Adverse Outcome Pathways (AOPs) as an information support system

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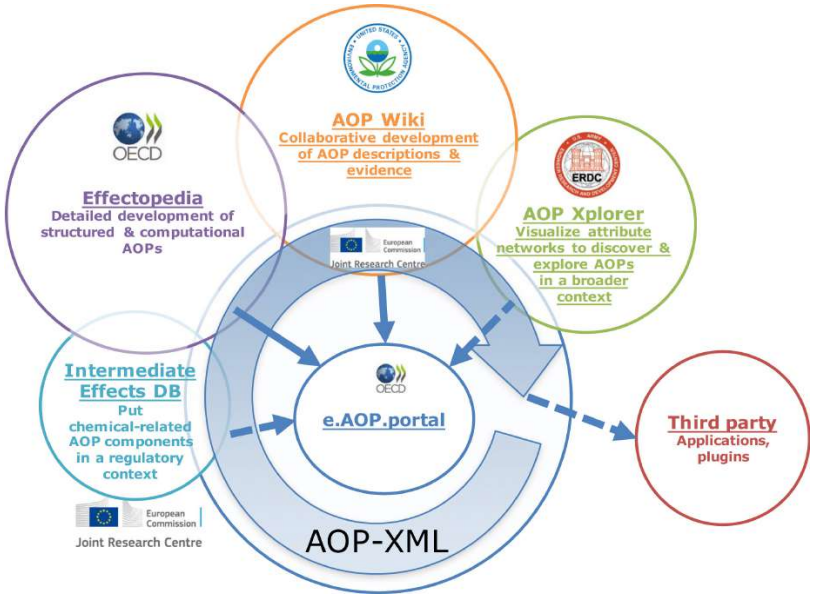
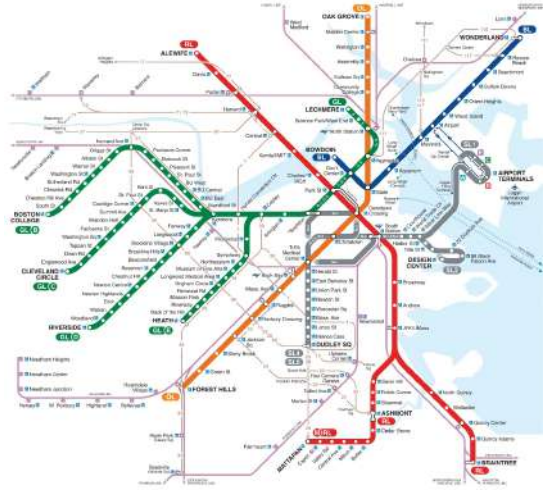
Humane Society of the United States / International

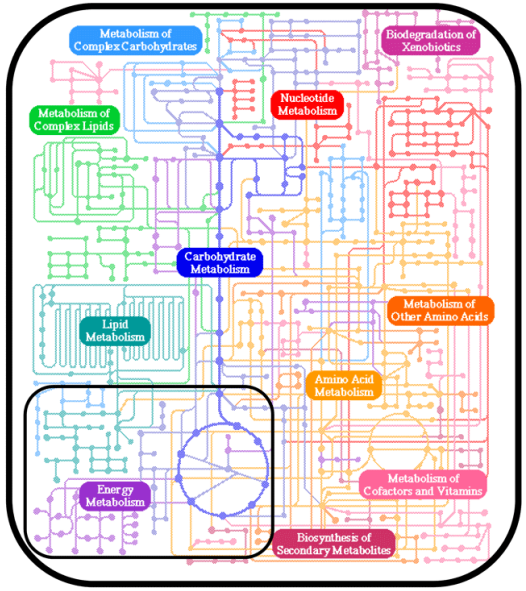
Outline:

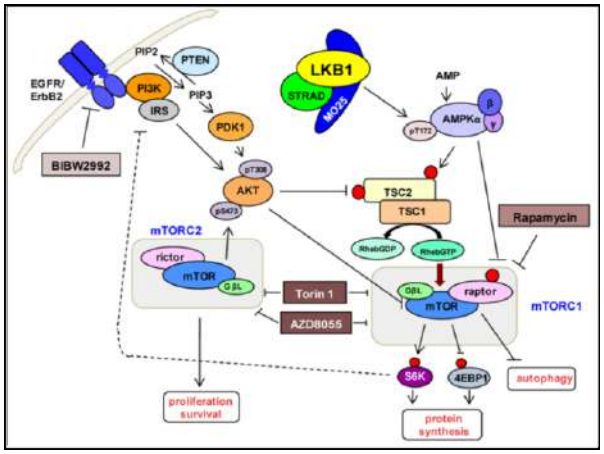
- Brief discussion of "pathways"
- What is an "AOP"?
- how are AOPs different from other "Pathway-based" approaches?
- AOP construction, curation and review

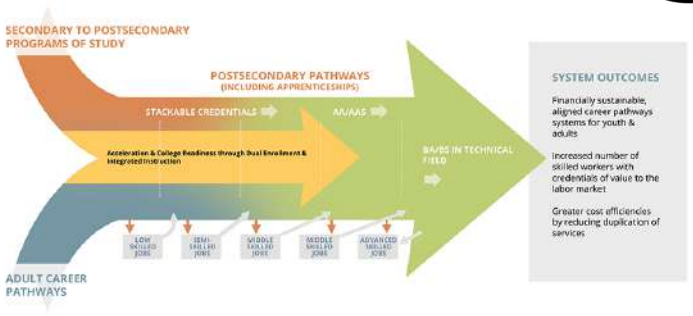


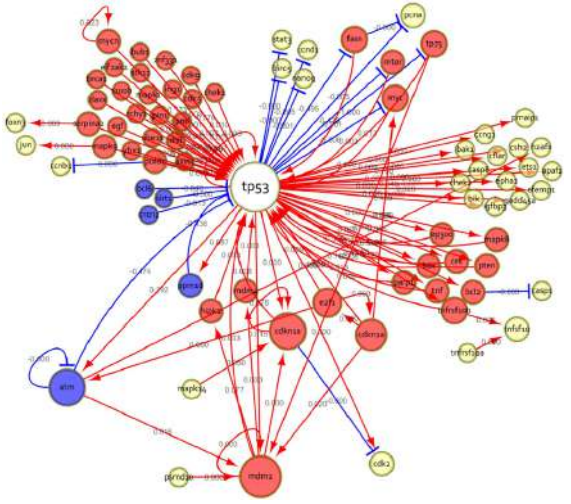
“Pathway” means different things to different people



