



Adverse Outcome Pathway Knowledge Base

Stephen Edwards

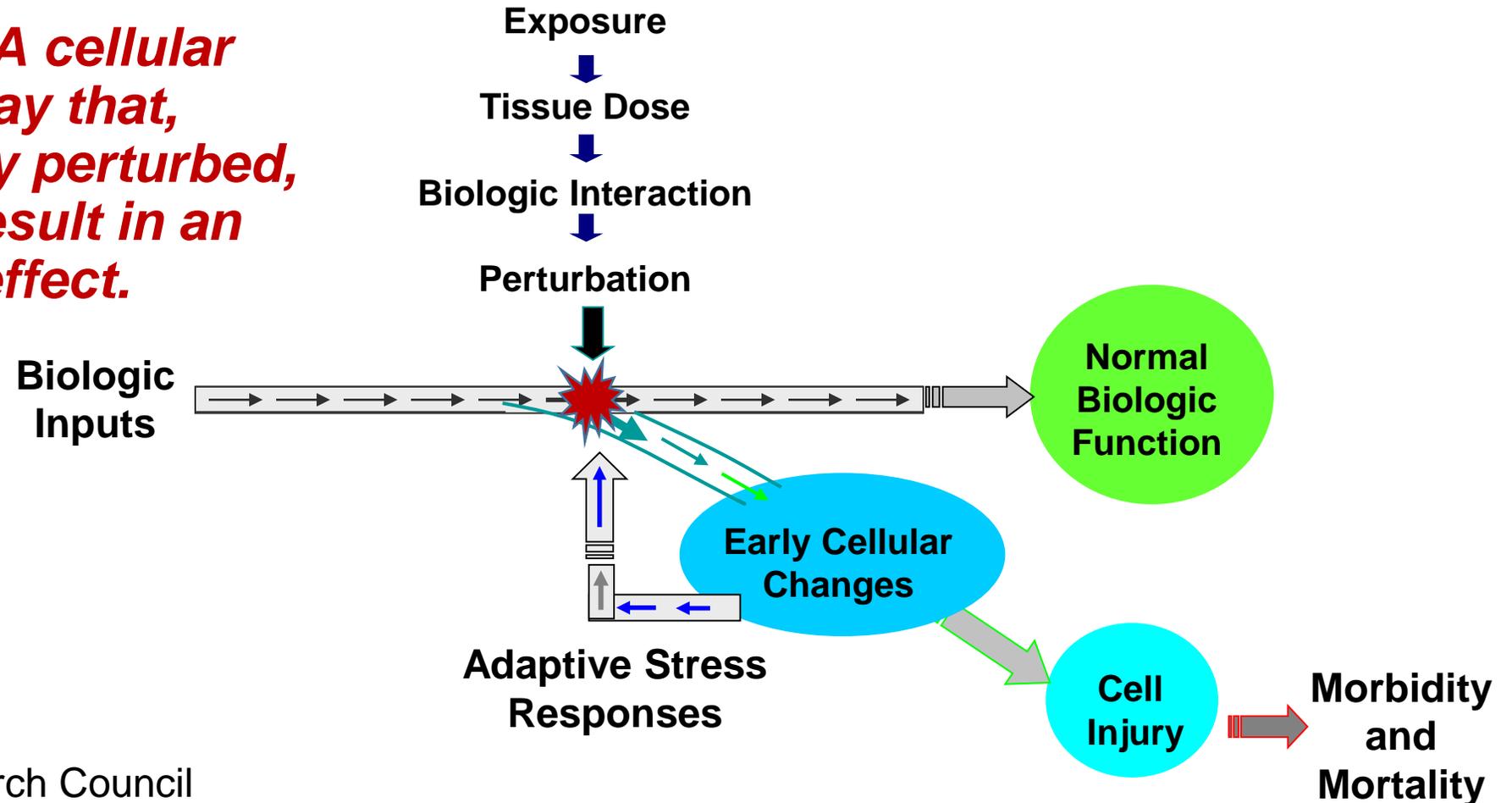
US EPA National Health & Environmental Effects
Research Laboratory

