Adverse Outcome Pathway Knowledge Base

Stephen Edwards

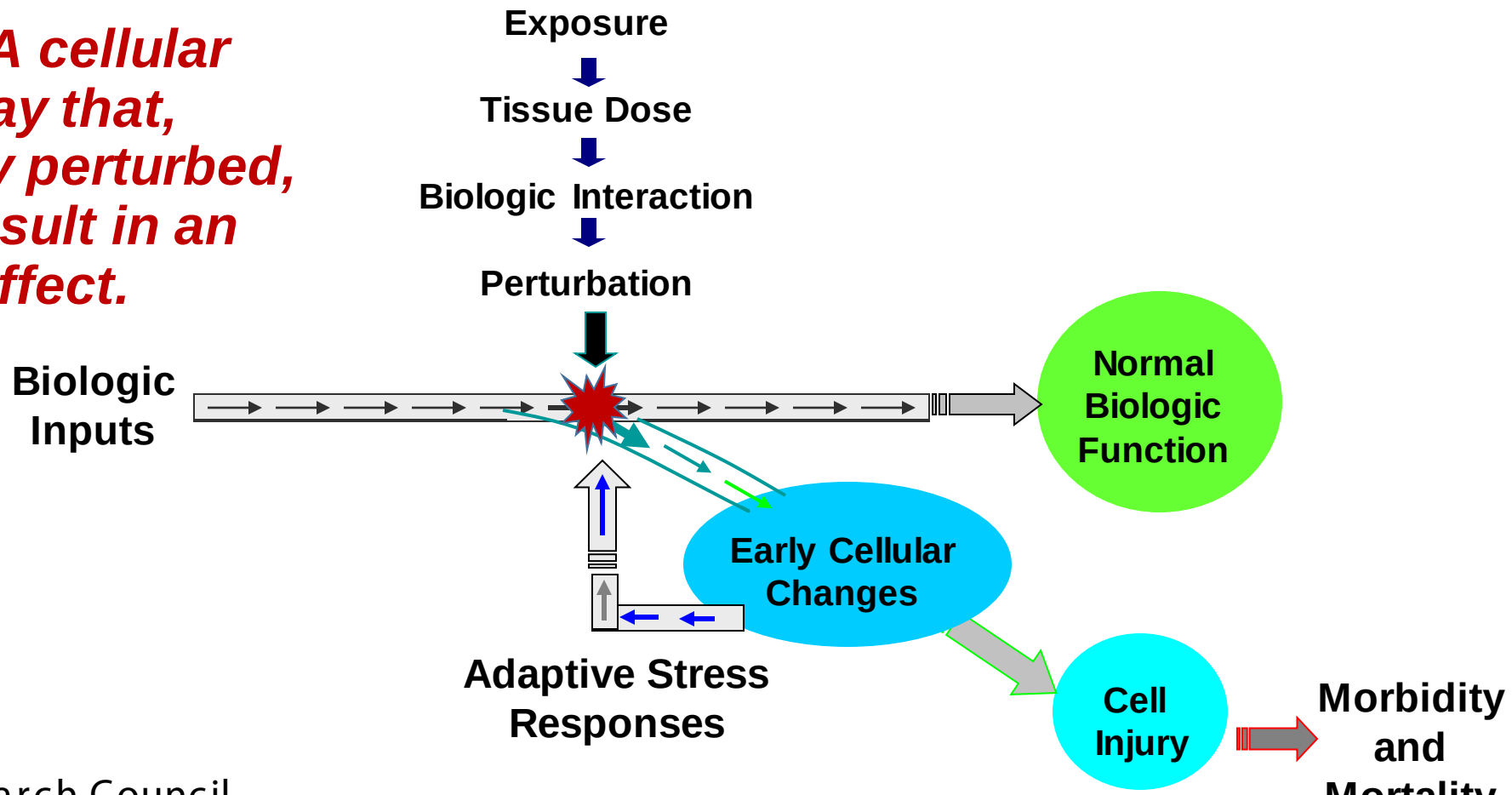
US EPA National Health & Environmental Effects Research Laboratory

U.S. Environmental Protection Agency

The views expressed in this presentation are those of the presenter, and do not necessarily reflect the views and policies of the Agency.

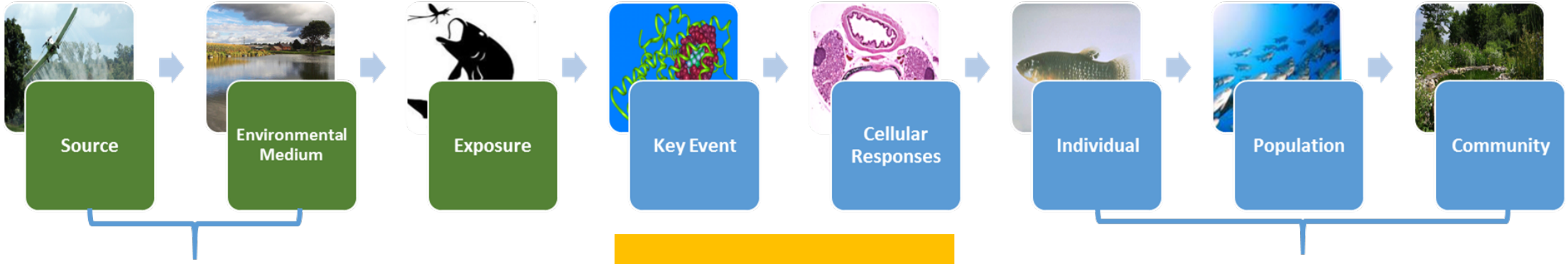
A New Paradigm: Activation of Toxicity Pathways

Toxicity Pathway: A cellular response pathway that, when sufficiently perturbed, is expected to result in an adverse health effect.



Dan Krewski & National Research Council Committee on Toxicity Testing in the 21st Century

Application of Research to Levels of Organization Based on Source to Outcome

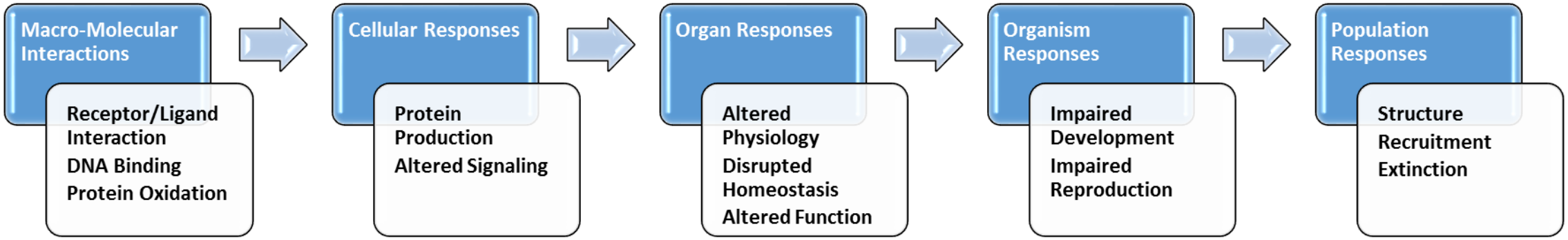


Mode of Action, IPCS/EPA/ILSI 2001-2008

Aggregate Exposure Pathway, Teeguarden 2016

Adverse Outcome Pathway, Ankley 2010, Villeneuve 2014

AOP Components



- Key Events (KEs) - nodes
  - Change in biological state
  - Measurable and essential for progression
  - Molecular Initiating Event (MIE): Initial point of chemical interaction
  - Adverse Outcome (AO): Adverse outcome of regulatory significance
- Key Event Relationships (KERs) - edges
  - Connections between two key events
  - Critical for assembling evidence in support of the AOP
- Does not explicitly include chemicals

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

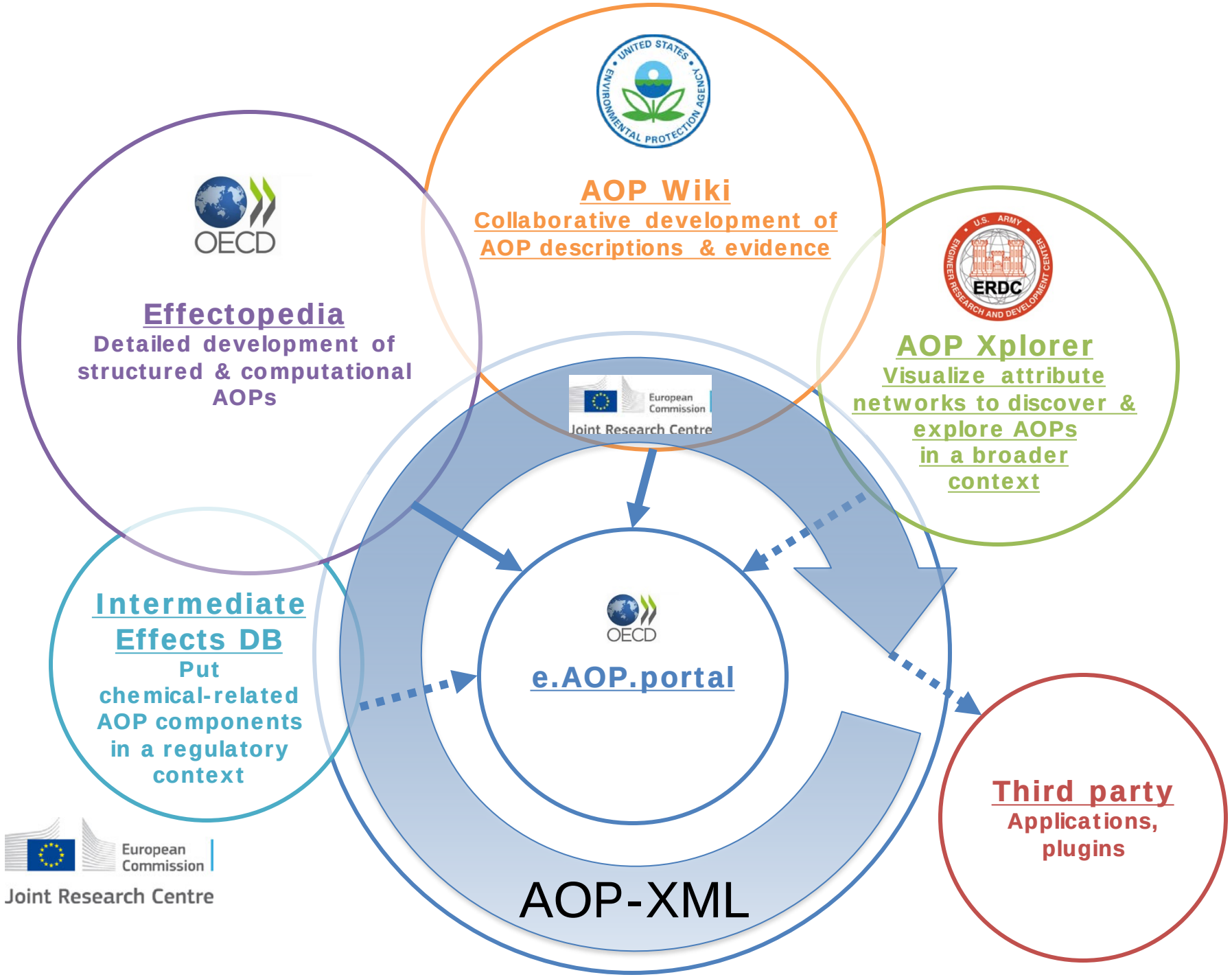
OECD AOP Development Programme

What is an Adverse Outcome Pathway (AOP)

In 2012, the OECD launched a new programme on the development of Adverse Outcome Pathways. An Adverse Outcome Pathway (AOP) is an analytical construct that describes a sequential chain of causally linked events at different levels of biological organisation that lead to an adverse health or ecotoxicological effect (see figure). AOPs are the central element of a toxicological knowledge framework being built to support chemical risk assessment based on mechanistic reasoning.

- Extended Advisory Group for Molecular Screening & Toxicogenomics (EAGMST)
- Guidance & Training
  - Guidance, User Handbook, many training options
- International Knowledgebase to capture information
  - >100 AOPs at various stages of development

http://www.oecd.org/chemicalsafety/testing/adverse-outcome-pathways-molecular-screening-and-toxicogenomics.htm


AOP Wiki
Collaborative development of AOP descriptions & evidence
Effectopedia
Detailed development of structured & computational AOPs
AOP Xplorer
Visualize attribute networks to discover & explore AOPs in a broader context
Intermediate Effects DB
Put chemical-related AOP components in a regulatory context
e.AOP.portal
AOP-XML
Third party
Applications, plugins
European Commission
Joint Research Centre

Five Principles of AOP Development

1. AOPs are not chemical specific
2. AOPs are modular (consisting of KEs and KERs)
3. An individual AOP is a pragmatic unit of development and evaluation
4. For most real-world applications, AOP networks are the functional unit of prediction
5. AOPs are living documents

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

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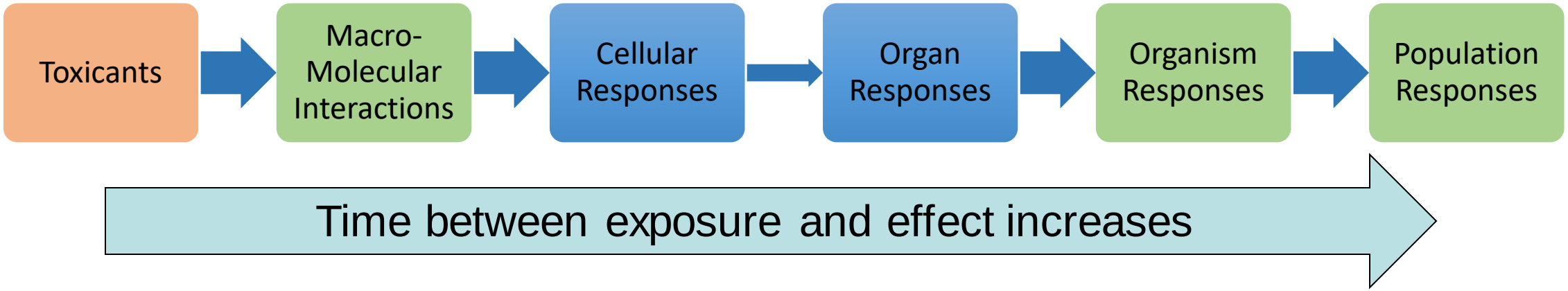
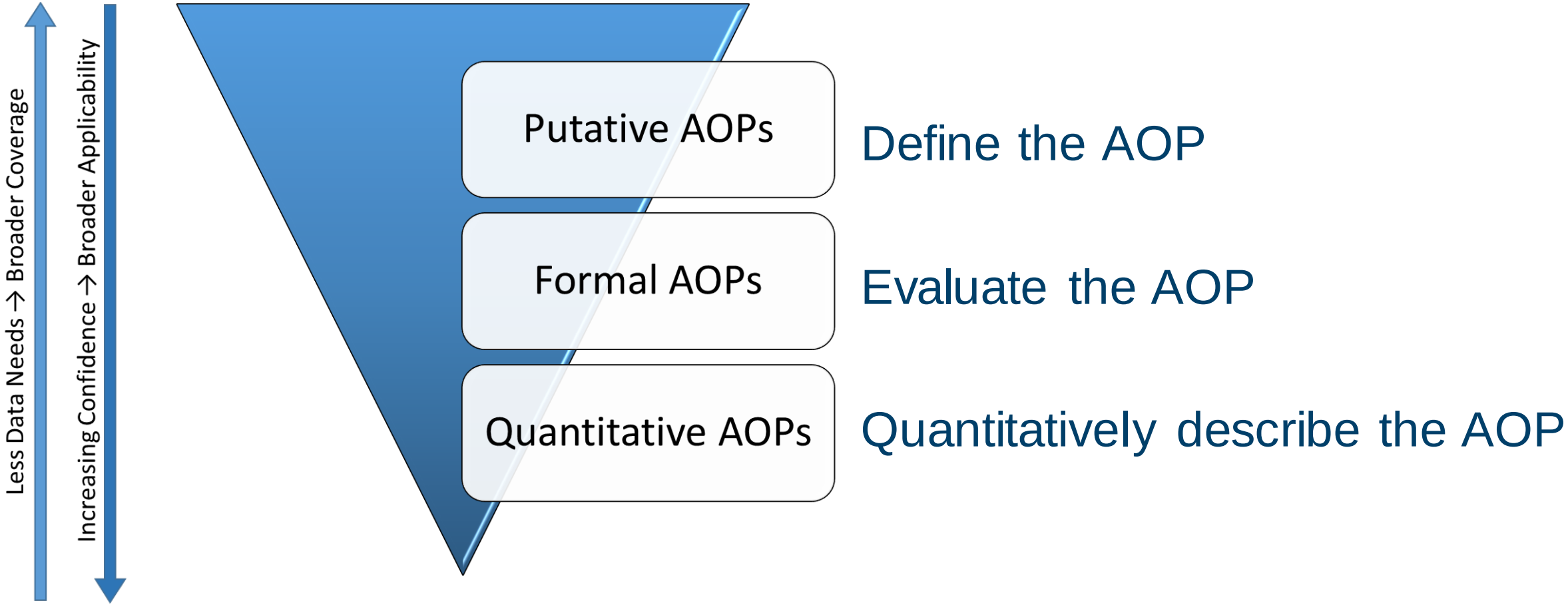
Villeneuve, et al. Tox Sci., 2014, 142:312-320