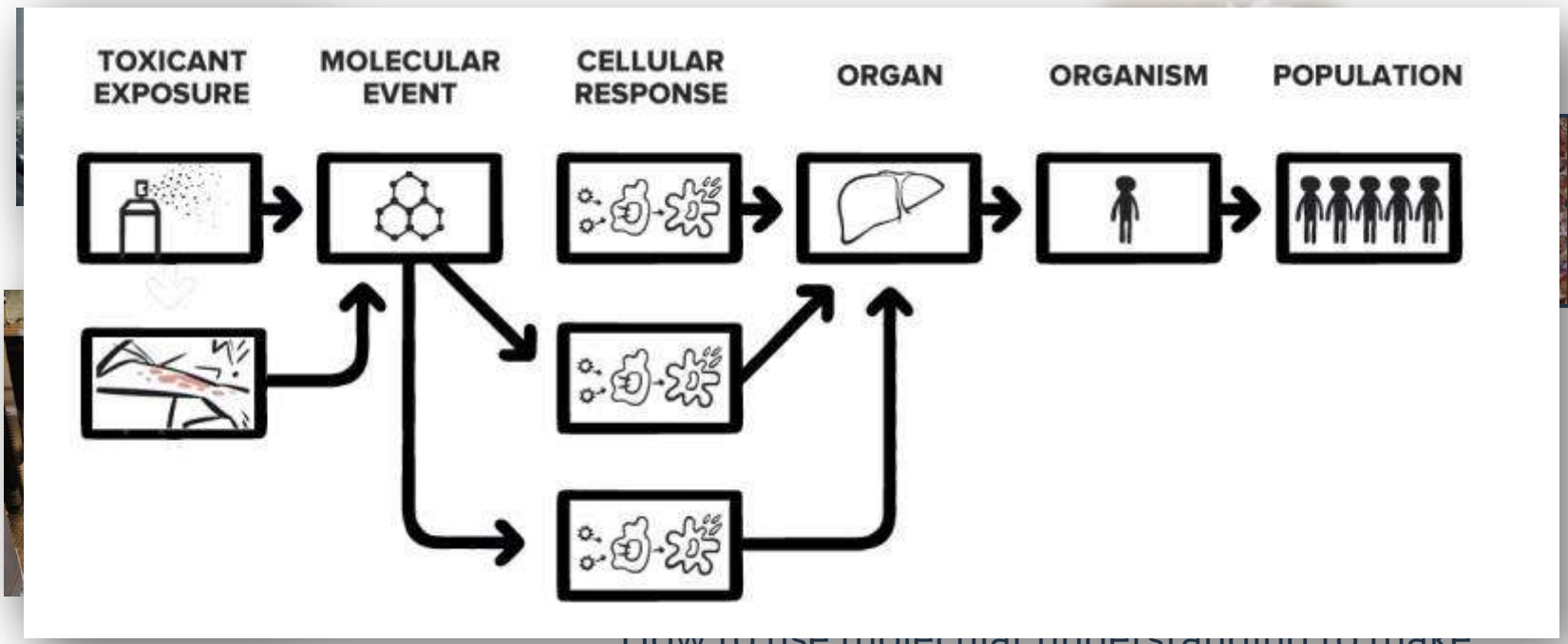






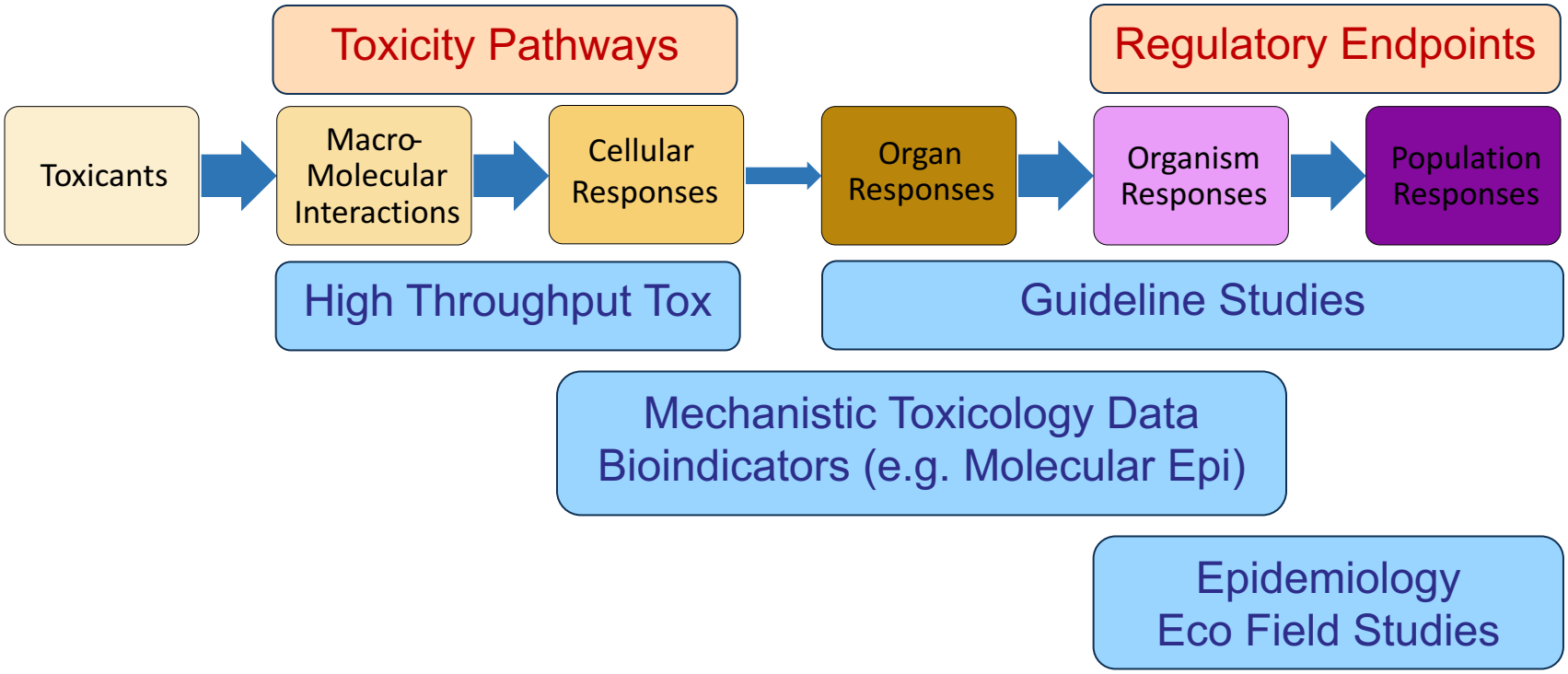


Adverse Outcome Pathways: linking molecular initiation to adverse outcomes

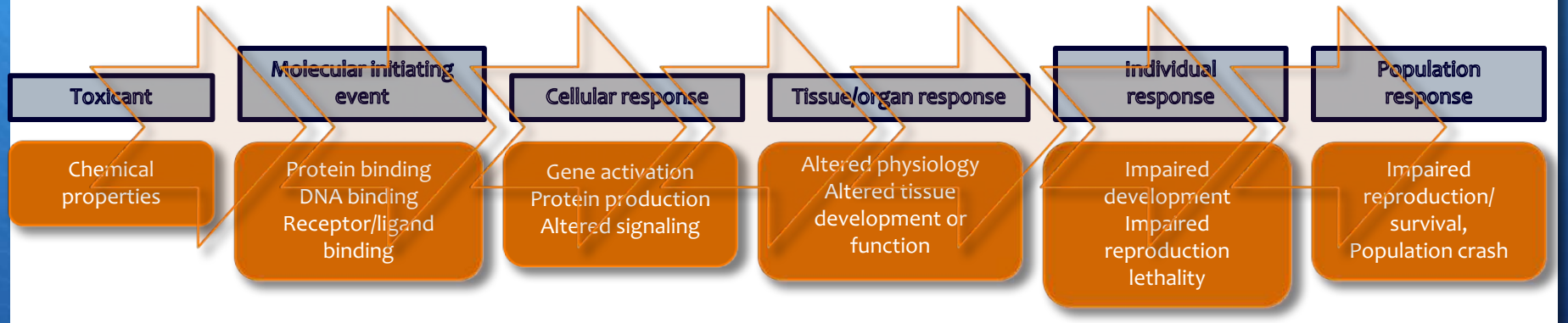


How to use molecular understanding to make better decisions about chemical safety