U.S. Environmental Protection Agency

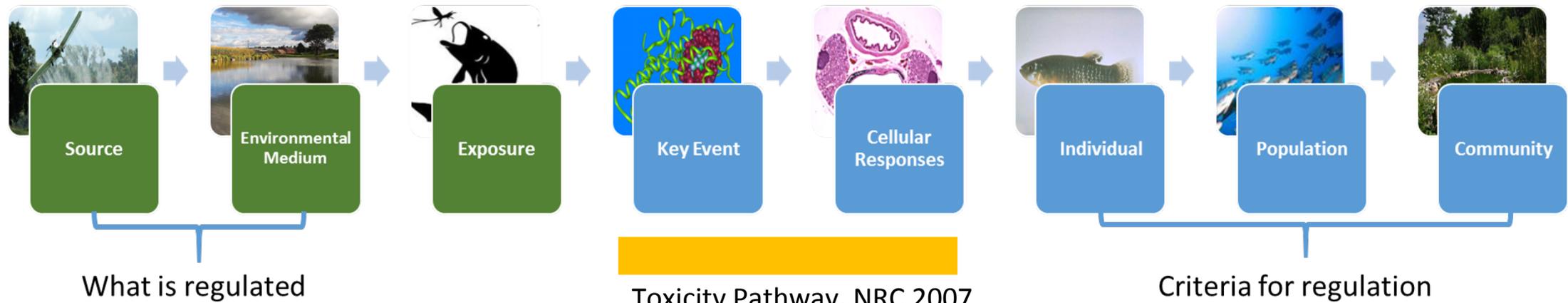
The views expressed in this presentation are those of the presenter, and do not necessarily reflect the views and policies of the Agency.

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.



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

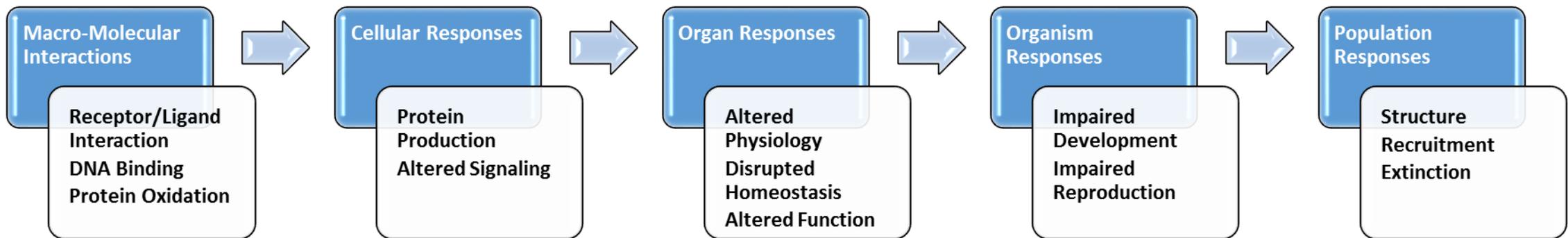


Mode of Action, IPCS/EPA/ILSI 2001-2008



Aggregate Exposure Pathway, Teeguarden 2016 Adverse Outcome Pathway, Ankley 2010, Villeneuve 2014