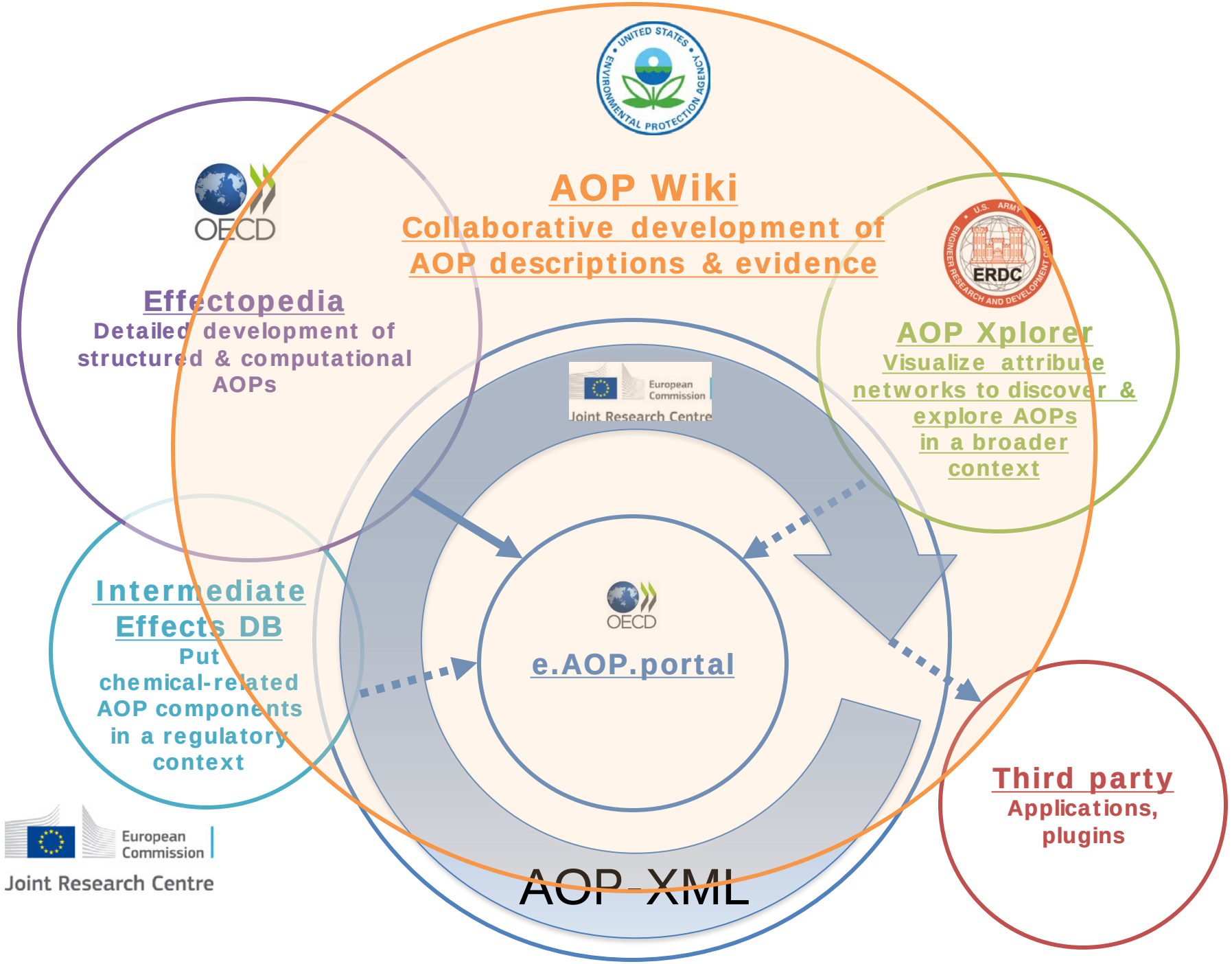
Factors Determining Predictivity of Early Key Events



- Evidence supporting the KERs between that KE and the AO
- Quantitative understanding of the downstream KERs
- Modifying factors that influence downstream KEs & KERs

Overlapping Phases of AOP Development

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ERDC

OECD Handbook

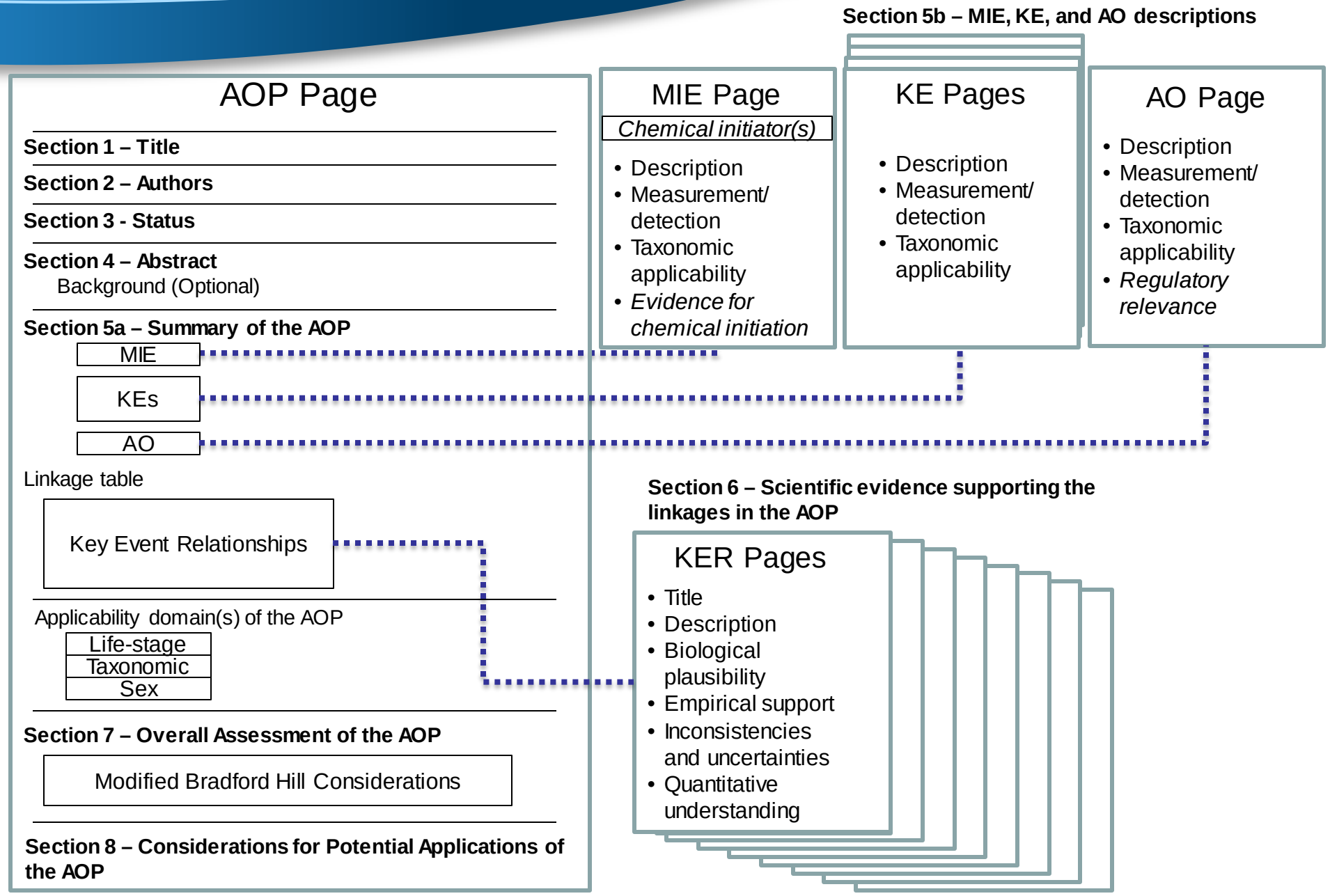
Step by step guide to AOP development

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

AOP-Wiki

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

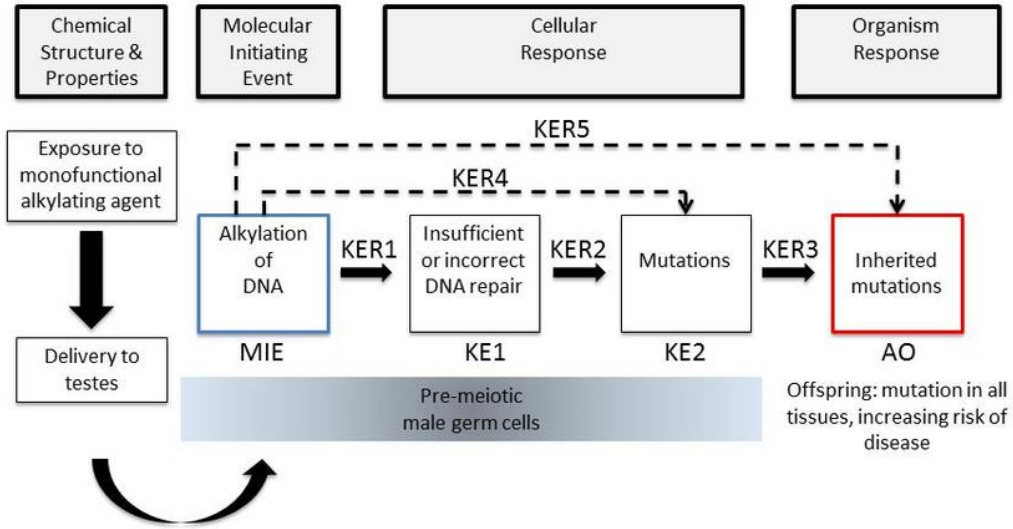
http://aopwiki.org/

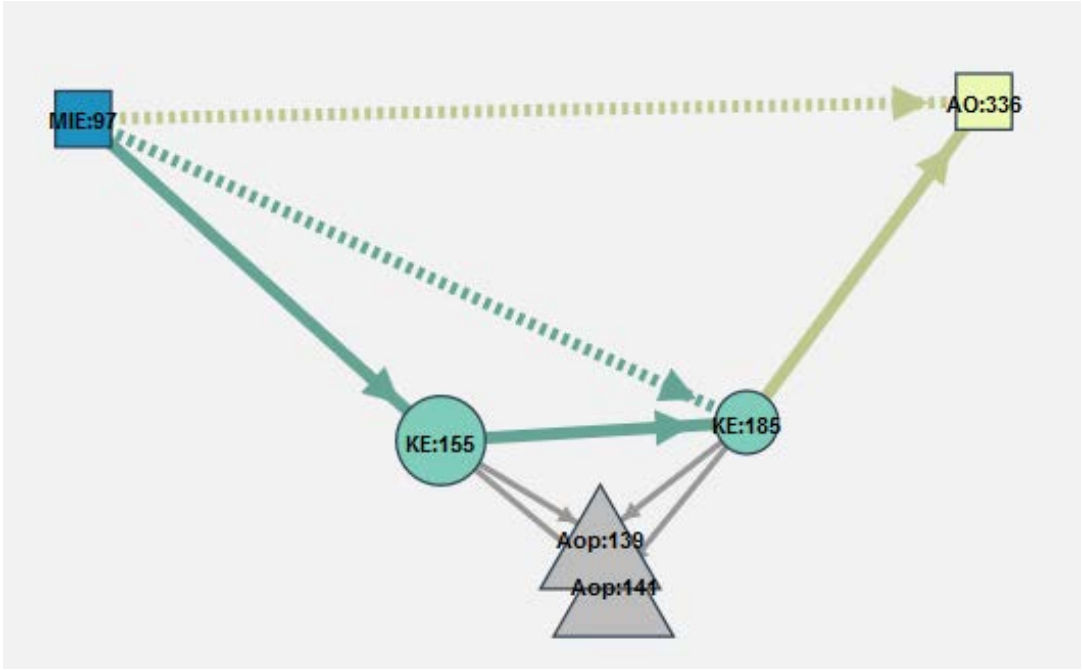


AOP Title

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

Short name: Alkylation of DNA leading to heritable mutations



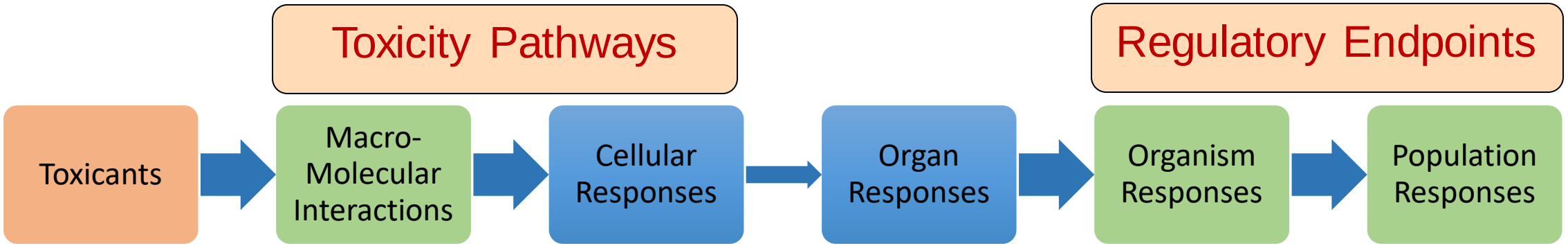


Carole Yauk – https://aopwiki.org/wiki/index.php/Aop:15

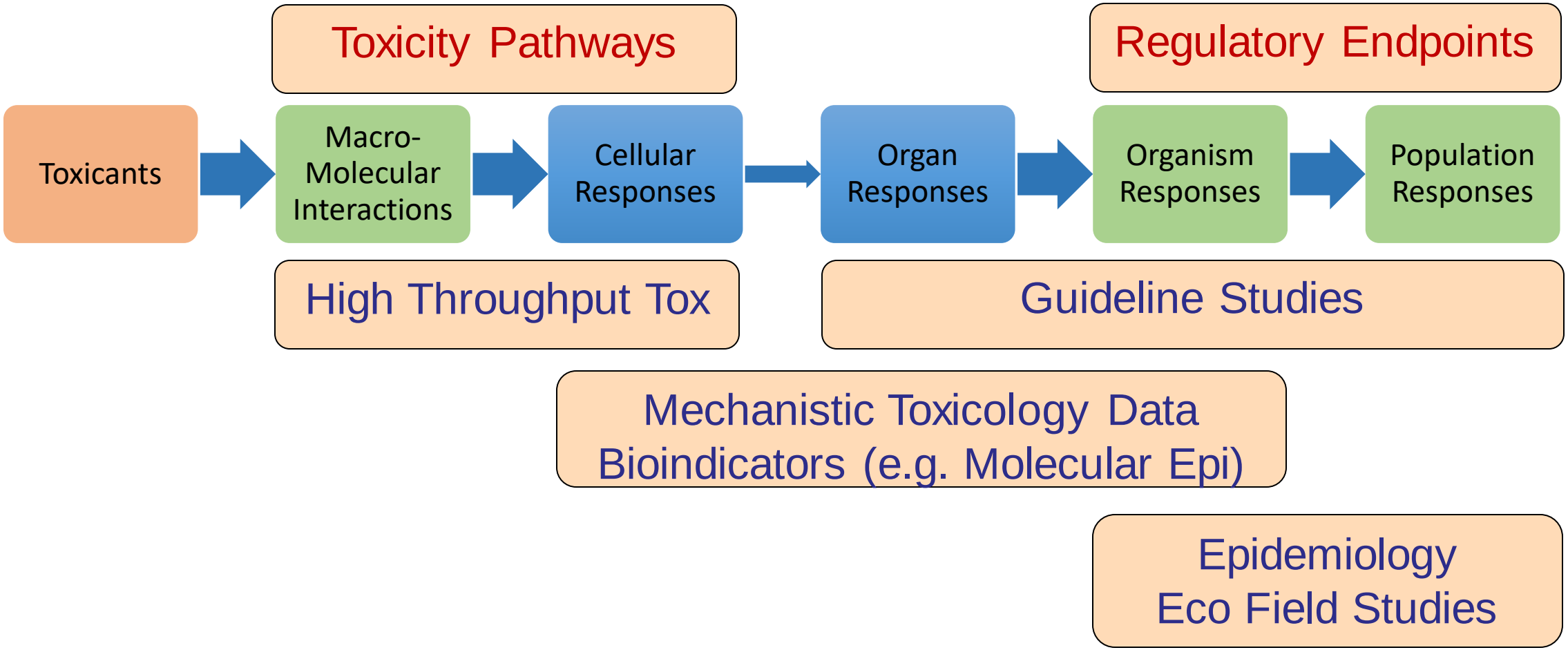
Relationships Among Key Events and the Adverse Outcome

