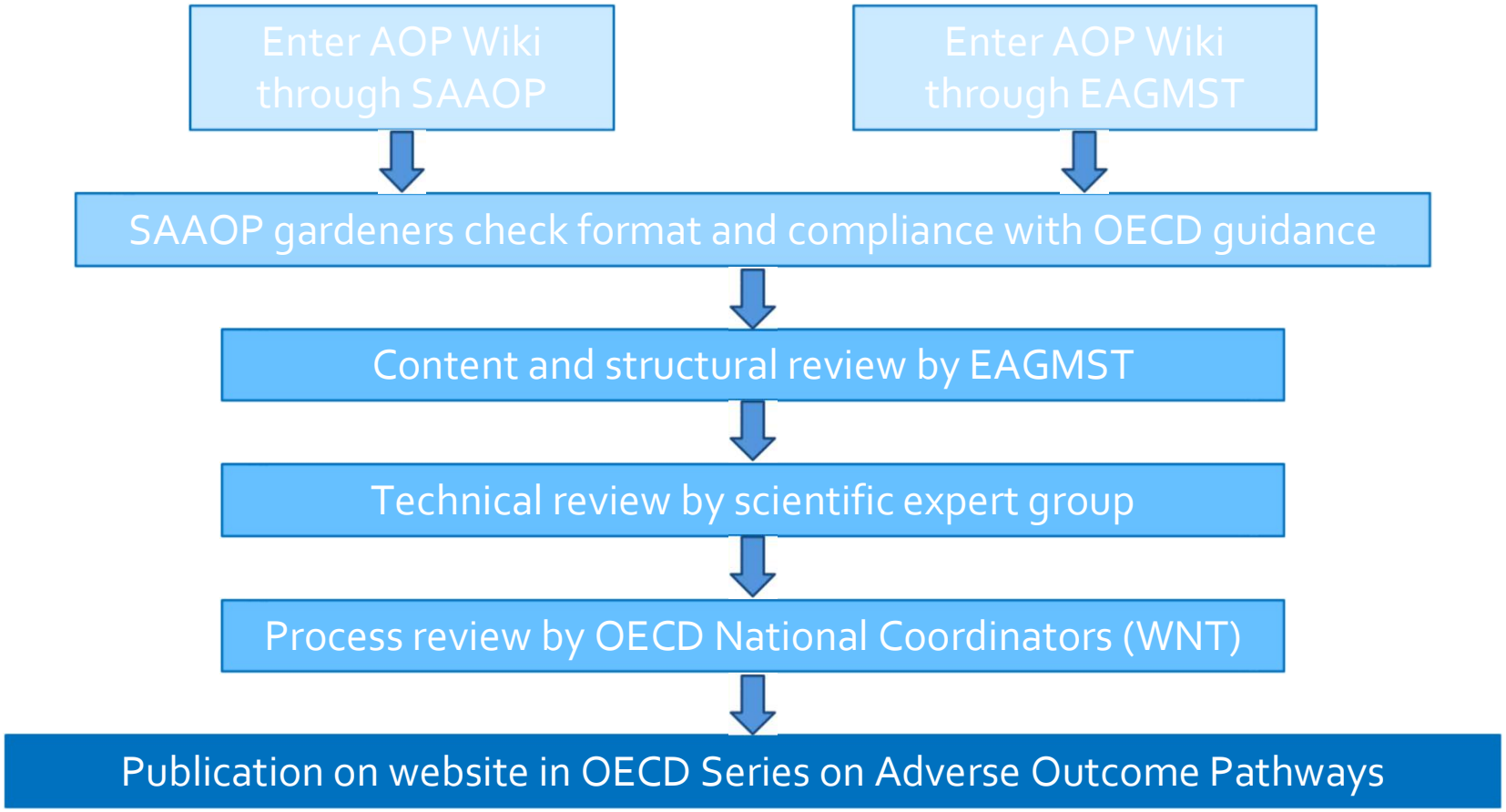
- Not officially part of the OECD programme
- Any person active in developing an AOP in the wiki can join
- Is another way to enter the AOP wiki
- Provides “gardening” and other support functions
- www.saaop.org

OECD AOP Development Programme

AOP Wiki Access: three levels

1. Read access: anyone can access the wiki, search and read entries
2. Commenter access: a self-created account is needed to leave comments
   - Create an account on the wiki
3. Author access: to write and edit AOPs
   - must be requested through the wiki
   - You should have a familiarity with the wiki and desire to build an AOP