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



Linking molecular information to adverse outcomes: Adverse Outcome Pathways

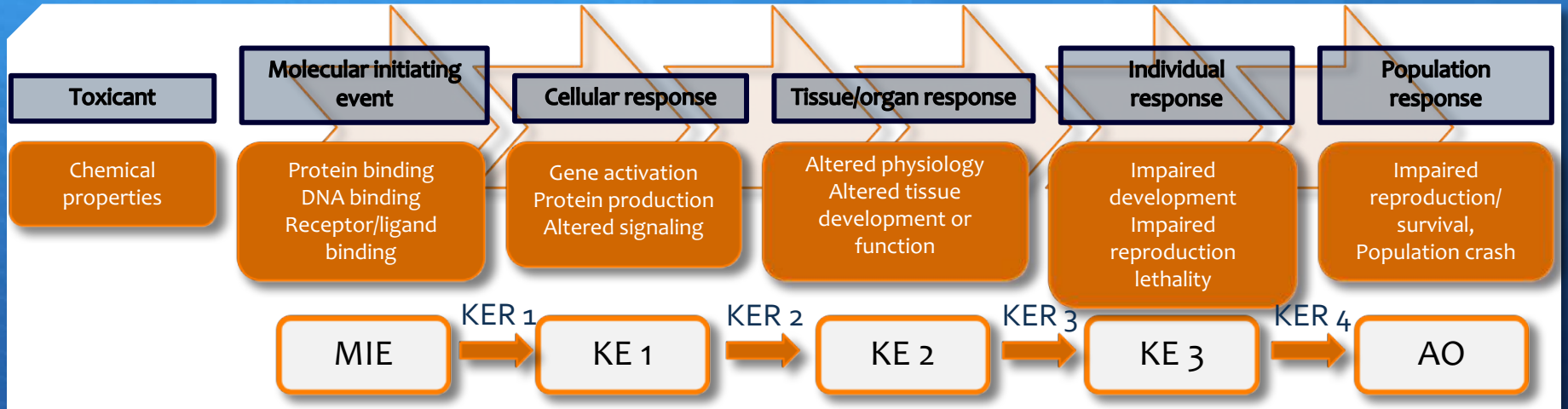


"Conceptually, an AOP can be viewed as a sequence of events commencing with initial interactions of a stressor with a biomolecule in a target cell or tissue (i.e., molecular initiating event), progressing through a dependent series of intermediate events and culminating with an adverse outcome."

"AOPs are typically represented sequentially, moving from one key event to another, as compensatory mechanisms and feedback loops are overcome."

OECD AOP User's Handbook: https://**aop**kb.org/common/**AOP_Handbook**.pdf

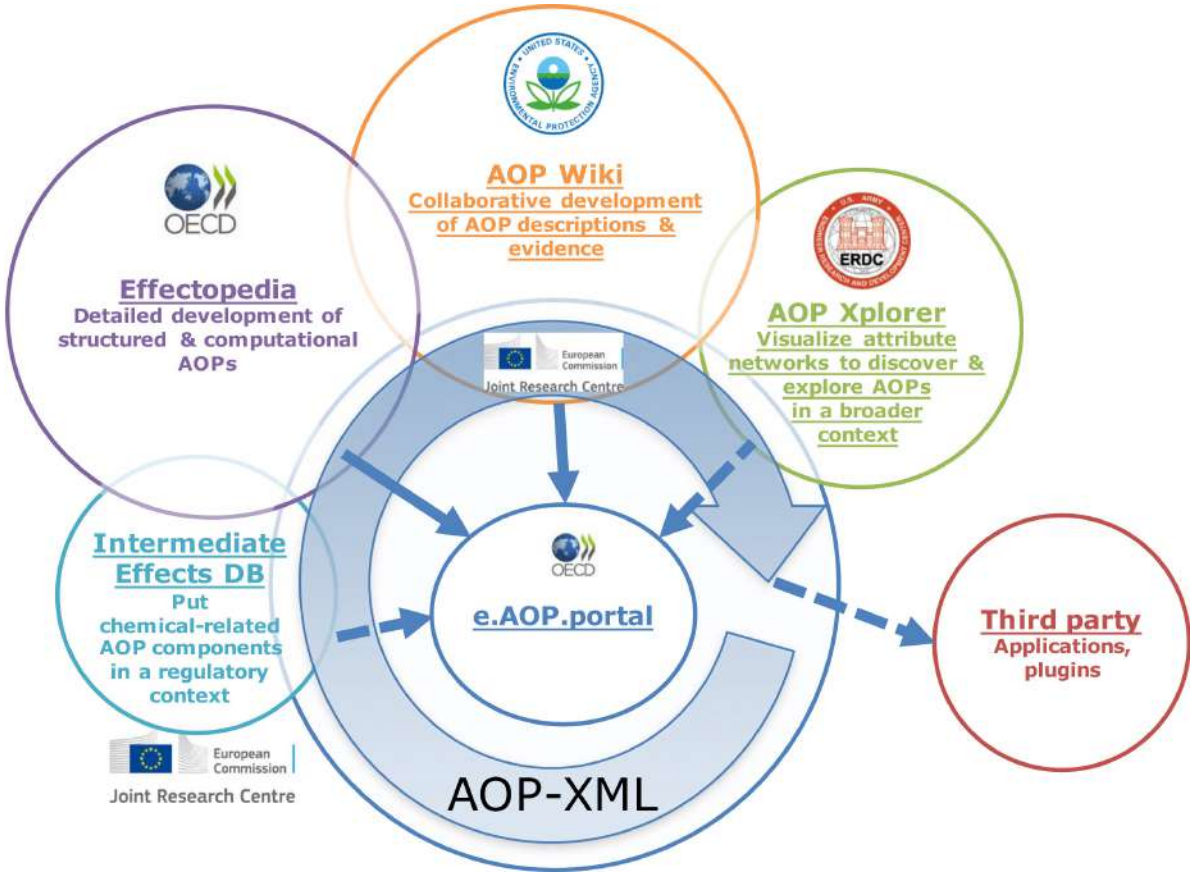
Essential Elements of an AOP



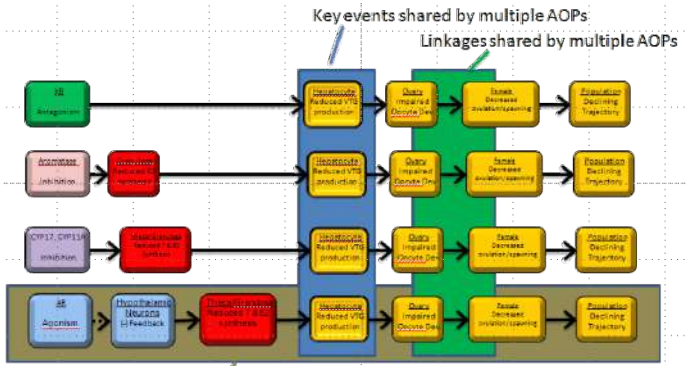
- Molecular Initiating Event (MIE): Initial point of chemical interaction
- Adverse Outcome (AO): Adverse outcome of regulatory significance
- Key Events (KEs) - nodes
  - Change in biological state
  - Measurable and ***essential for progression***
- Key Event Relationships (KERs) - edges
  - Connections between two key events
  - Critical for assembling evidence in support of the AOP

Villeneuve, et al. Tox Sci., 2014, 142:312-320

AOP Knowledgebase: information storage, evaluation, linkage, and modeling



AOP-KB supports principles of AOP development



AOPs are modular

- KEs and KERs are shared by multiple AOPs
- No need to re-write the same descriptions over and over
- Reusability (best practices)

AOPs are living documents

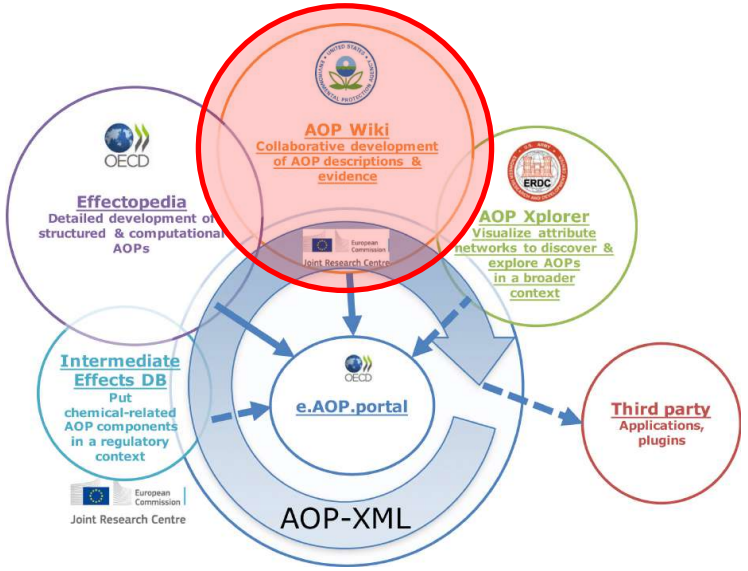
- KE and KER descriptions can be expected to evolve over time
- As descriptions are updated and expanded – all AOP descriptions they link to update automatically

AOP networks for prediction

- Entry of structured information in KB allows for de-facto assembly of AOP networks.