AOP Components



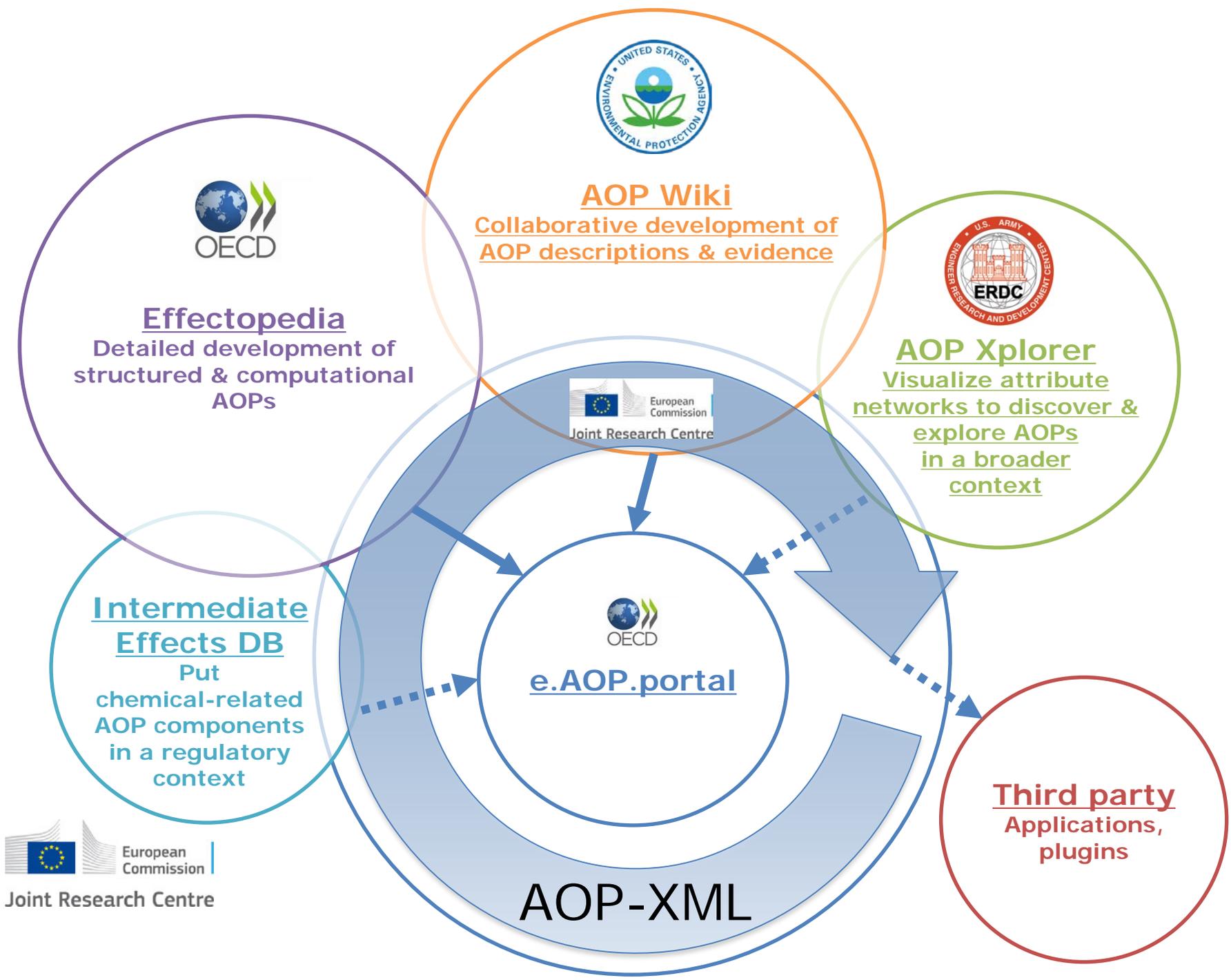
- **Key Events (KEs) - nodes**
 - Change in biological state
 - Measurable and essential for progression
 - Molecular Initiating Event (MIE): Initial point of chemical interaction
 - Adverse Outcome (AO): Adverse outcome of regulatory significance
- **Key Event Relationships (KERs) - edges**
 - Connections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