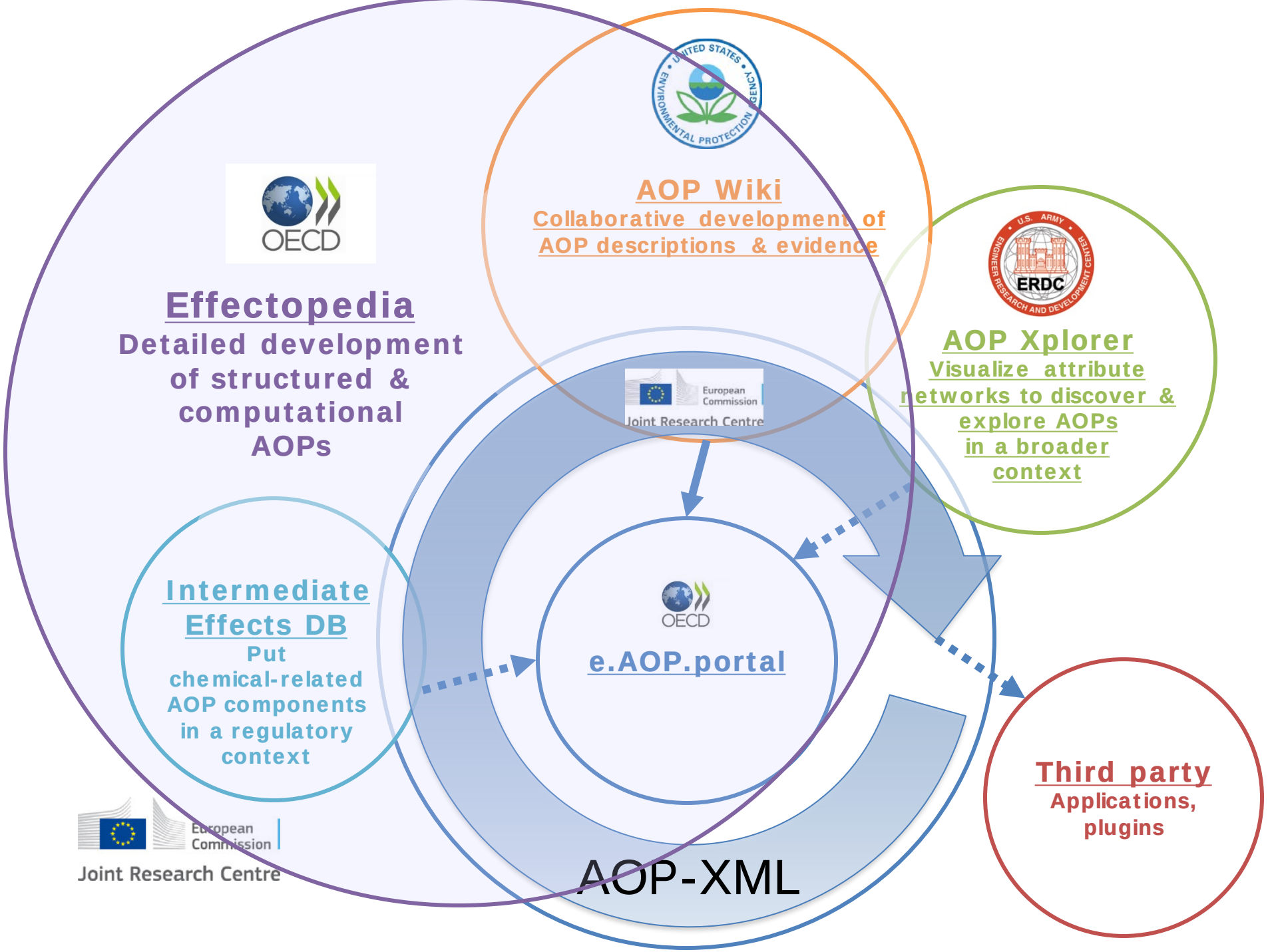
Event	Description	Triggers	Weight of Evidence	Quantitative Understanding
DNA, Alkylation	Directly Leads to	Insufficient or incorrect DNA repair, N/A	Strong	Moderate
Insufficient or incorrect DNA repair, N/A	Directly Leads to	Mutations, Increase	Strong	Moderate
DNA, Alkylation	Indirectly Leads to	Mutations, 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 Provides Understanding & Scaffold for Data



AOP Provides Understanding & Scaffold for Data

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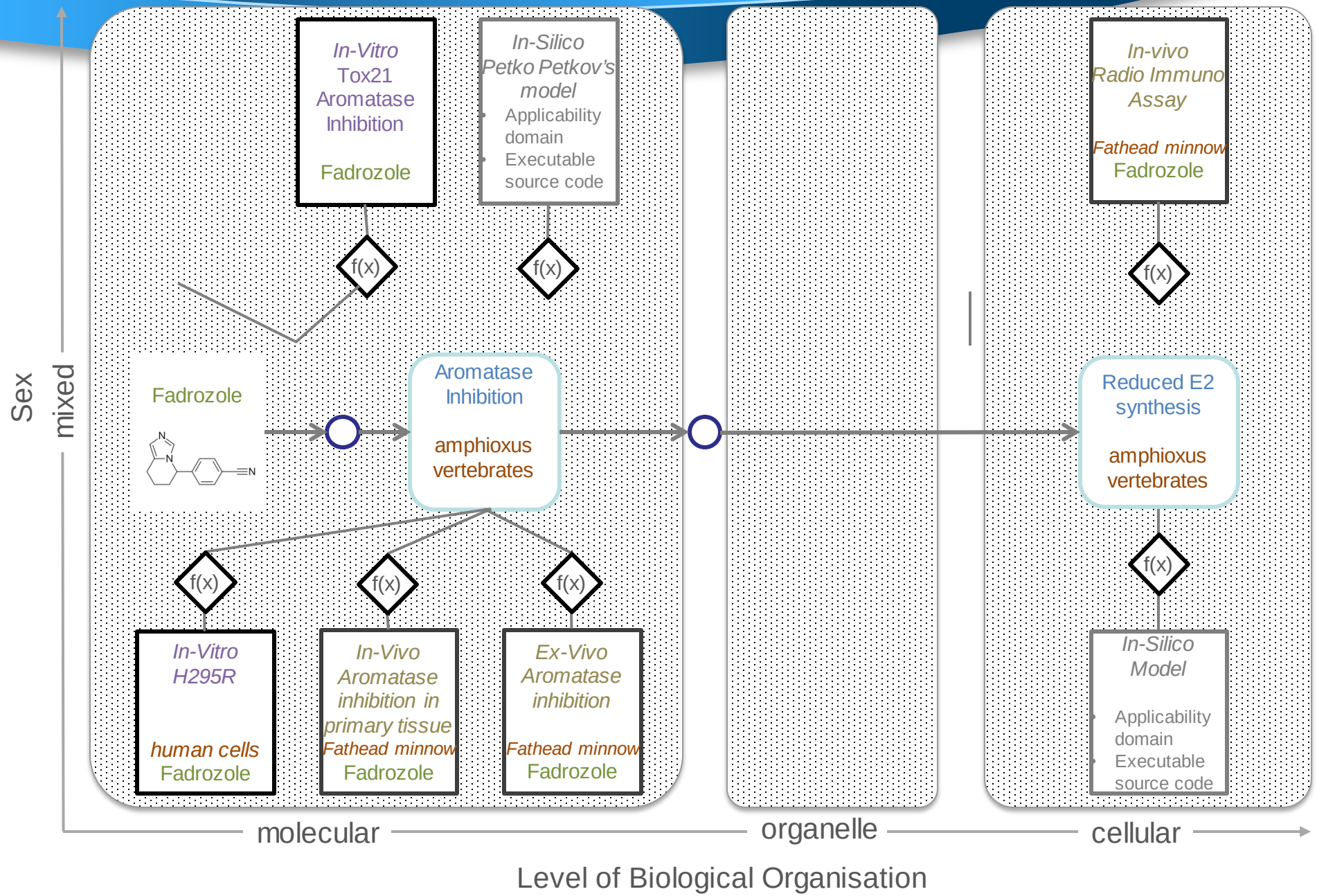
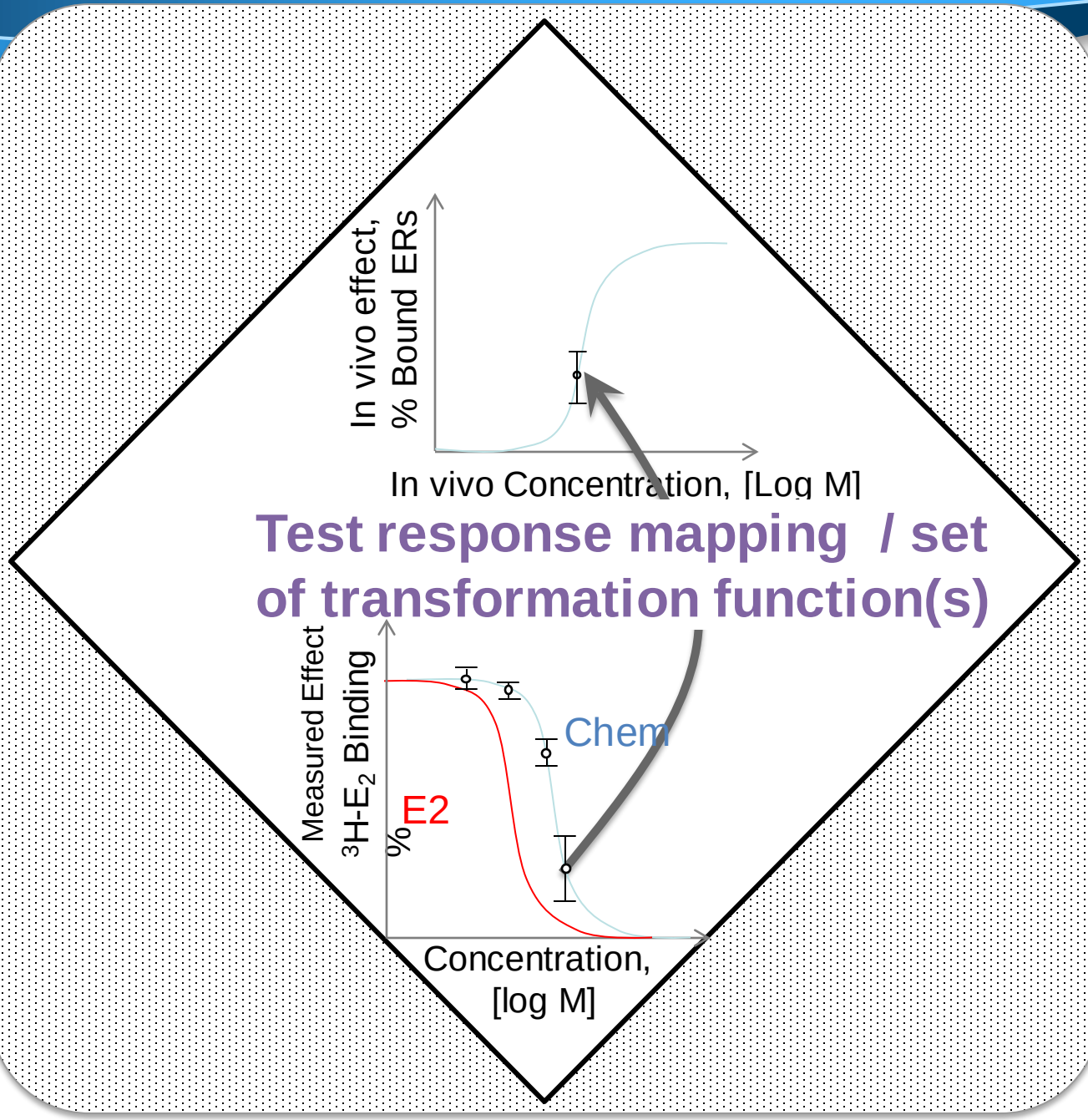
Pathway Elements and quantitative information



Effectopedia
Hristo Aladjov

Pathway elements – test response mapping



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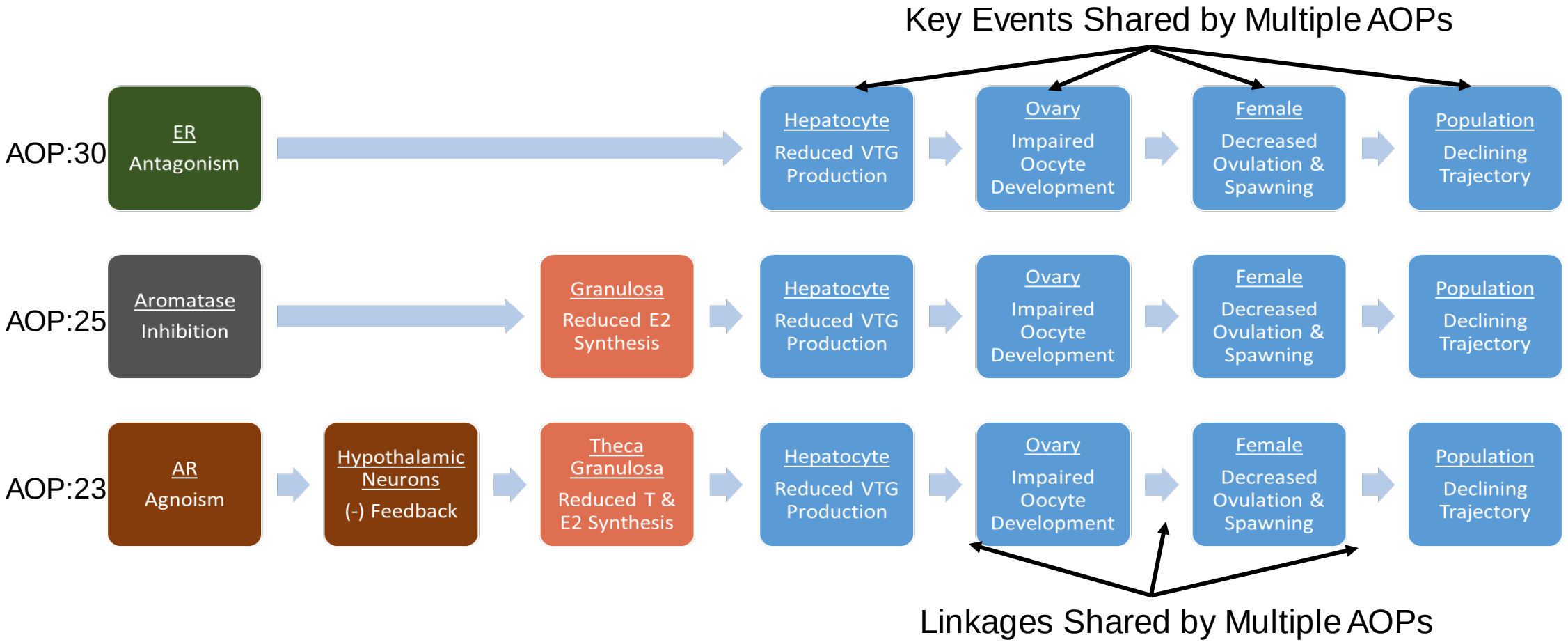
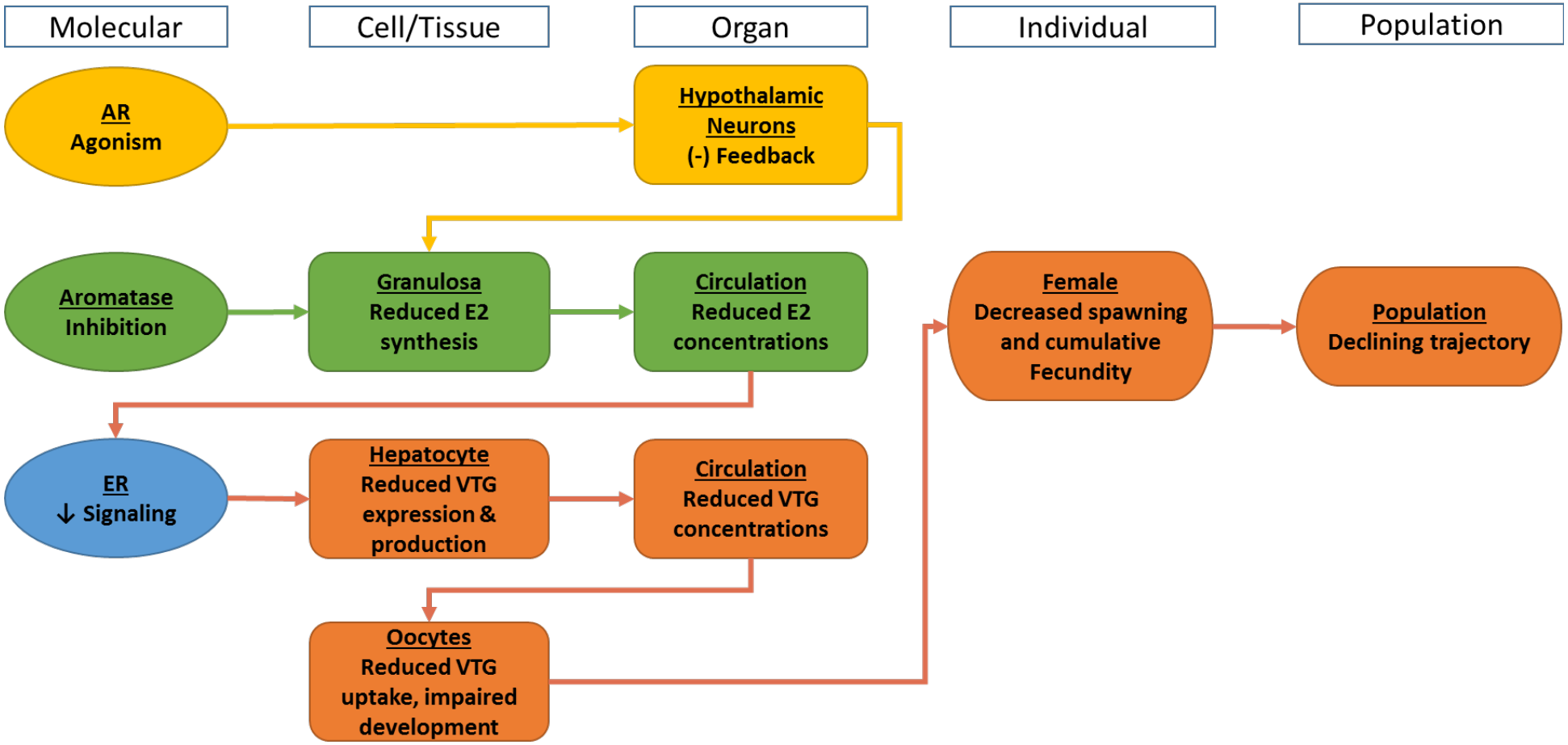
Villeneuve, et al. Tox Sci., 2014, 142:312-320