AOP Wiki:
information storage, evaluation, and linkage

- Captures and organizes all information and supporting documentation for KEs and KERs
- Supports OECD review and endorsement of formal AOPs
- Quantitative information is written in appropriate sections
- Not computational



Publically accessible since September 2014

AOP WIKI: Home page

AOPWiki AOPs Key Events KE Relationships Stressors sign in sign up

AOP Welcome

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

This wiki represents a joint effort between the European Commision - DG Joint Research Centre (JRC) and U.S Environmental Protection Agency (EPA). This serves as one component of a larger OECD-sponsored AOP Knowledgebase (AOP-KB) effort and represents the central repository for all AOPs developed as part of the OECD AOP Development Effort by the Extended Advisory Group on Molecular Screening and Toxicogenomics. The other major components of this knowledgebase are Effectopedia, produced by the Organisation for Economic Co-operation and Development (OECD), the AOP Xplorer, produced by the US Army Corps of Engineers - Engineering Research and Development Center, and the Intermediate Effects DB produced by the JRC. All AOPs from the AOP Knowledgebase are available via the e.AOP.Portal, which is the primary entry point for the AOP-KB.

This wiki is based upon the Chemical Mode of Action wiki developed by the EPA under the auspices of the WHO International Programme on Chemical Safety (IPCS) Mode of Action Steering Group.

Disclaimer

The content of this wiki is the sole responsibility of the individual contributors and does not necessarily represent the views of the authors' organizations nor the organizations responsible for development of the AOP-Wiki or the AOP-KB. Mention of trade names or commercial products does not constitute endorsement by any of these organizations.

Contents

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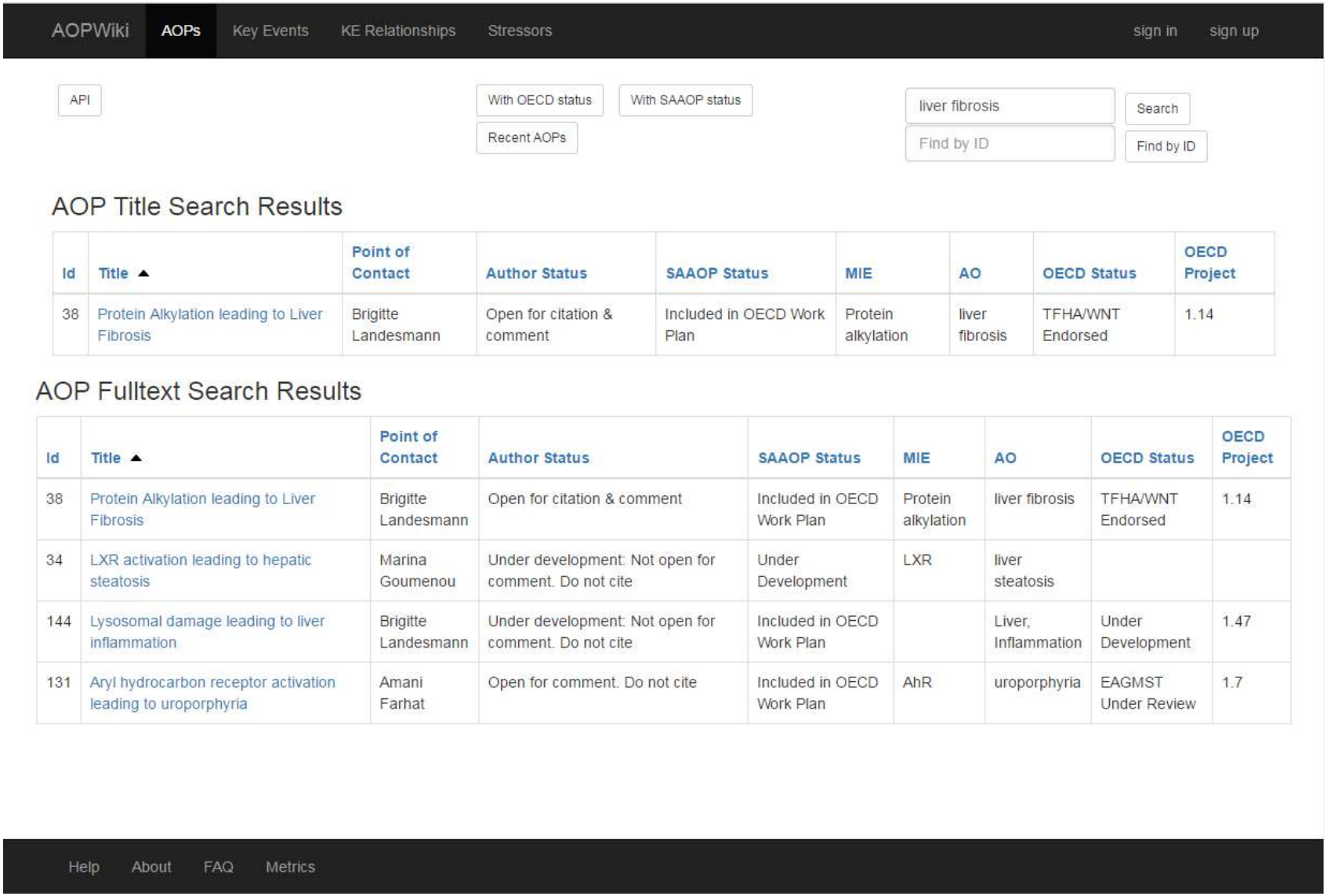
AOP WIKI: search “liver fibrosis”