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



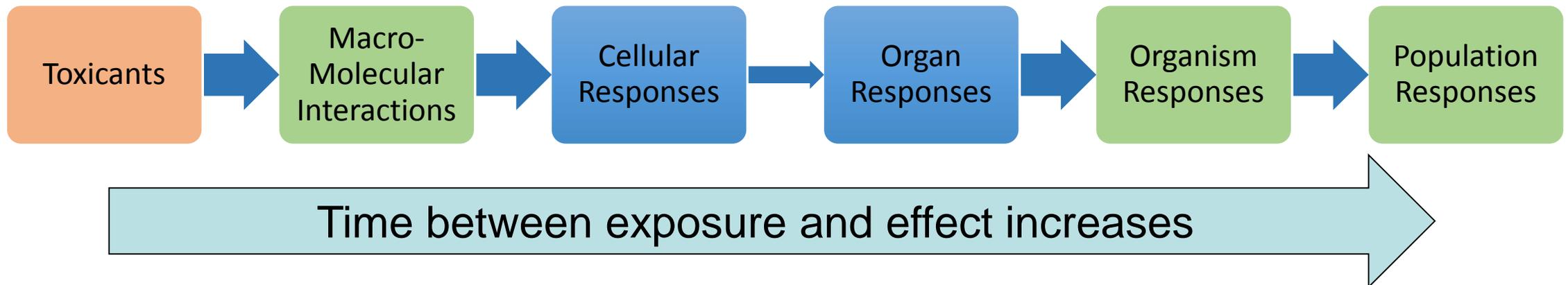
Five Principles of AOP Development

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

Five Principles of AOP Development

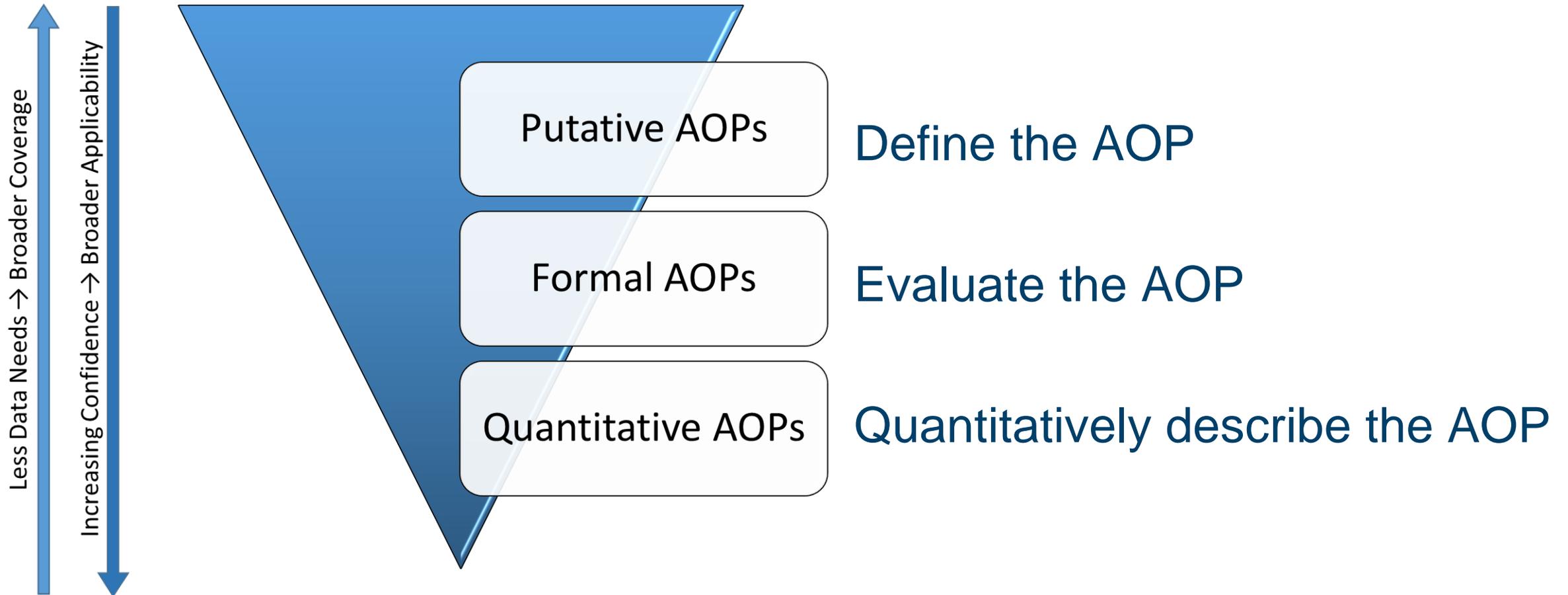
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Factors Determining Predictivity of Early Key Events