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



Courtesy of Dan Villeneuve

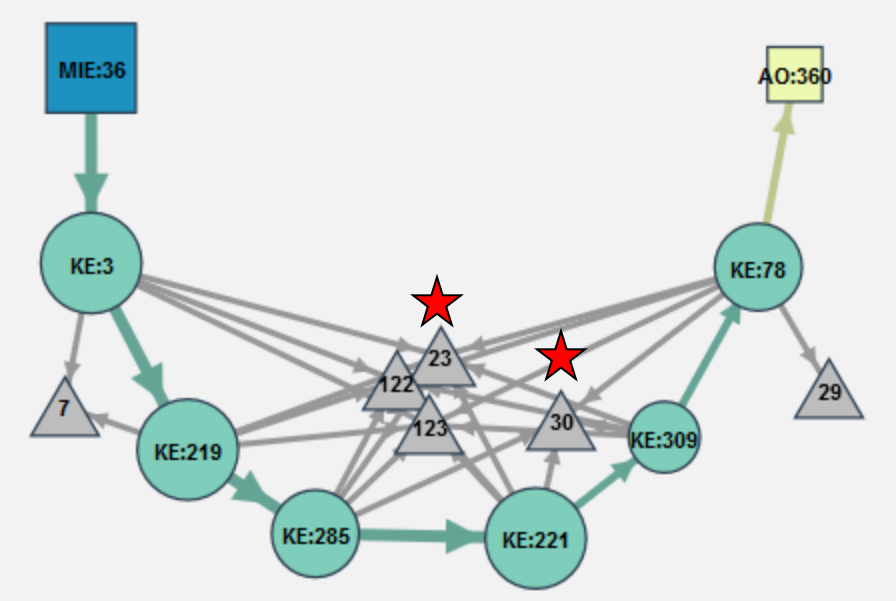
AOP Network as Stored in the AOP-Wiki



AOP Title [edit]

Aromatase inhibition leading to reproductive dysfunction (in fish)

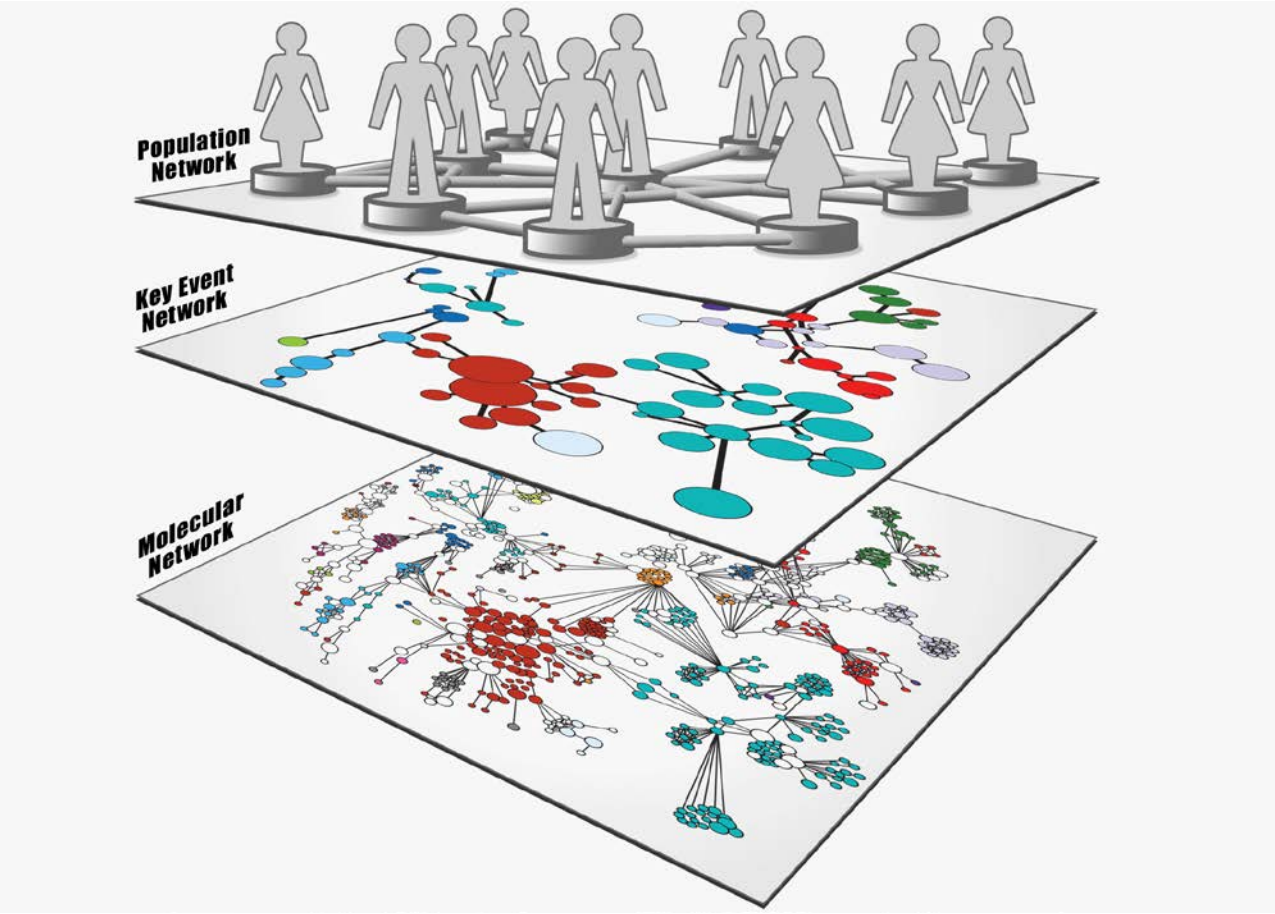
Short name: Aromatase inhibition leading to reproductive dysfunction (in fish)



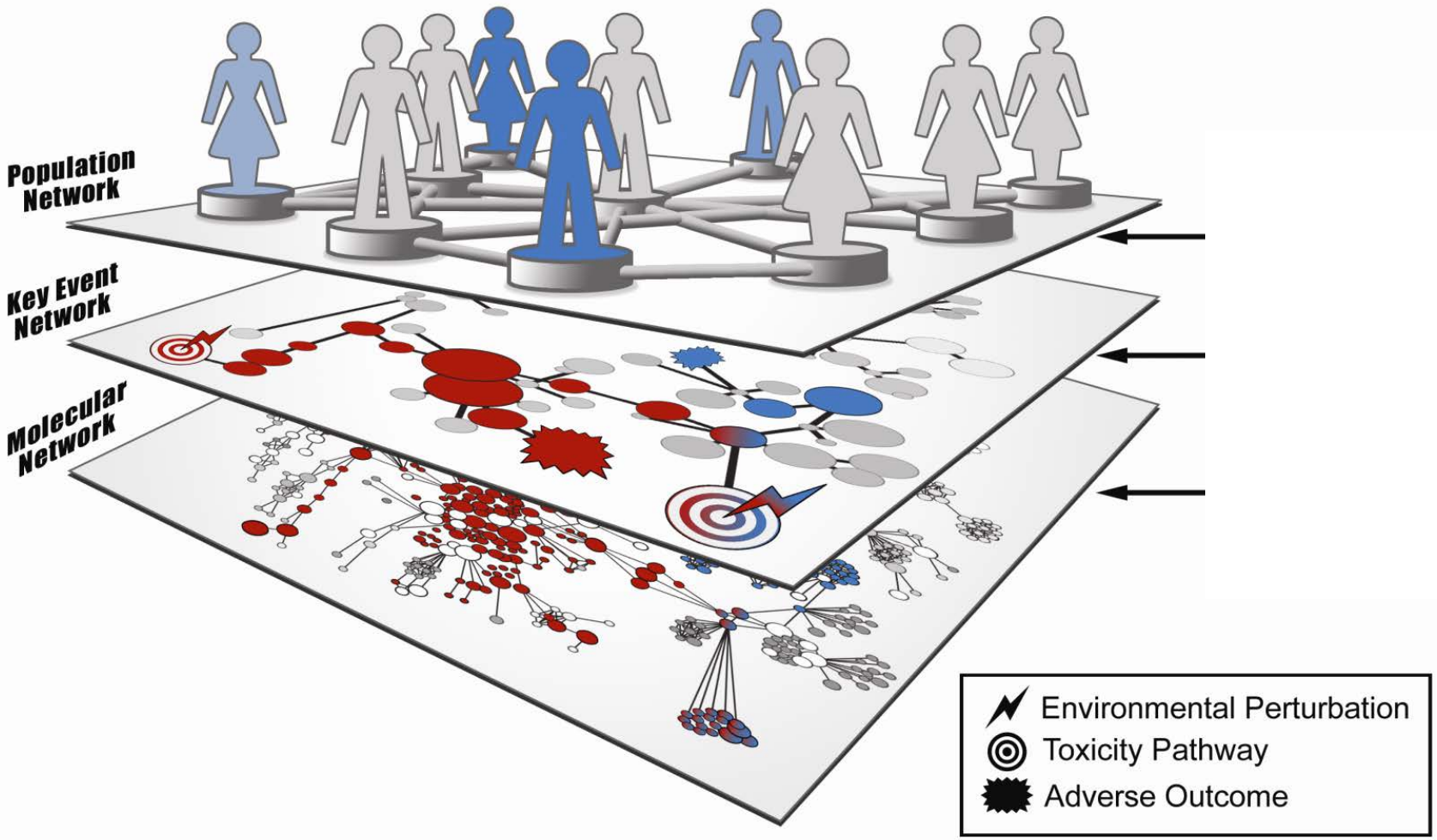
Relationships Among Key Events and the Adverse Outcome

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

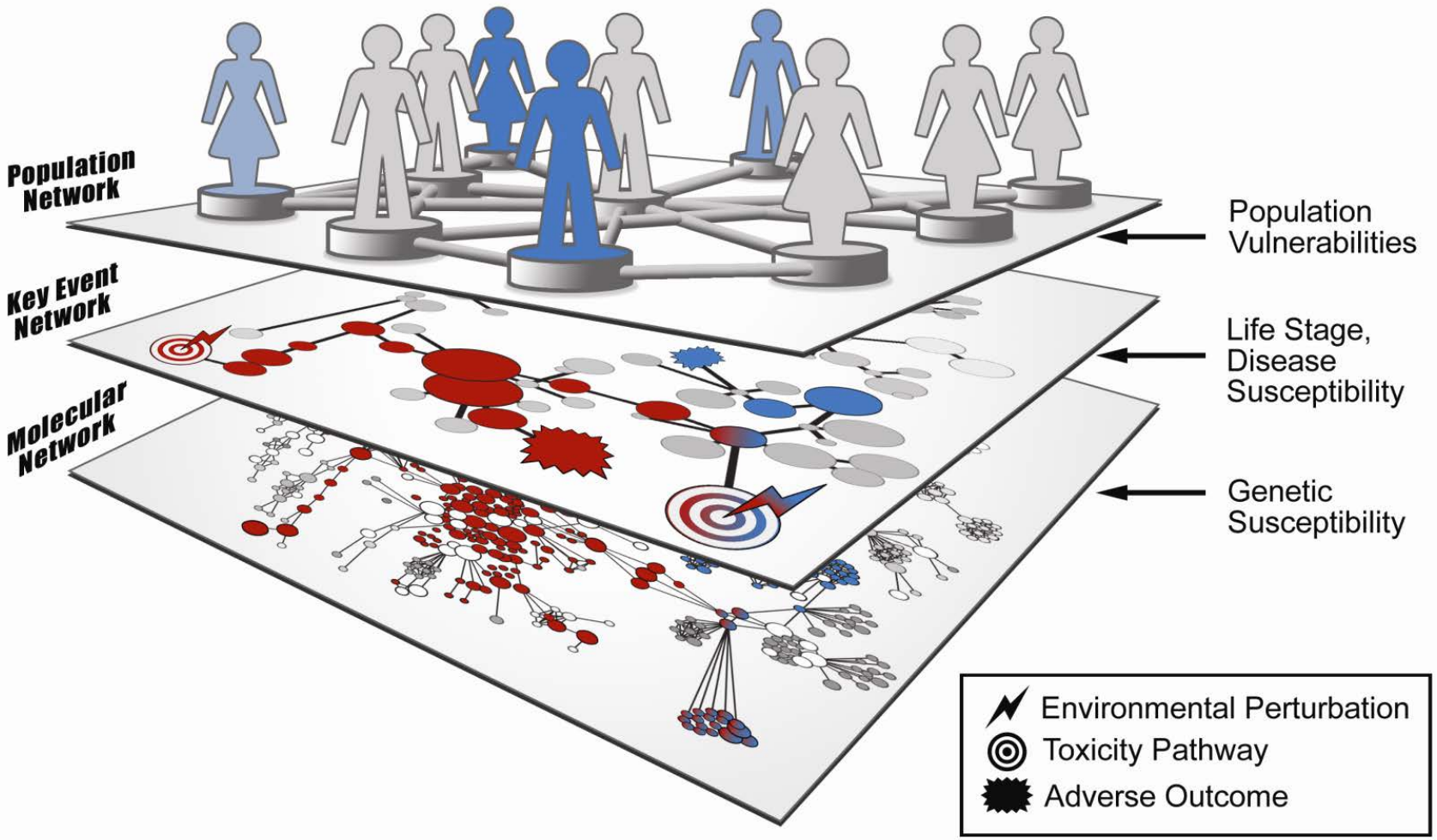
AOPs in a Systems Biology Context



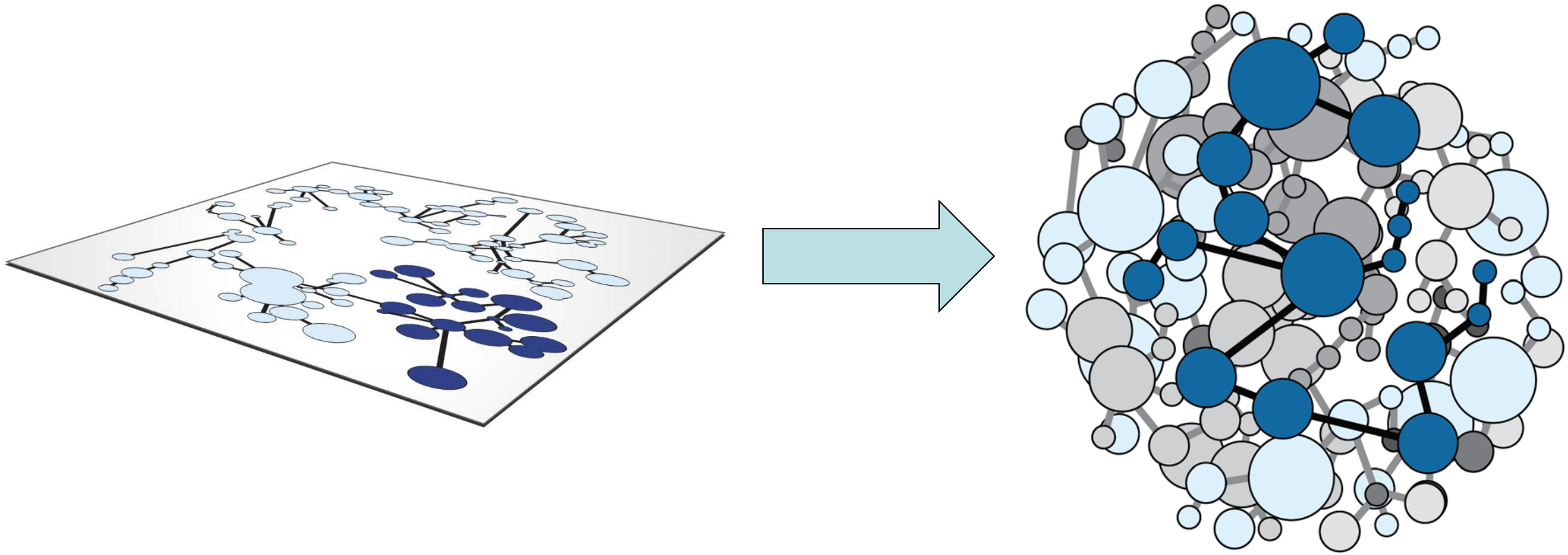
Chemical Interactions Emerge from AOP Networks