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

Help | About | FAQ | Metrics

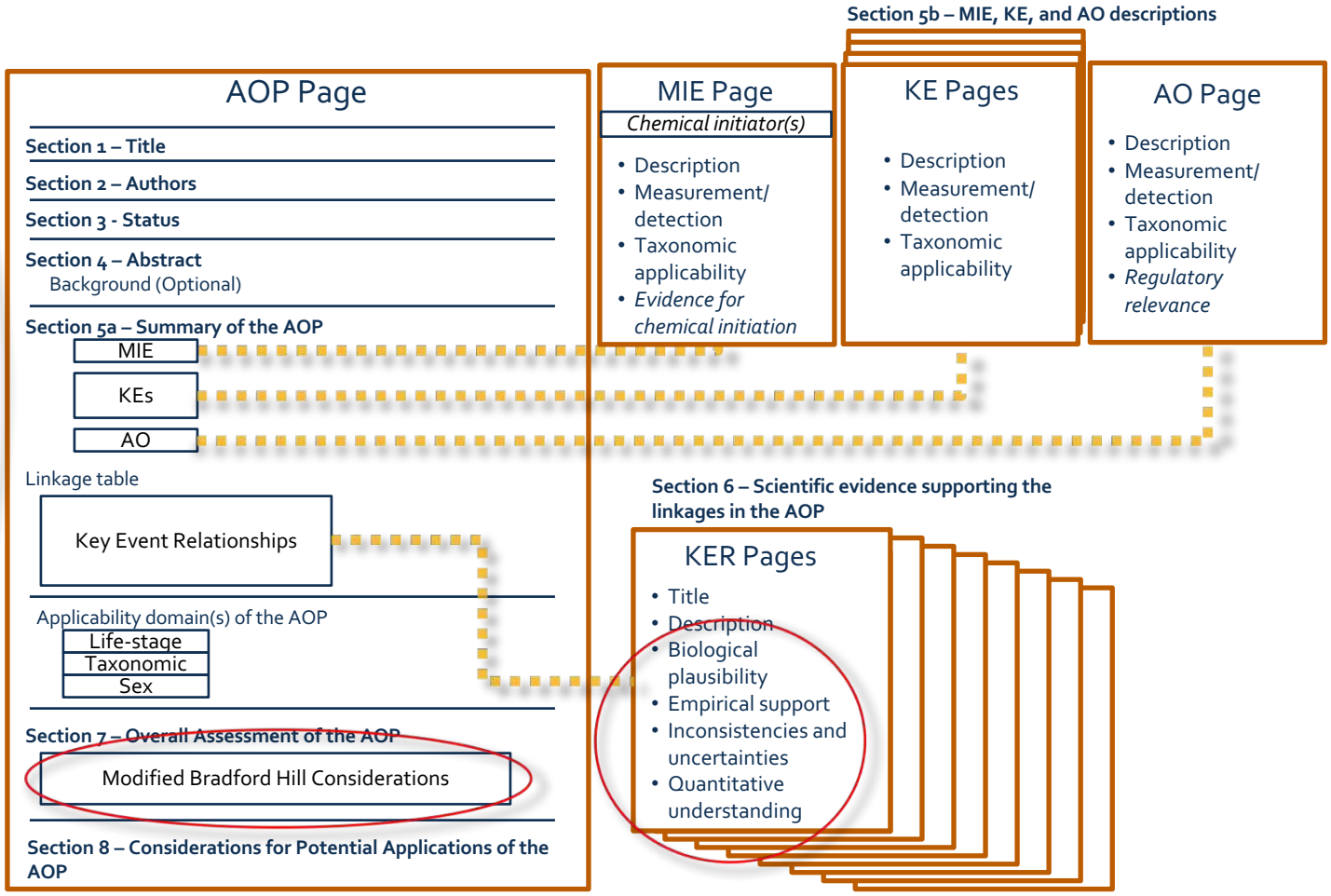
AOP WIKI: information storage and evaluation

OECD Handbook
Step by step guide to AOP development

https://aopkb.org/common/AOP_Handbook.pdf

AOP-Wiki
Provides consistent structure based on the OECD handbook and facilitates collaborative AOP development

http://aopwiki.org/



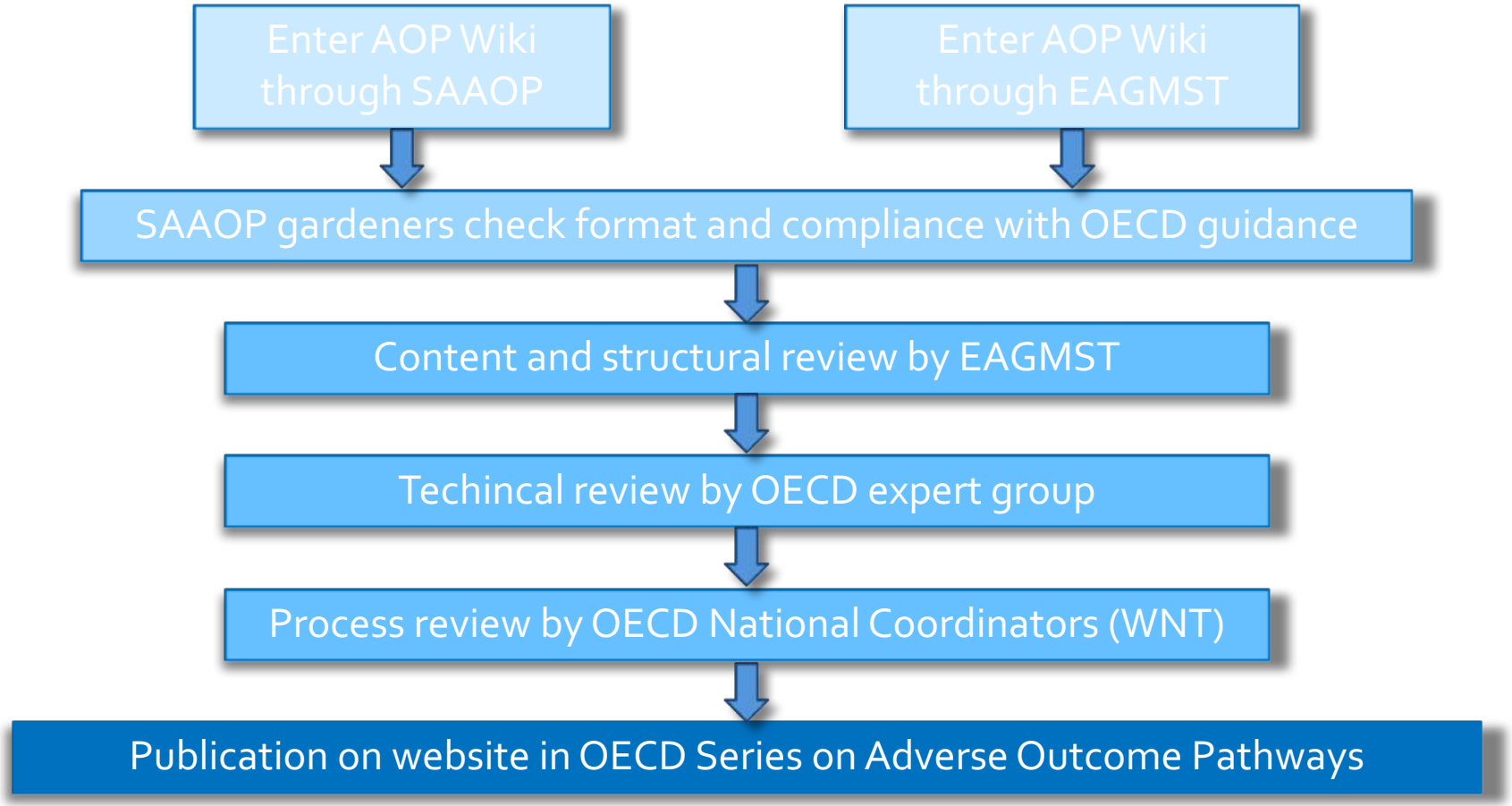
New version of AOP Wiki available in November, 2016

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 inconsitencies

OECD (2014) User's Handbook Supplement to the Guidance Document for Developing and Assessing AOPs. https://aopkb.org/common/AOP_Handbook.pdf.