- 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





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

Third party Applications, plugins

AOP-XML



OECD Handbook

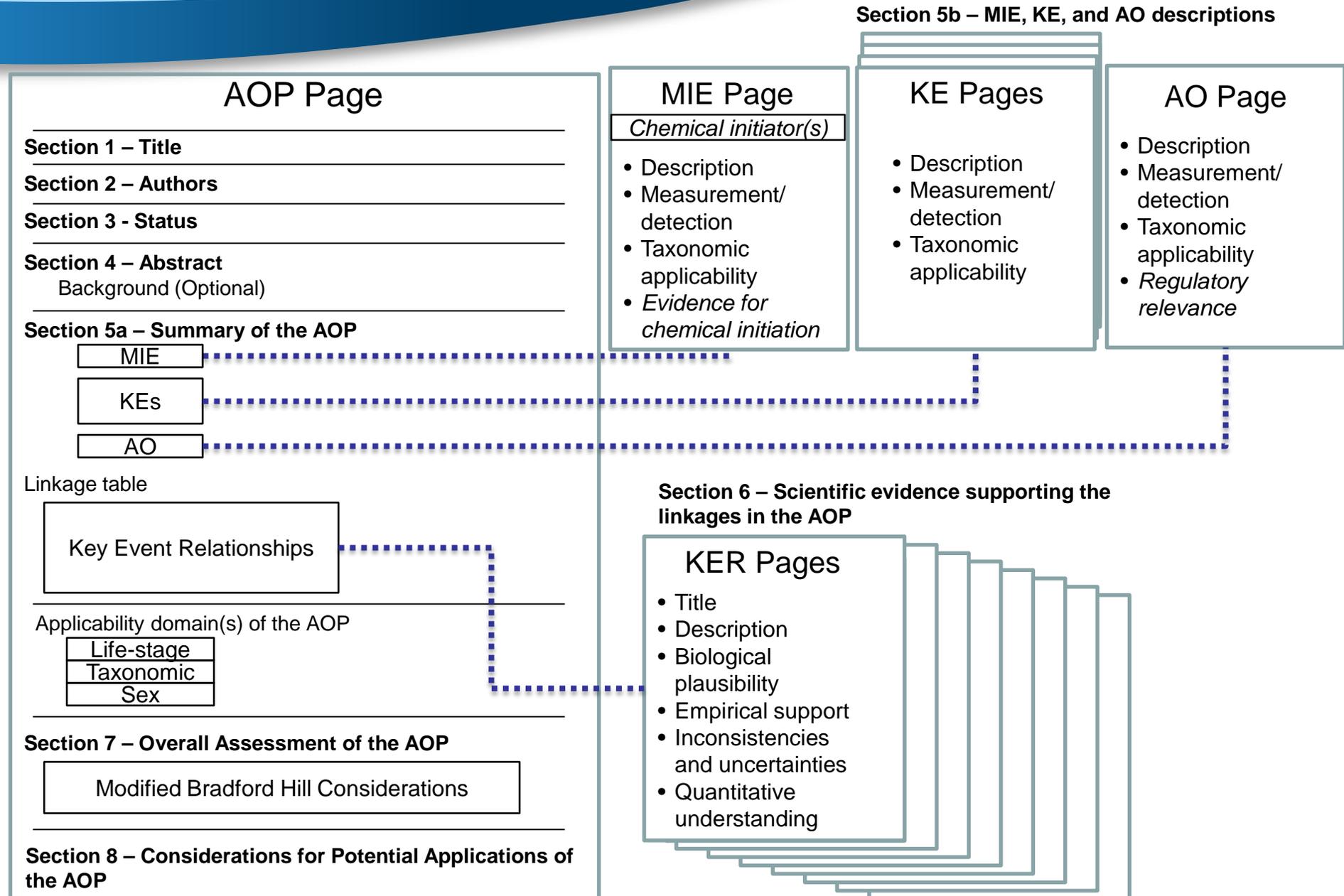
Step by step guide to AOP development

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

AOP-Wiki