Work Process for Development and Review of AOPs through OECD



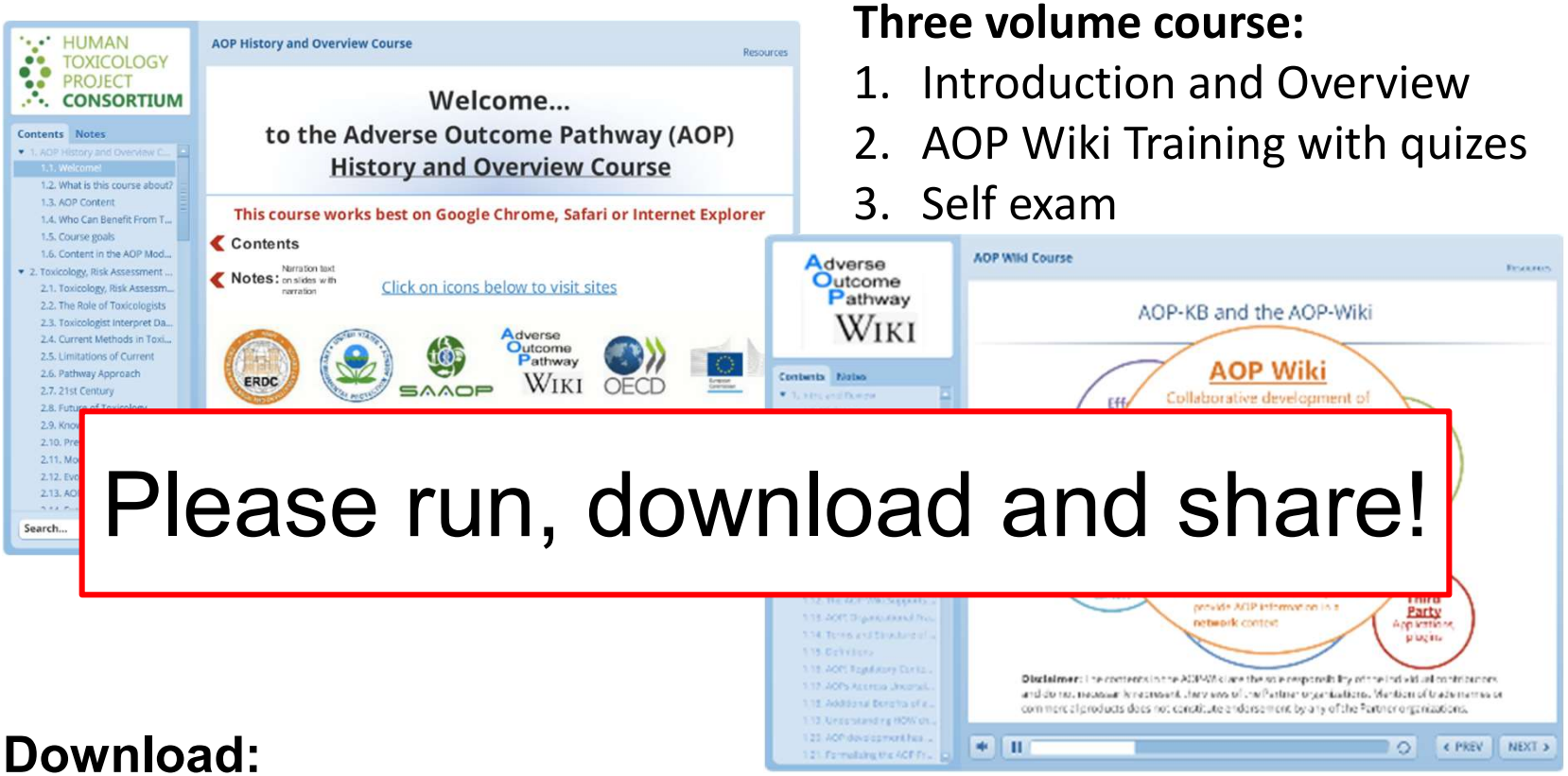
OECD Guidance for developing AOPs

Guidance Document for Developing and Assessing AOPs (2017)
Series on Testing & Assessment No. 233

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

Section of AOP Wiki	Section of Handbook
AOP Description	Section 1
KE descriptions (unique pages)	Section 2
KER descriptions (unique pages) KER evaluation	Section 3
Overall AOP assessment	Section 4

AOP Online Training Course



Three volume course:

1. Introduction and Overview
2. AOP Wiki Training with quizes
3. Self exam

Please run, download and share!

Download:

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

Run:

https://aopwiki.org/

Current state of the AOP Wiki

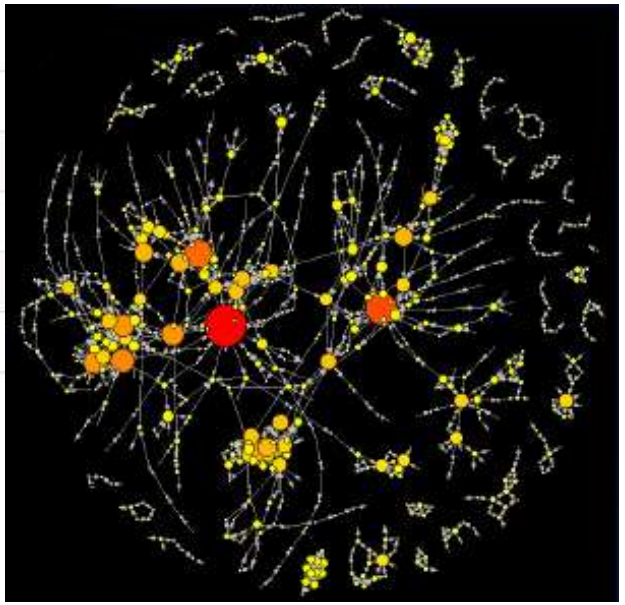
AOPWiki AOPs Key Events KE Relationships Stressors

Available Reports

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

Reports Summary

Report	Count
AOPs	218
Key events	1104
KE relationships	1352
Stressors	345



23 June 2017 D. Villeneuve

The more participation, the better it will be!