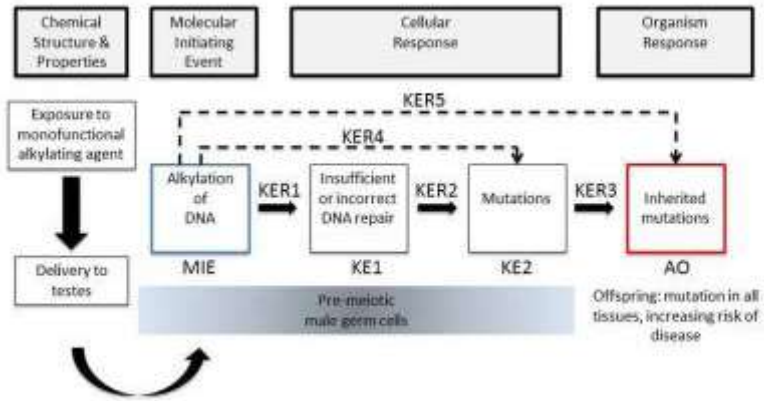
Work Process for Development and Review of AOPs through OECD

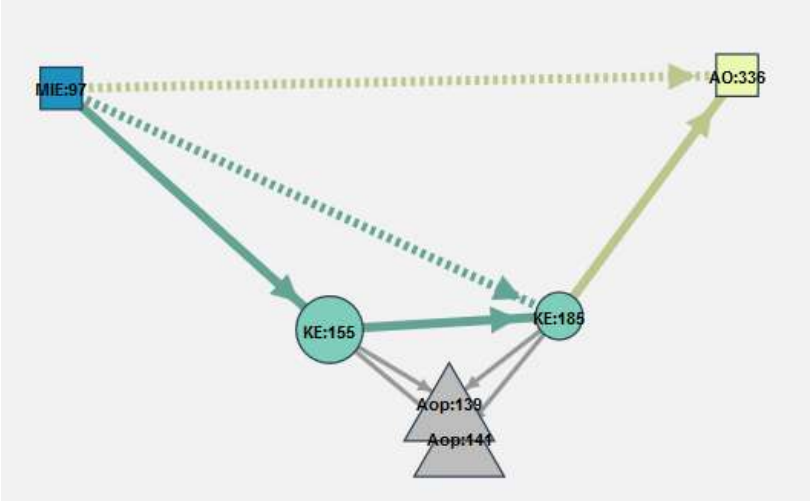


AOP Title

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

Short name: Alkylation of DNA leading to heritable mutations



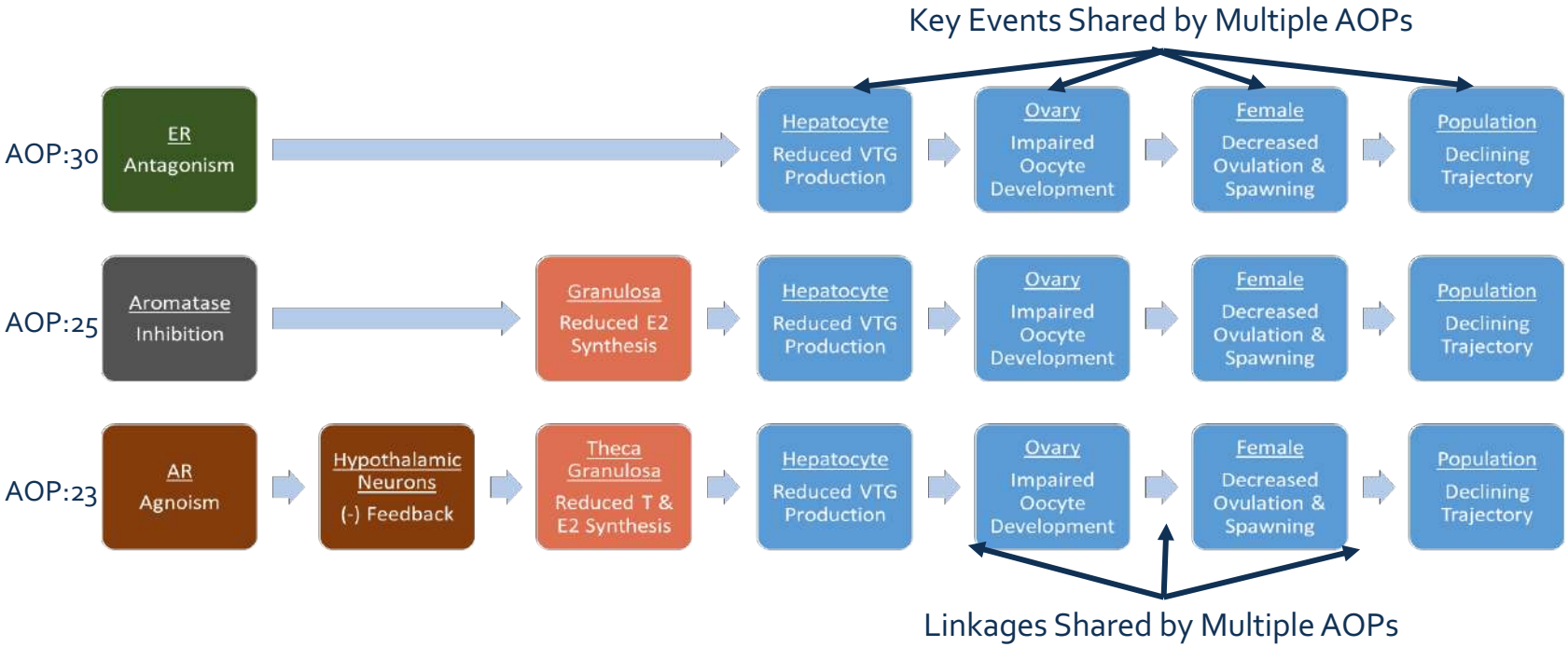


Carole Yauk – https://aopwiki.org/wiki/index.php/Aop:15

Relationships Among Key Events and the Adverse Outcome

Event	Description	Triggers	Weight of Evidence	Quantitative Understanding
DNA, Alkylation	Directly Leads to	Insufficient or incorrect DNA repair, N/A	Strong	Moderate
Insufficient or incorrect DNA repair, N/A	Directly Leads to	Mutations, Increase	Strong	Moderate
DNA, Alkylation	Indirectly Leads to	Mutations, Increase	Strong	Moderate
DNA, Alkylation	Indirectly Leads to	Heritable mutations in offspring, Increase	Strong	Moderate
Mutations, Increase	Directly Leads to	Heritable mutations in offspring, Increase	Strong	Moderate

AOP networks emerge as AOPs are entered into the AOP-Wiki

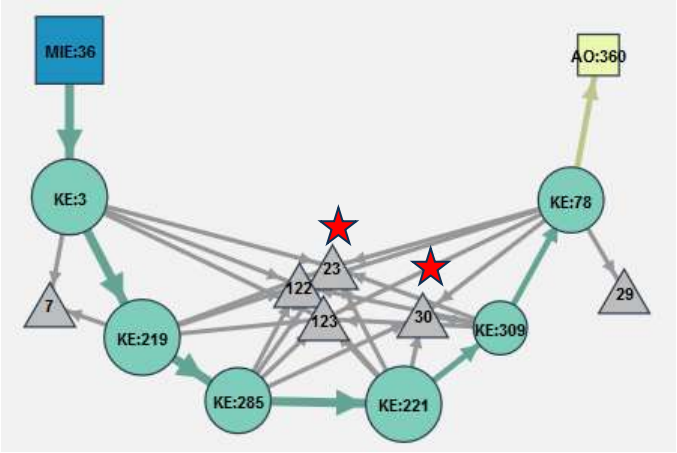


Courtesy of Dan Villeneuve

AOP Title [edit]

Aromatase inhibition leading to reproductive dysfunction (in fish)

Short name: Aromatase inhibition leading to reproductive dysfunction (in fish)