Modifying Factors Emerge from AOP Networks

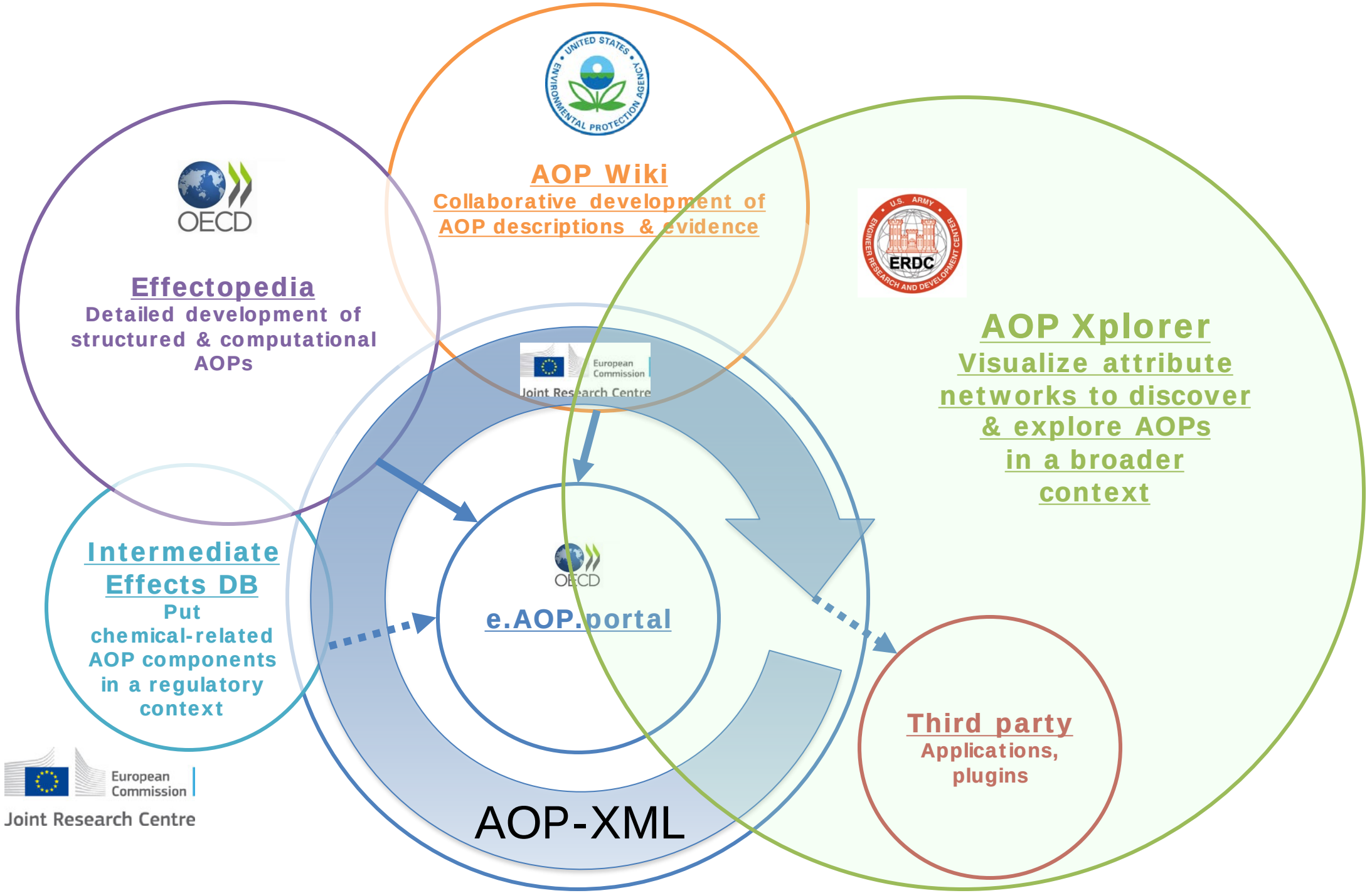


Too many AOPs, too little time…



Accelerating AOP Development

Associations derived from public data sources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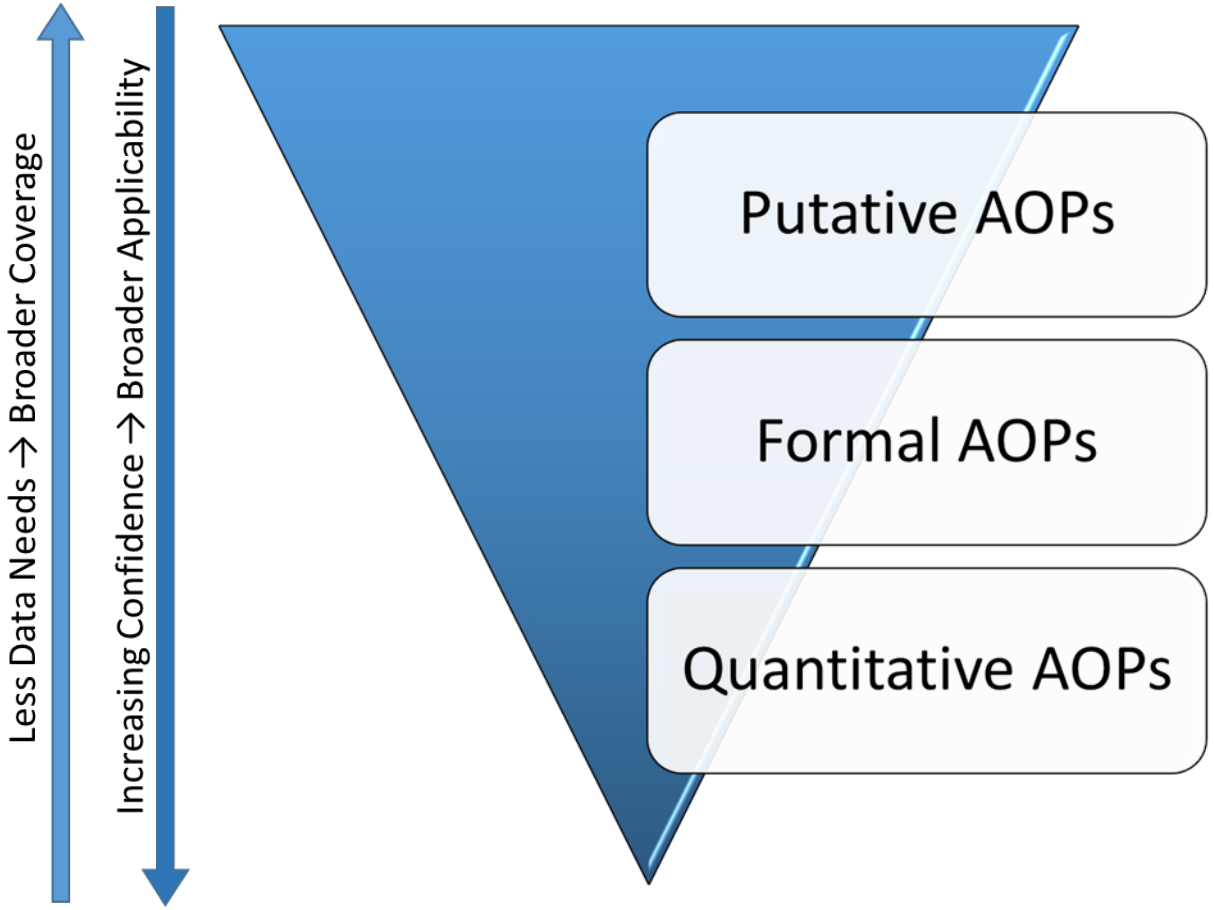
Current Status of AOP Development



> 100 putative AOPs in the AOP-Wiki
(Most not under active development)

13 formal AOPs undergoing OECD review & 6 endorsed

Increasing number of quantitative AOPs under development

OECD Endorsed AOPs

Working Group of the National Coordinators for the Test Guidelines (WNT)
Task Force on Hazard Assessment (TFHA)

OECD Endorsed (WNT and TFHA)

Click here for links to the official OECD versions

Title
Alkylation of DNA in male pre-meiotic germ cells leading to heritable mutations
Aromatase inhibition leading to reproductive dysfunction
Binding of agonists to ionotropic glutamate receptors in adult brain causes excitotoxicity that mediates neuronal cell death, contributing to learning and memory impairment.
Chronic binding of antagonist to N-methyl-D-aspartate receptors (NMDARs) during brain development induces impairment of learning and memory abilities
Covalent Protein binding leading to Skin Sensitisation
Protein Alkylation leading to Liver Fibrosis

OECD AOP-KB Working Group

- Stephen Edwards
- Dan Villeneuve
- Kevin Crofton
- Gary Ankley
- Robert Kavlock

- David Lyons
- Max Felsher
- Rose Combs
- Landon Grindheim
- Cataia Ives
- Brendan Ferreri-Hanberry
- Evgeniia Kazymova

- Clemens Wittwehr
- Brigitte Landesmann
- Ivana Campia
- Sharon Munn
- Ahmed Sayed
- Maurice Whelan

- Hristo Aladjov
- Magda Sachana
- Joop DeKnecht

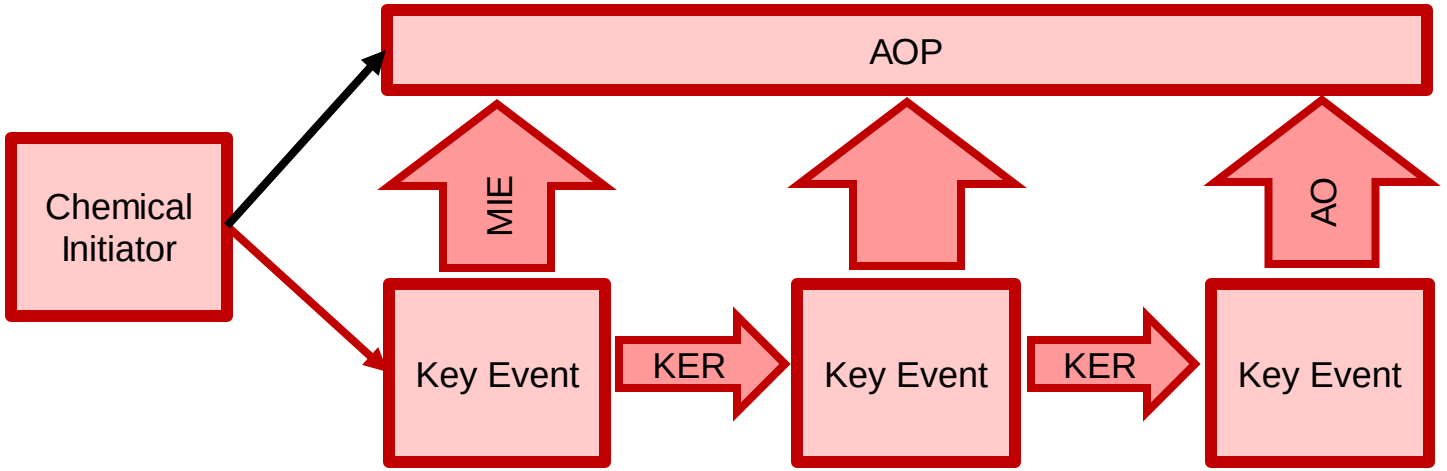
- Ed Perkins
- Lyle Burgoon
- Natalia Garcia Reyero

- Collaborative Partners
  - OECD External Advisory Group on Molecular Screening & Toxicogenomics
  - IPCS/WHO Mode of Action Steering Committee

AOP-Wiki 2.0 Release – November 2016

- Ability to provide more information through web services
  - Most new web services will come online in 2017
- Will incorporate ontologies to better characterize key events
- Improved snapshots for OECD reviews
- Improved help
- Will include better handling of chemicals
  - Connection with the EPA CompTox Dashboard (https://comptox.epa.gov/dashboard)
- Test version available in September

Core AOP Ontology
Describes AOP components only



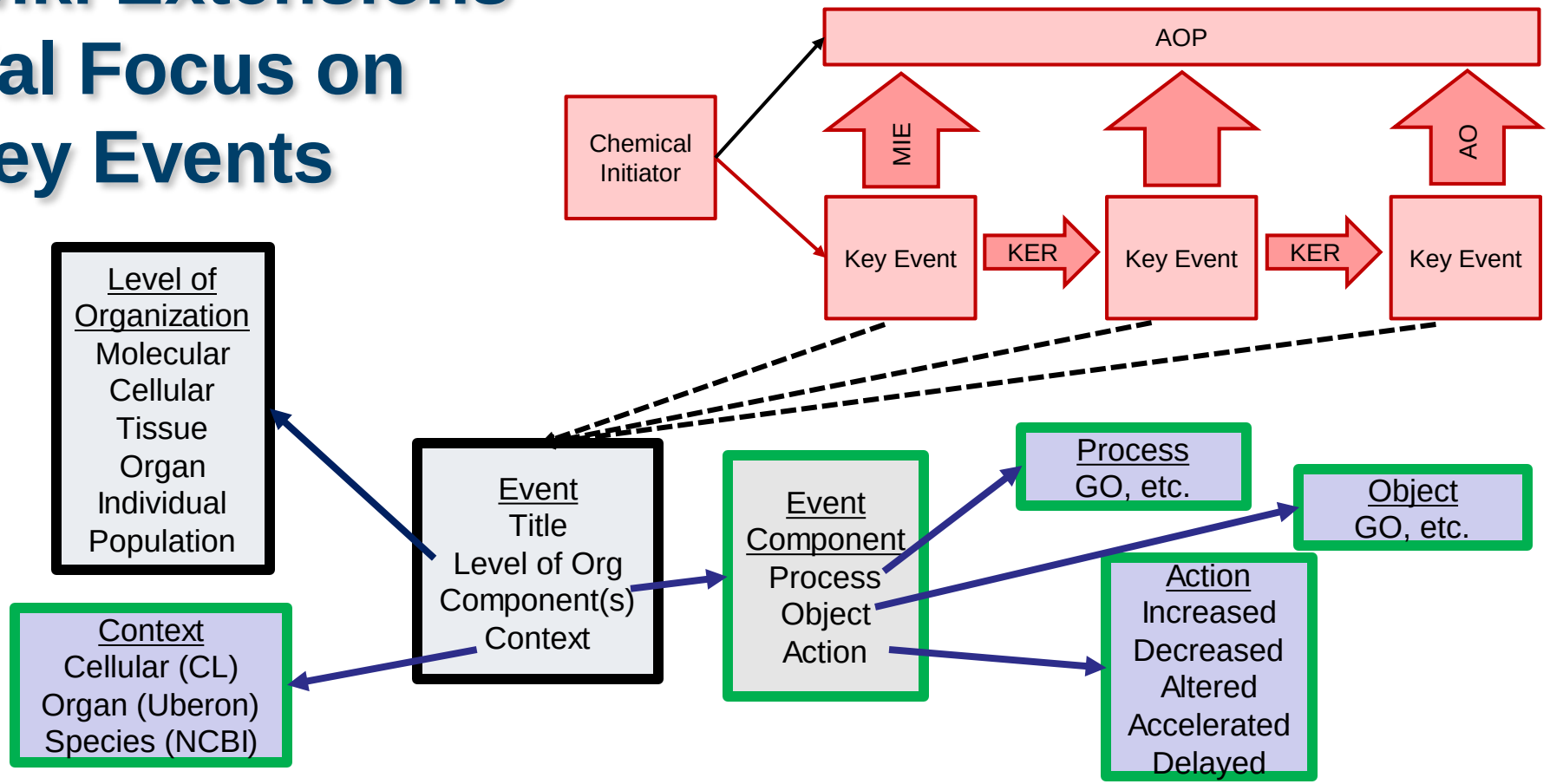
AOP Ontology Developed & Maintained by Lyle Burgoon:
https://github.com/DataSciBurgoon/aop-ontology