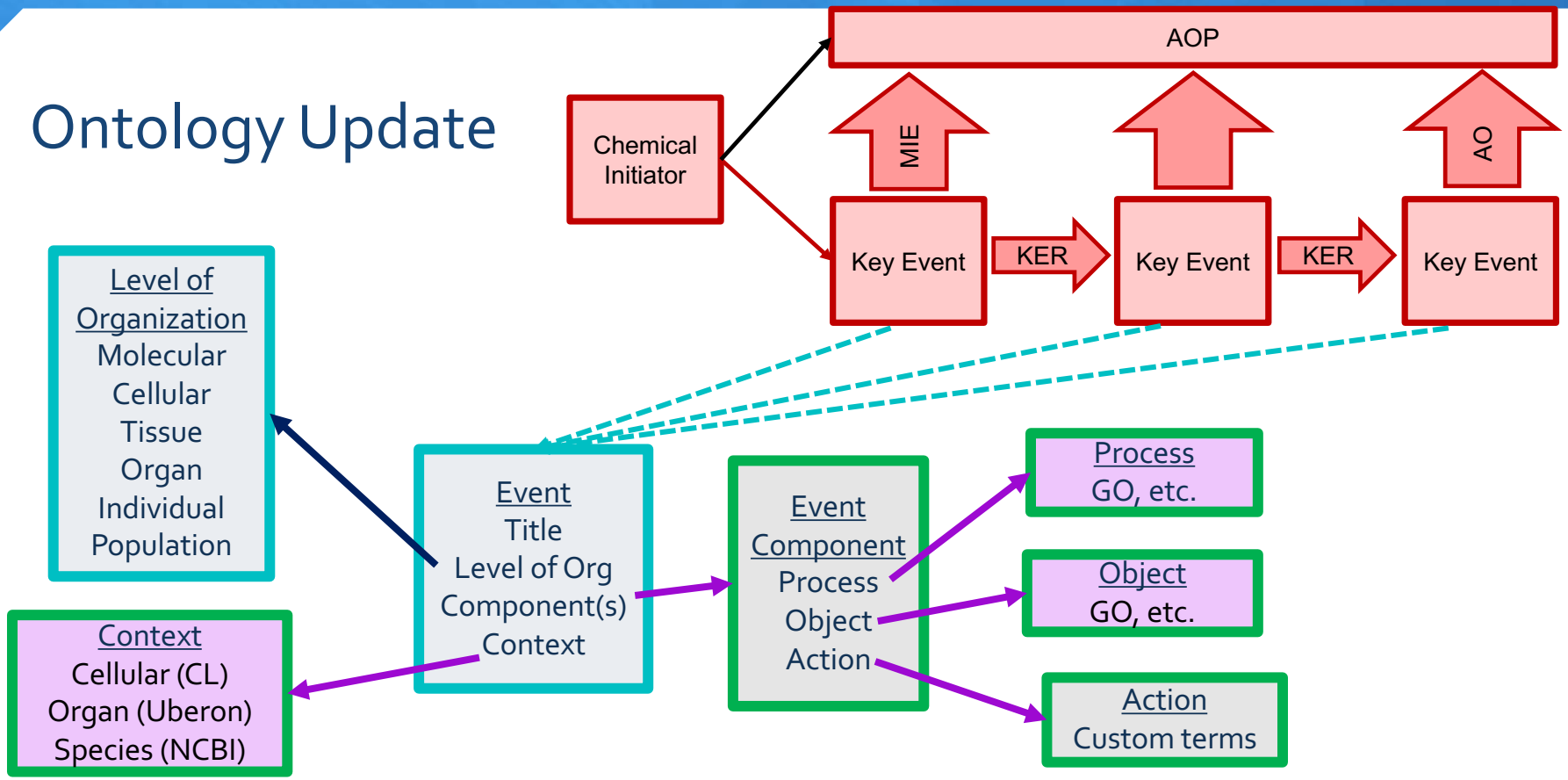


Relationships Among Key Events and the Adverse Outcome

Event	Description	Triggers	Weight of Evidence	Quantitative Understanding
Aromatase, Inhibition	Directly Leads to	17beta-estradiol synthesis by ovarian granulosa cells, Reduction	Strong	Moderate
17beta-estradiol synthesis by ovarian granulosa cells, Reduction	Directly Leads to	Plasma 17beta-estradiol concentrations, Reduction	Strong	Moderate
Plasma 17beta-estradiol concentrations, Reduction	Directly Leads to	Transcription and translation of vitellogenin in liver, Reduction	Strong	Moderate
Transcription and translation of vitellogenin in liver, Reduction	Directly Leads to	Plasma vitellogenin concentrations, Reduction	Strong	Moderate
Plasma vitellogenin concentrations, Reduction	Directly Leads to	Vitellogenin accumulation into oocytes and oocyte growth/development, Reduction	Moderate	Weak
Vitellogenin accumulation into oocytes and oocyte growth/development, Reduction	Directly Leads to	Cumulative fecundity and spawning, Reduction	Moderate	Moderate
Cumulative fecundity and spawning, Reduction	Directly Leads to	Population trajectory, Decrease	Moderate	Moderate

AOP-Wiki Fall 2017 Update

Ontology Update



Steve Edwards, US EPA

Incorporated ontologies

Data Source	Domain	Level of Biological Organizatio					
		M	C	T	O	I	P
OBO Foundry							
Ontology for Biomedical Investigations (OBI)	experiments	Y	X	X	X	X	X
Sequence types and features (SO)	biological sequence	Y	X	X	X	X	X
Chemical Entities of Biological Interest (CHEBI)	biochemistry	Y	X	X	X	X	X
Protein Ontology (PRO)	proteins	Y	X	X	X	X	X
GO	biology	Y	Y	Y	Y	Y	?
Molecular Process Ontology (MOP)	molecular process	Y	X	X	X	X	X
Protein-protein interaction (mi)	experiments	Y	X	X	X	X	X
Cell Ontology (CL)	cells	X	Y	X	X	X	X
Cell Line Ontology (CLO)	in vitro cell line	X	Y	X	X	X	X
BRENDA tissue/enzyme source (bto)*	enzyme source	X	Y	Y	Y	X	X
Foundational Model of Anatomy (FMA)	anatomy	Y	Y	Y	Y	X	X
Uberon	anatomy	?	Y	Y	Y	?	?
Mammalian phenotype (MP)	phenotype	X	Y	Y	Y	Y	X
Human Phenotype Ontology (HP)	phenotype	X	Y	Y	Y	Y	X
Vertebrate Trait (VT)	vertebrate trait	X	X	Y	Y	Y	X
Phenotypic Quality (PATO)	phenotype	Y	Y	Y	Y	Y	Y
Neuro Behavior Ontology (NBO)	behavioral phenotypes	x	x	x	x	Y	x
Population and Community Ontology (PCO)	populations and communities	X	X	X	X	X	Y
NCBI Taxon	taxonomy	X	X	X	X	Y	Y
Non-OBO Foundry							
Experimental Factor Ontology (EFO)*	experiments	Y	Y	Y	Y	Y	Y
AOP-Ontology	adverse outcome pathways	Y	Y	Y	Y	Y	Y
Controlled Vocabulary							
UMLS/Medical Subject Headings (MeSH)	biomedical information	Y	Y	Y	Y	Y	Y