Lyle Burgoon
Kyle Painter

Extending the Core AOP Ontology

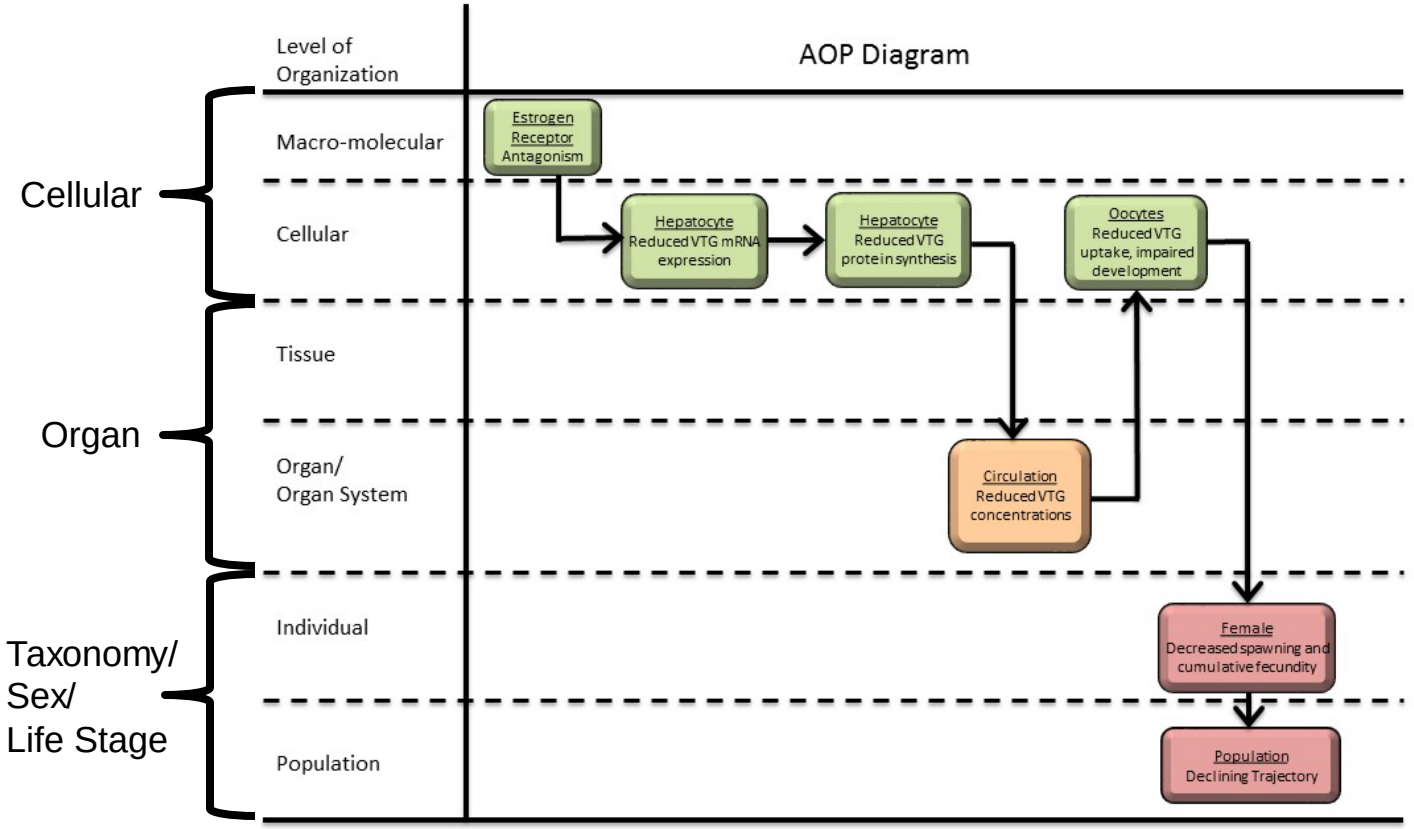
- Core AOP Ontology is extended by incorporating existing chemical and biological ontologies
- US ACE – Extending core ontology to illustrate proof of concept for reasoners in risk assessment
- US EPA – Extending core ontology to capture AOP-Wiki information
- EC JRC – Extending core ontology to inform OECD 201 and the Intermediate Effects Database
- OECD Ontology Working Group – Oversees efforts and ensures compatibility with other related ontology efforts

AOP-Wiki Extensions Initial Focus on Key Events



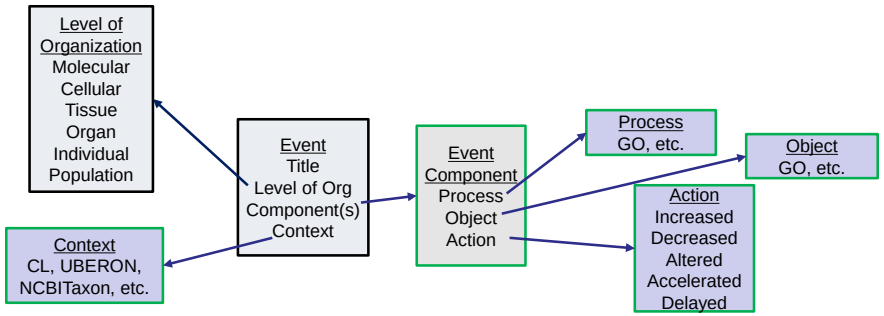
Cataia Ives

Context changes across levels of biological organization

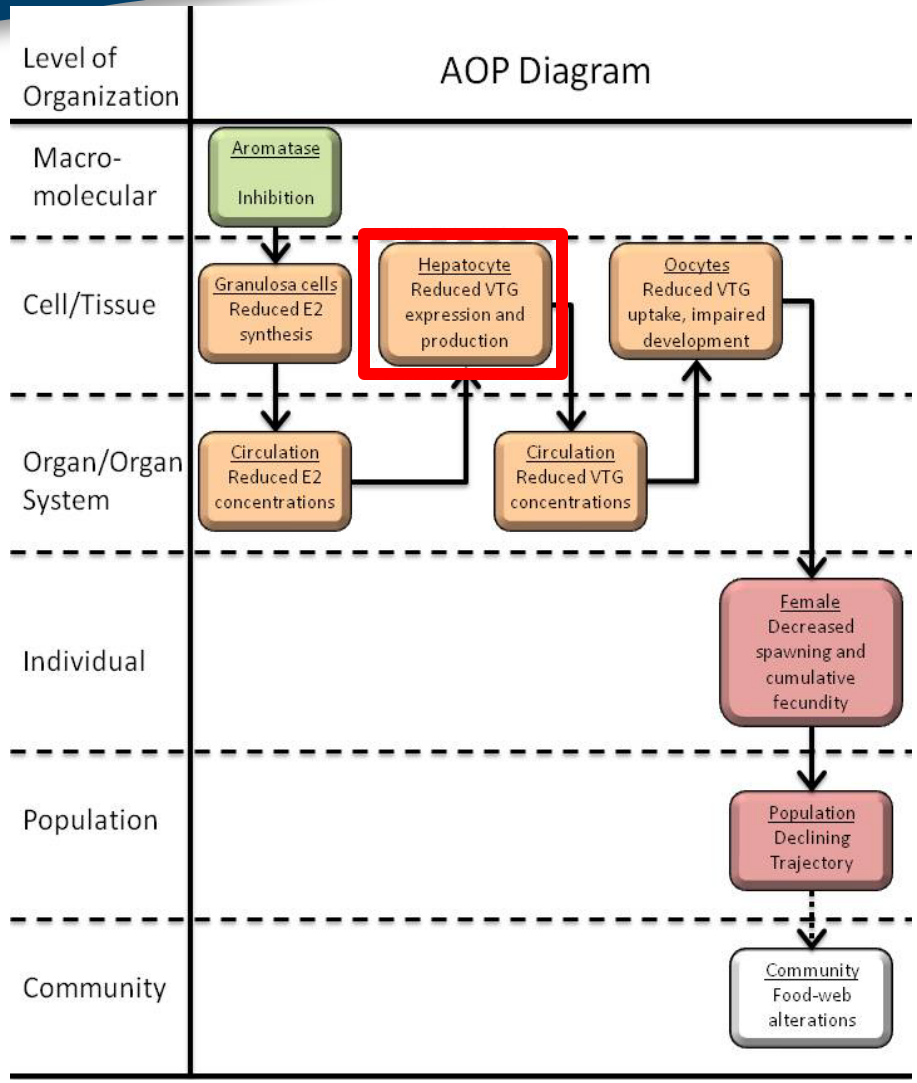


Cataia Ives

Using ontology to tag existing wiki entry



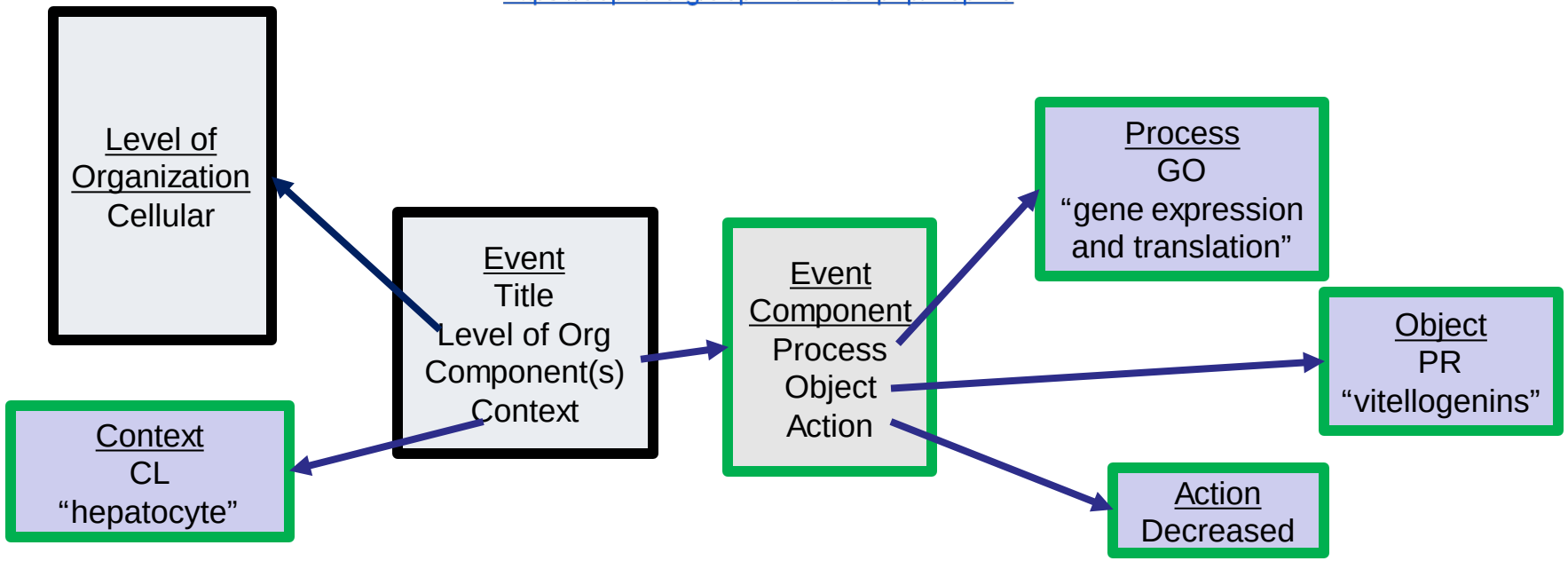
https://aopkb.org/aopwiki/index.php/Aop:25



Cataia Ives

AOP: “Aromatase inhibition leading to reproductive dysfunction (in fish)”
KE: Title “Transcription and Translation of Vitellogenin in Liver, Reduction”