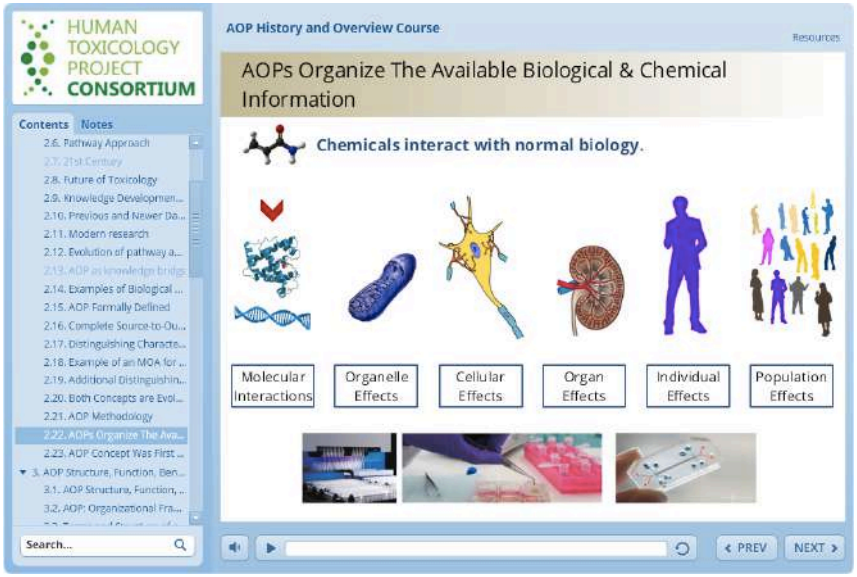
*Molecular, Cellular, Tissue, Organ, Individual, Population
Y = definitely covers this level of organization.
X = definitely doesn't covers this level of organization
?=maybe
*upper level data source

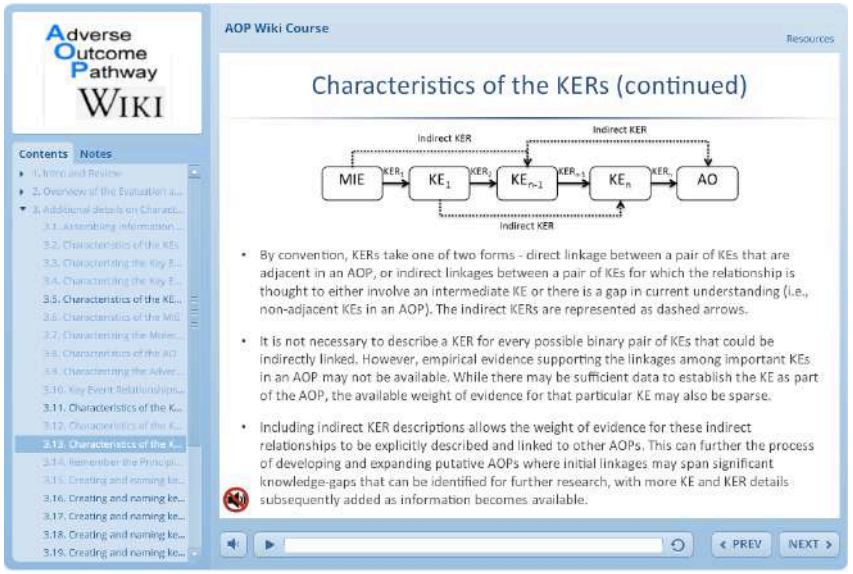
Ontologies and Controlled Vocabularies for Naming Key Events

HTPC Online Course

HUMAN TOXICOLOGY PROJECT CONSORTIUM

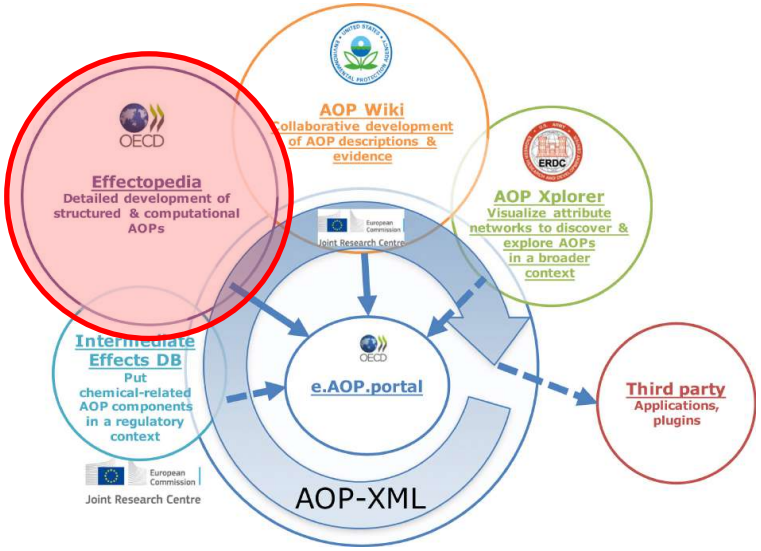
- Two modules: Introduction to AOPs, AOP Wiki Training
- Available as downloads: https://humantoxicologyproject.org/aop-online-course/
- Run directly from AOP Wiki home page: https://aopwiki.org/





Effectopedia

- "Explicitly captures quantitative information"
- Supports OECD review & endorsement of quantitative AOPs
- Quantitative information is intrinsic, supports model development
- 2017



AOP Wiki metrics

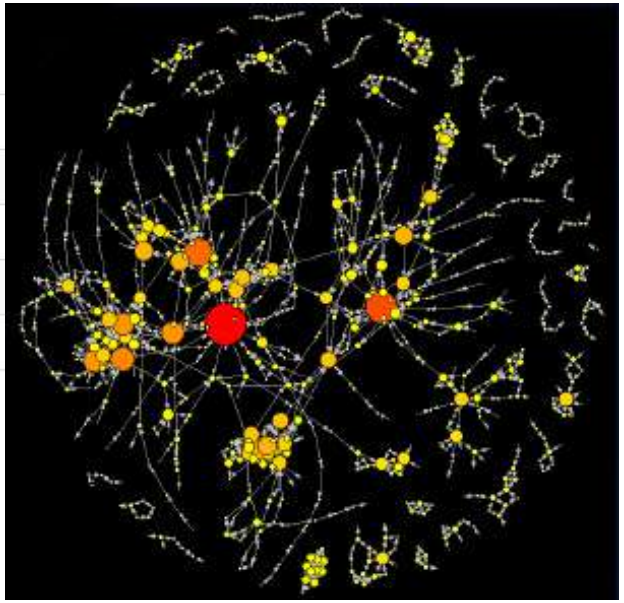
AOPWiki AOPs Key Events KE Relationships Stressors sign in sign up

Available Reports

Summary | AOPS | Key events | KE relationships | Stressors

Reports Summary

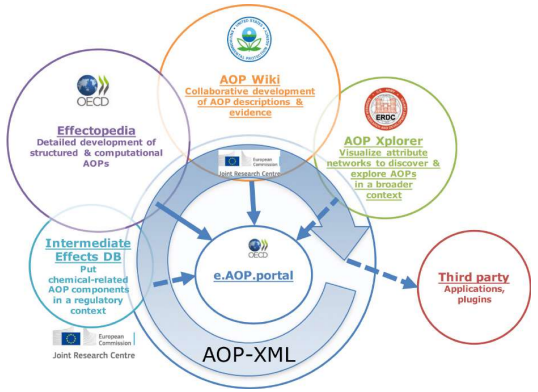
Report	Count
AOPs	207
Key events	1039
KE relationships	1242
Stressors	302

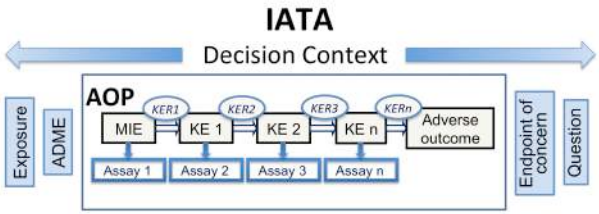


23 June 2017
D. Villeneuve

Concluding remarks

- The "AOP" project is a formal process to collect, organize, link, and evaluate biological information
- Practical solution to a practical problem:
  - Transparent, highly curated, living document representing current knowledge
  - Support better regulatory decisions regarding chemical safety
- Issues:
  - Time and labor-intensive
  - Utility dependent on wide adoption
  - Potential for misunderstanding and mis-application





Thank you!

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