https://aopkb.org/aopwiki/index.php/Aop:25



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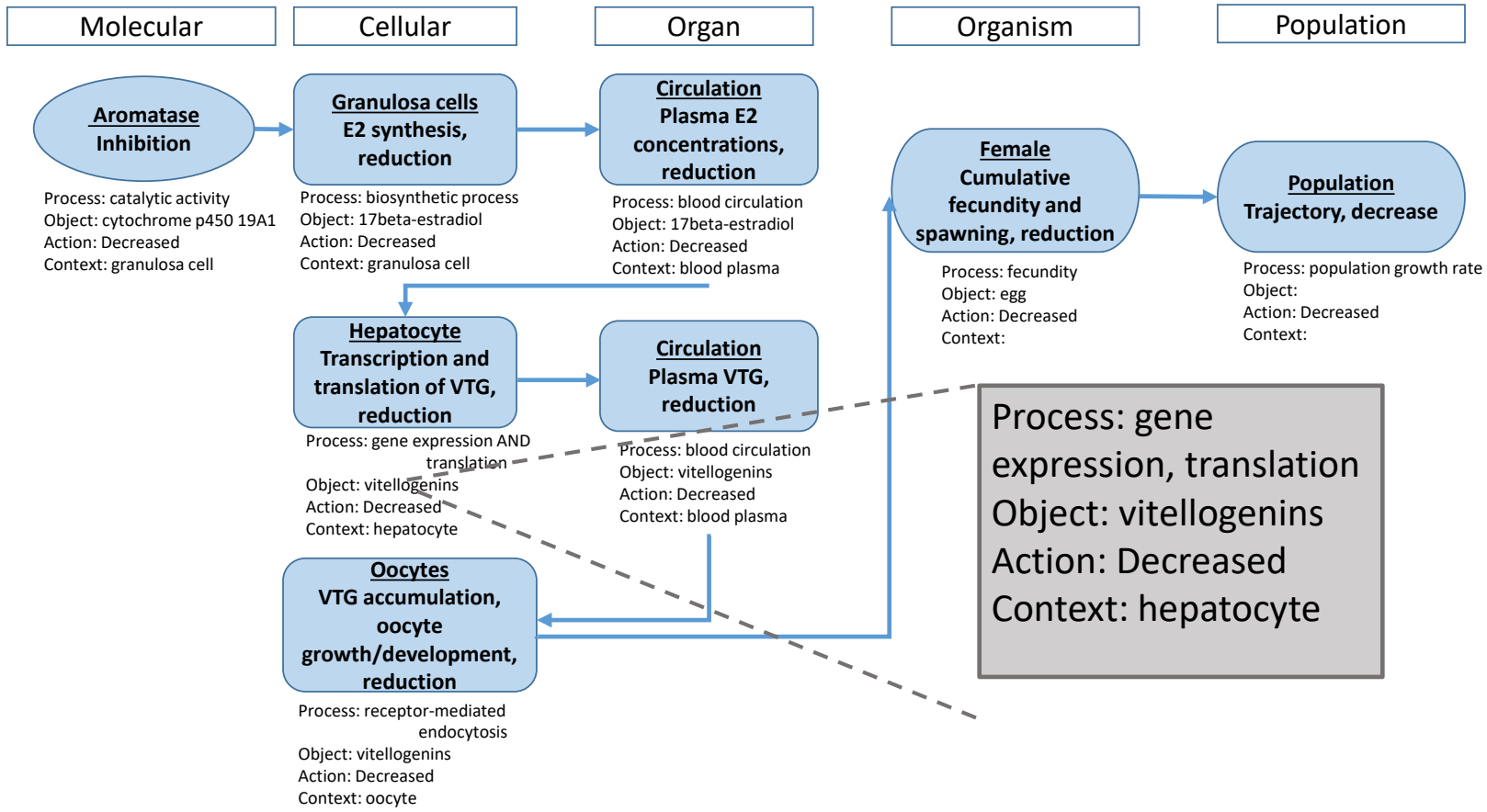
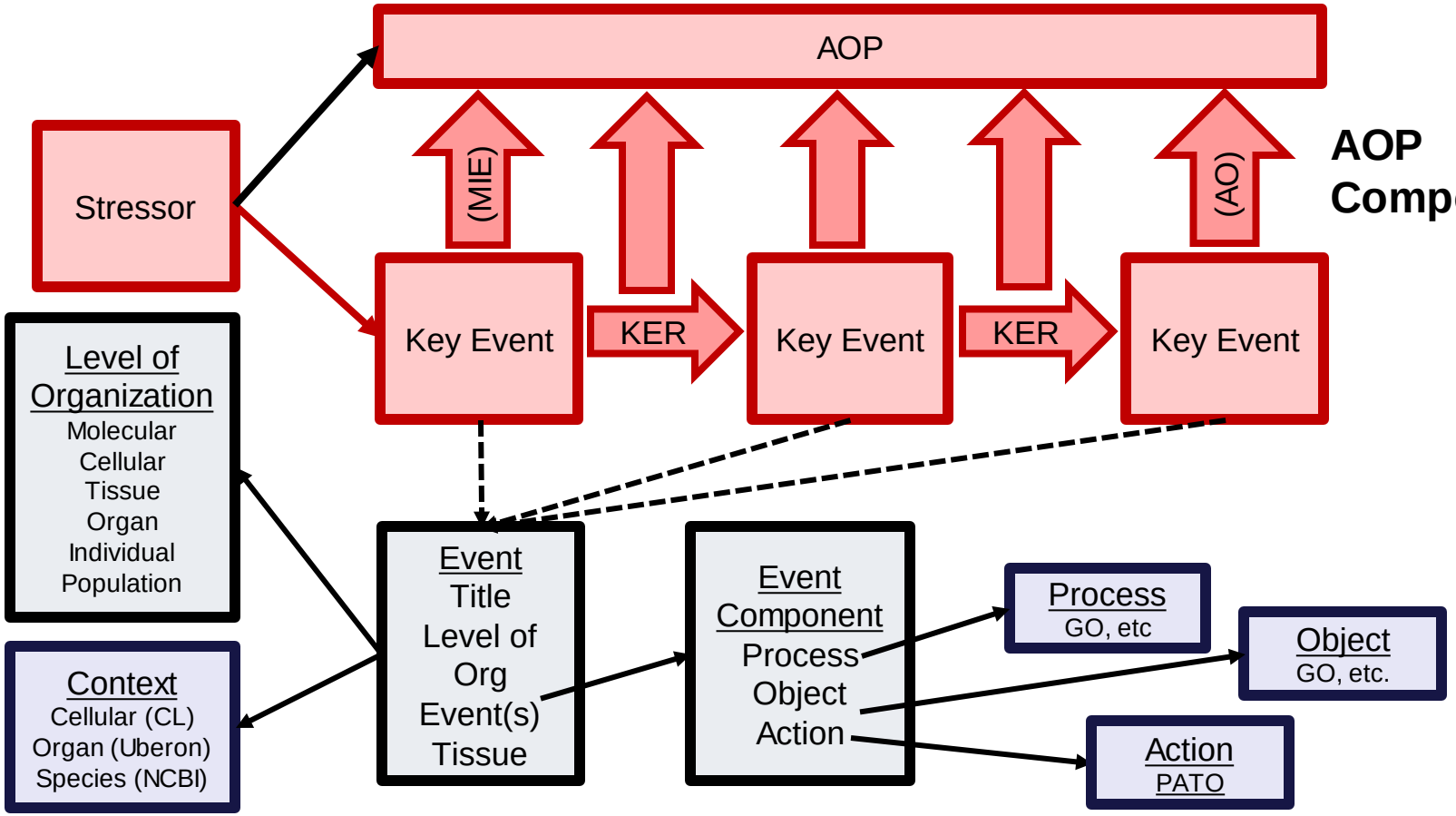

Molecular
Cellular
Organ
Organism
Population
Aromatase Inhibition
Process: catalytic activity
Object: cytochrome p450 19A1
Action: Decreased
Context: granulosa cell
Granulosa cells E2 synthesis, reduction
Process: biosynthetic process
Object: 17beta-estradiol
Action: Decreased
Context: granulosa cell
Circulation Plasma E2 concentrations, reduction
Process: blood circulation
Object: 17beta-estradiol
Action: Decreased
Context: blood plasma
Female Cumulative fecundity and spawning, reduction
Process: fecundity
Object: egg
Action: Decreased
Context:
Population Trajectory, decrease
Process: population growth rate
Object:
Action: Decreased
Context:
Hepatocyte Transcription and translation of VTG, reduction
Process: gene expression AND translation
Object: vitellogenins
Action: Decreased
Context: hepatocyte
Circulation Plasma VTG, reduction
Process: blood circulation
Object: vitellogenins
Action: Decreased
Context: blood plasma
Oocytes VTG accumulation, oocyte growth/development, reduction
Process: receptor-mediated endocytosis
Object: vitellogenins
Action: Decreased
Context: oocyte
Process: gene expression, translation
Object: vitellogenins
Action: Decreased
Context: hepatocyte

Cataia Ives

Ontologies that describe key events in existing AOPs



Lyle Burgoon
Cataia Ives

OECD AOP Ontology Efforts

- AOP-KB Ontology Effort

- Stephen Edwards
- Cataia Ives

- Clemens Wittwehr
- Ivana Campia
- Brigitte Landesmann
- Ahmed Abdelaziz

- Hristo Aladjov
- Magda Sachana

- Lyle Burgoon

- OECD Ontology WG

  - Richard Currie (chair)
  - Annamaria Colacci
  - George Fotakis
  - Ignacio Tripodi
  - Nikolai Georgiev Nikolov
  - Nina Jeliazkova
  - Olga Tcheremenskaia

  - AOP-KB Representatives

- Cataia Ives
- Rong-Lin Wang
- Lyle Burgoon
- Kyle Painter

Main Page

Main Page

Navigation
Main page
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AOP Table
EAGMST Approved AOPs
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FAQ
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Release notes
Actions
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Feedback
Tools
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Related changes
Special pages
Printable version
Permanent link
Page information

Announcements

There was a minor software upgrade for the AOP-Wiki on 2/13/2016. A list of the bug fixes and new features is available here: Release_Notes#Release_1.5_.281.2F17.2F2016.29. If you notice any problems, please email aopwiki@googlegroups.com and/or report here: Bug Reports.

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

If you are interested in contributing AOP-related knowledge to the AOP-KB, please follow the instructions laid out at the OECD Adverse Outcome Pathways, Molecular Screening and Toxicogenomics page. The Guidance on Developing and Assessing AOPs document is the basis for all work related to contributing and sharing AOP-related knowledge. A Users' Handbook Supplement to this Guidance has been written to aid systematic development and transparent assessment of Adverse Outcome Pathways (AOPs). The handbook contains a template to guide AOP description and

Add Linked Page

Home

Announcements

OECD User Handbook

Wiki authors please refer to the OECD Users' Handbook when developing your AOP. If you notice any bugs, please report them.

Edit Destroy

Commenting on AOPs

To avoid spammers, we now require email confirmation before any user is allowed to edit. We apologize for any inconvenience this may cause. Instructions for confiming your email if you already have an account are given here: Confirm Email. If you have any troubles confirming your email, please email us ataopwiki@googlegroups.com. Before commenting on AOPs, plesae read the AOP Wiki Editing & Comments Policy.Additional guidance for commenting is available here: Commenter Information

Edit Destroy

AOP Welcome

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

If you are interested in contributing AOP-related knowledge to the AOP-KB, please follow the instructions laid out at the OECD

Contents add

AOPWiki | AOPs | Events | Relationships | Chemical Initiators | Allie

API

Links to OECD & SAAOP AOP Pages: OECDs SAAOPs

alkylation Search

New AOP

AOP Search Results

Title	Corresponding Author	Author Status	SAAOP Status	MIE	AO	OECD Status	OECD Project	
Alkylation of DNA in male pre-meiotic germ cells leading to heritable mutations	Arthur Author	Open for citation & comment	Included in OECD work plan	DNA alkylation	heritable mutations	TFHA/WNT Endorsed	1.11	Edit status Destroy
Alkylation of DNA leading to cancer	Arthur Author	Under development: Not open for comment. Do not cite	Under Development	DNA alkylation	cancer			Edit status Destroy
Alkylation of DNA leading to cancer	Arthur Author	Not under active development	Archived	DNA alkylation	cancer			Edit status Destroy
Protein Alkylation leading to Liver Fibrosis	Arthur Author	Open for citation & comment	Included in OECD work plan	Protein alkylation	liver fibrosis	TFHA/WNT Endorsed	1.14	Edit status Destroy

Listing of AOPs with OECD status

TFHA/WNT Endorsed

Open for citation & comment

Title	Corresponding Author	MIE	AO	OECD Project	
Alkylation of DNA in male pre-meiotic germ cells leading to heritable mutations	Arthur Author	DNA alkylation	heritable mutations	1.11	Edit

Contents

Listing of AOPs with SAAOP status

Under Development

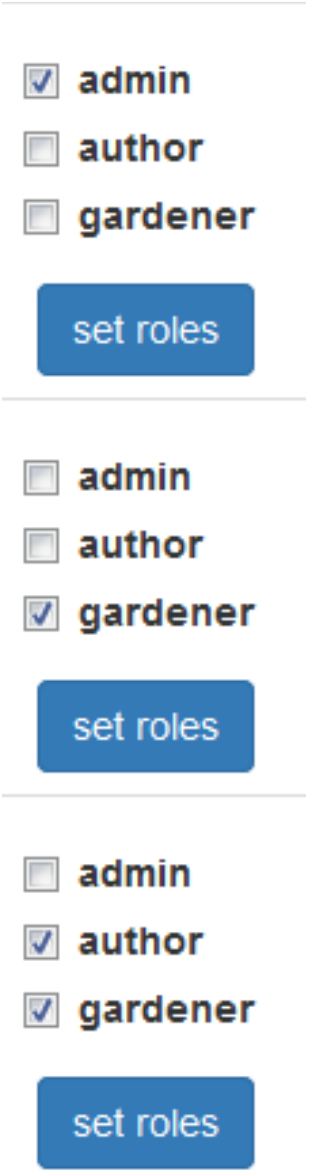
Under development: Not open for comment. Do not cite

Title	Corresponding Author	MIE	AO	
AhR activation leading to uroporphyria	Arthur Author	AhR	uroporphyria	Edit

Contents

User Roles

- Gardener
  - Experienced AOP developers to help ensure consistency with published principles and OECD guidelines
- Author
  - Can create new AOPs and edit AOP components
- Authenticated User (self created account)
  - Can comment on AOPs, KEs, & KERs
- Anonymous
  - Read only



Edited on AOP page by Authors

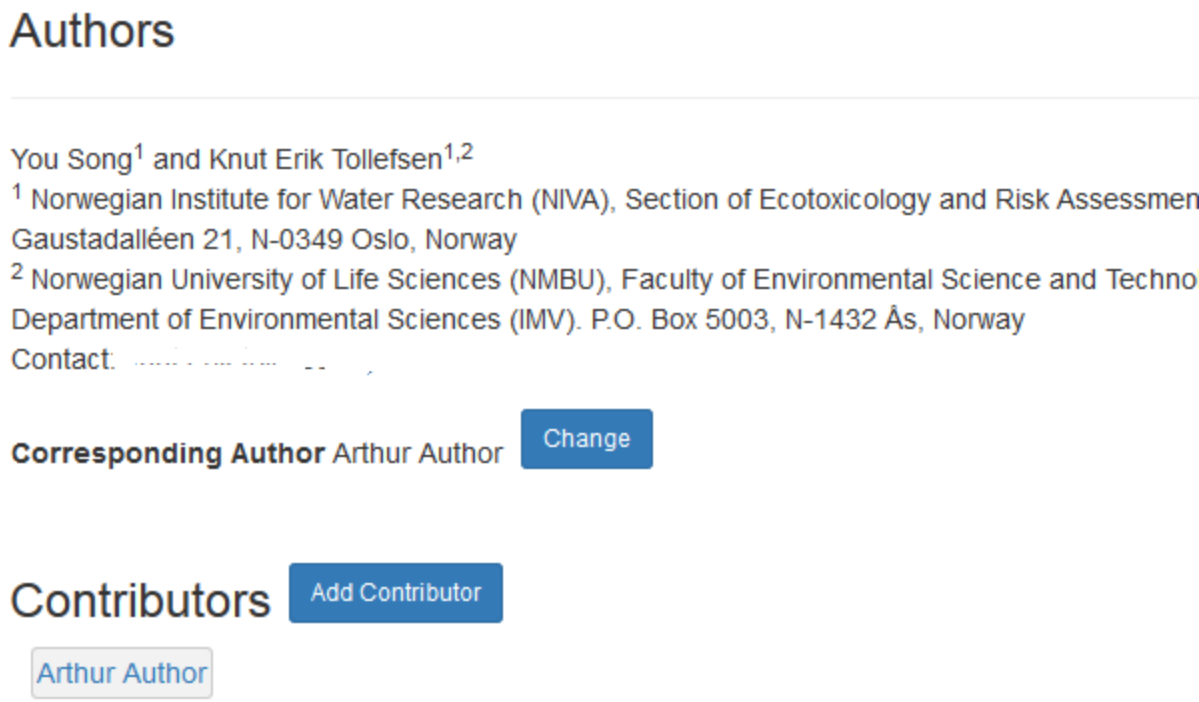
Edited on this page by Gardeners

Gardeners only

Title	Corresponding Author	Author Status	SAAOP Status	MIE	AO	OECD Status	OECD Project	
Alkylation of DNA in male pre-meiotic germ cells leading to heritable mutations	Arthur Author	Open for citation & comment	Included in OECD work plan	DNA alkylation	heritable mutations	TFHA/WNT Endorsed	1.11	Edit status Destroy
Alkylation of DNA leading to cancer	Arthur Author	Under development: Not open for comment. Do not cite	Under Development	DNA alkylation	cancer			Edit status Destroy
Alkylation of DNA leading to cancer	Arthur Author	Not under active development	Archived	DNA alkylation	cancer			Edit status Destroy
Protein Alkylation leading to Liver Fibrosis	Arthur Author	Open for citation & comment	Included in OECD work plan	Protein alkylation	liver fibrosis	TFHA/WNT Endorsed	1.14	Edit status Destroy

AOP Authors

- Corresponding author
  - Controls access
  - Point of contact for questions/comments
- Contributors
  - Able to edit the AOP
- Author list
  - Free text field as in current wiki



API

Search Events

Search

New Event

Listing Events

Title	Short name	Biological organization	
N/A, 1) Aniline and 2,4-DNT are converted to the reactive hydroxylamino form which oxidizes heme Iron(II) in hemoglobin to Iron(III)	1) Aniline and 2,4-DNT are converted to the reactive hydroxylamino form which oxidizes heme Iron(II) in hemoglobin to Iron(III)		Edit Destroy
Reduction, 17beta-estradiol concentrations	17beta-estradiol concentrations		Edit Destroy
Reduction, 17beta-estradiol synthesis by ovarian granulosa cells	17beta-estradiol synthesis by ovarian granulosa cells		Edit Destroy
Decreased, 17β-estradiol synthesis	17β-estradiol synthesis		Edit

Authors & Gardeners

Gardeners Only

Edit all text sections from a single page

Editing Aop

Title

Aromatase inhibition leading to reproductive dysfunction (in fish

Short name

Aromatase inhibition leading to reproductive dysfunction (in fish

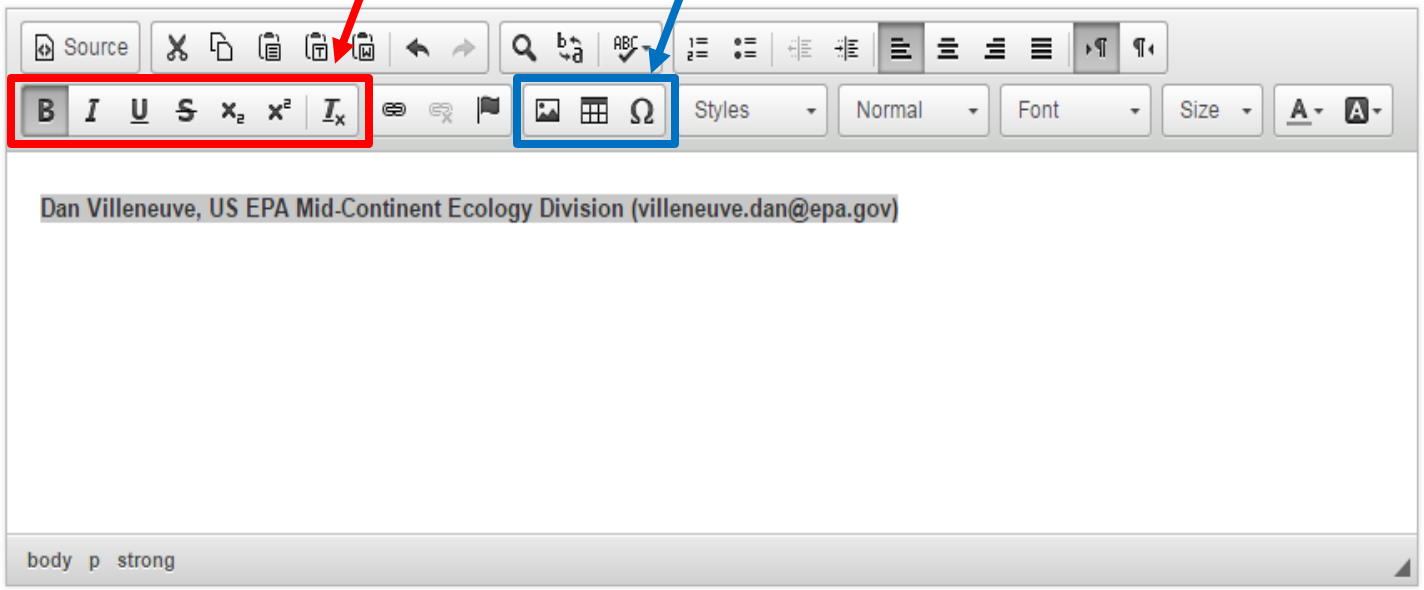
Corresponding author

Undefined

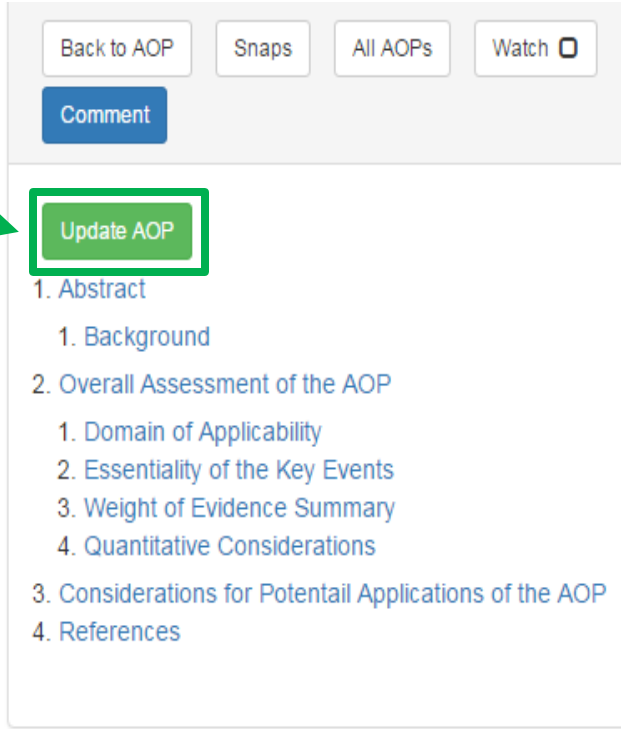
Authors

WYSIWYG

Easily create tables and add images

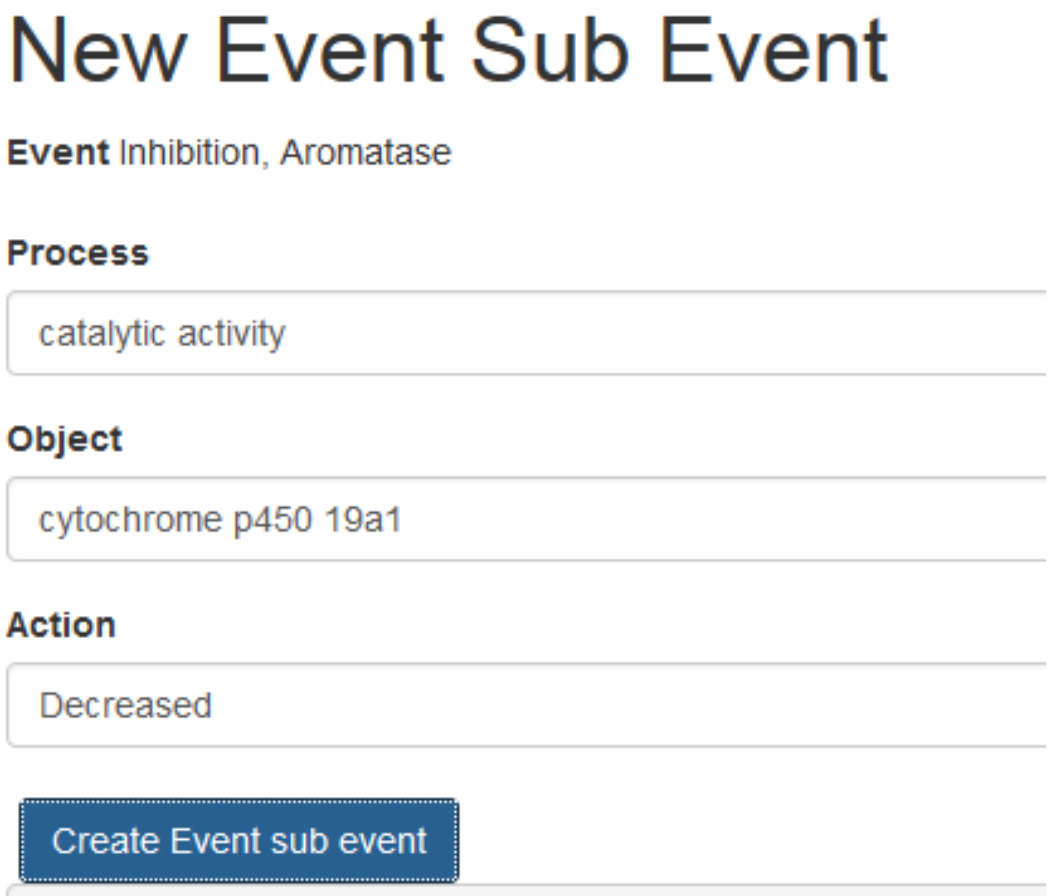


Save changes to all sections with one click



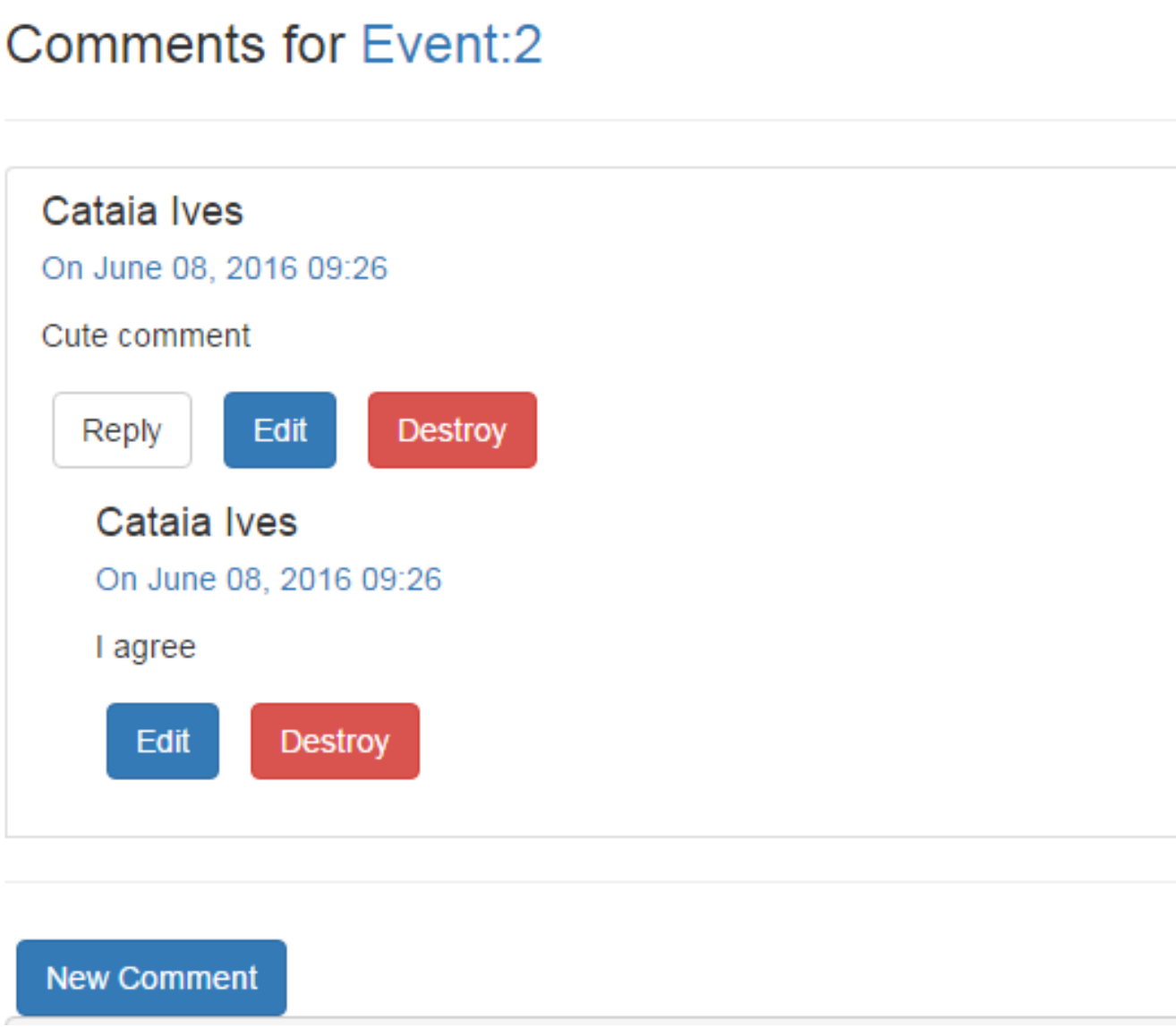
Ontology Tags for Key Events

- Event Components
  - Process
  - Object
  - Action
- Event Context
  - Tied to level of organization
  - Cellular, Organ, Taxonomy
- All terms driven by biological ontologies



Comments

- Modern look & feel
- Allows comments on comments



Versions of Aop:154

Aop as of:	Created By	from | to
June 07, 2016 10:30	Cataia Ives	
May 20, 2016 16:10	Cataia Ives	
May 20, 2016 15:45	Cataia Ives	
		Compare

Change log

Date	User	Description
June 08, 2016 09:43	Cataia Ives	ChemInit:11 was added to AOP.
May 20, 2016 16:13	Cataia Ives	Abstract and Authors updated.
May 20, 2016 16:10	Cataia Ives	Abstract, Authors, Domain of Applicability, Essentiality of the Key Events, Weight of Evidence Summary, Considerations for Potential Applications of the AOP, References, Overall Assessment of the AOP, and Background updated. Status changed from null to Archived.

AOPWiki AOPs Events Relationships Chemical Initiators AOPs Table

Aop:154 as of May 20, 2016 16:10	**Aop:154 as of June 07, 2016 10:30**
Title	
nothing to show	nothing to show
Short Name	
nothing to show	nothing to show
Authors	
nothing to show	`<p>Great author</p>`
Abstract	
nothing to show	`<p>This AOP is concise</p>`

Acknowledgements

OECD AOP-KB Working Group

- Stephen Edwards
- Dan Villeneuve
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- Robert Kavlock

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- Evgeniia Kazymova

- Clemens Wittwehr
- Brigitte Landesmann
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- Maurice Whelan

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- Joop DeKnecht

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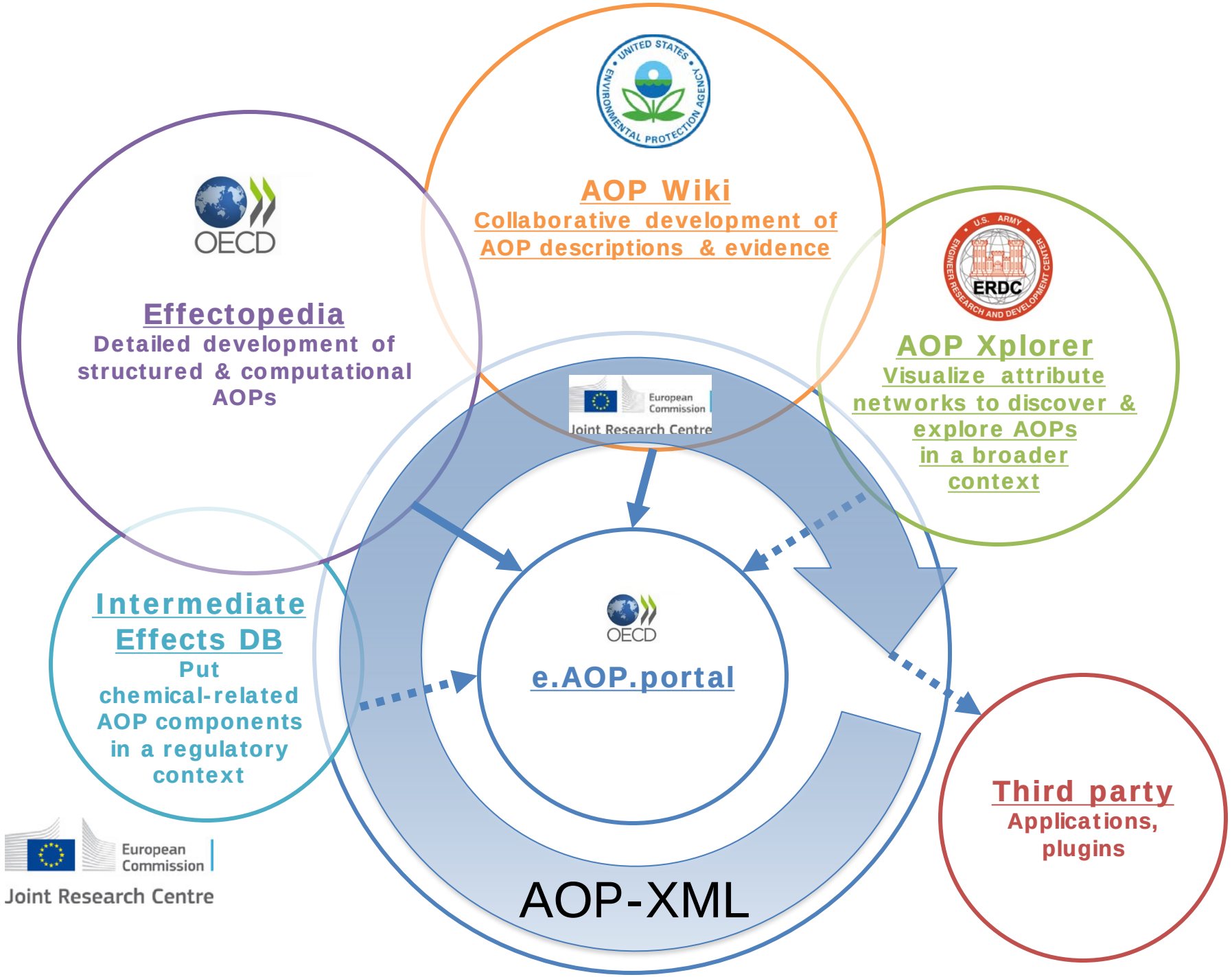
- Lyle Burgoon
- Natalia Garcia Reyero

- Collaborative Partners
  - OECD External Advisory Group on Molecular Screening & Toxicogenomics
  - IPCS/WHO Mode of Action Steering Committee

- Rose Combs
- Landon Grindheim
- Cataia Ives
- Brendan Ferreri-Hanberry
- Evgeniia Kazymova


AOP Wiki
Collaborative development of AOP descriptions & evidence
Effectopedia
Detailed development of structured & computational AOPs
AOP Xplorer
Visualize attribute networks to discover & explore AOPs in a broader context
Intermediate Effects DB
Put chemical-related AOP components in a regulatory context
e.AOP.portal
AOP-XML
Third party
Applications, plugins
European Commission
Joint Research Centre

Questions?


Population Network
Key Event Network
Molecular Network
SYSTEMS TOXICOLOGY