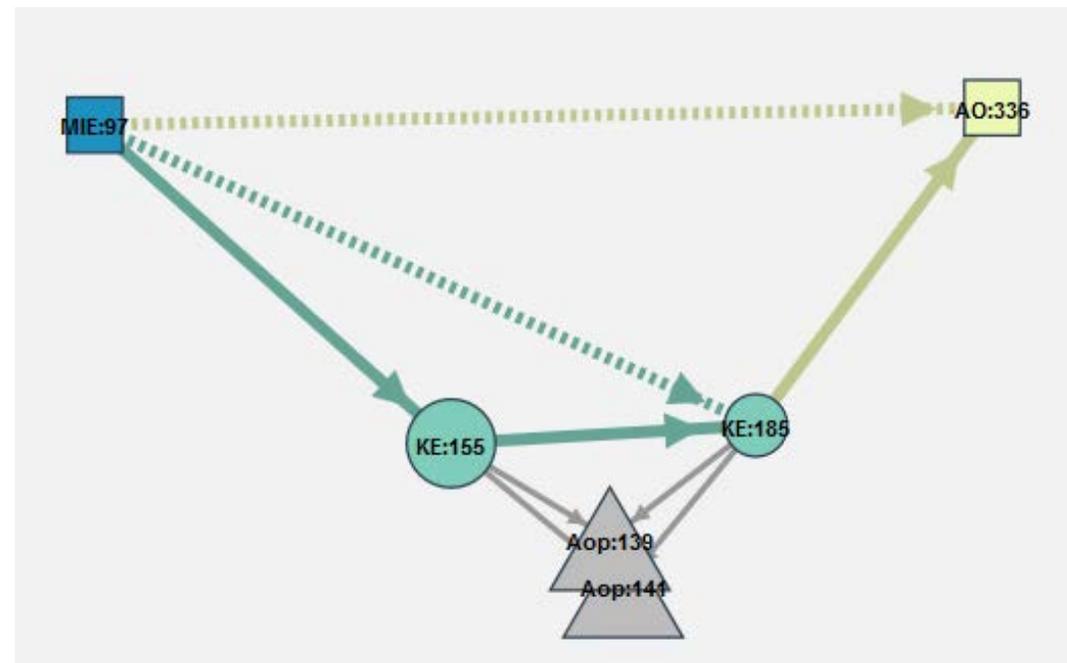
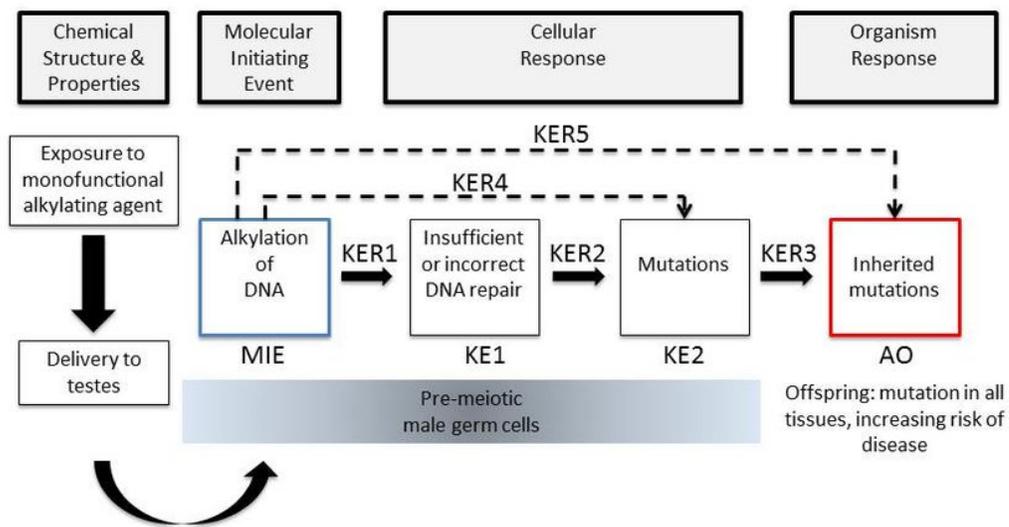
Provides consistent structure based on the OECD handbook and facilitates collaborative AOP development

<http://aopwiki.org/>



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

Short name: Alkylation of DNA leading to heritable mutations



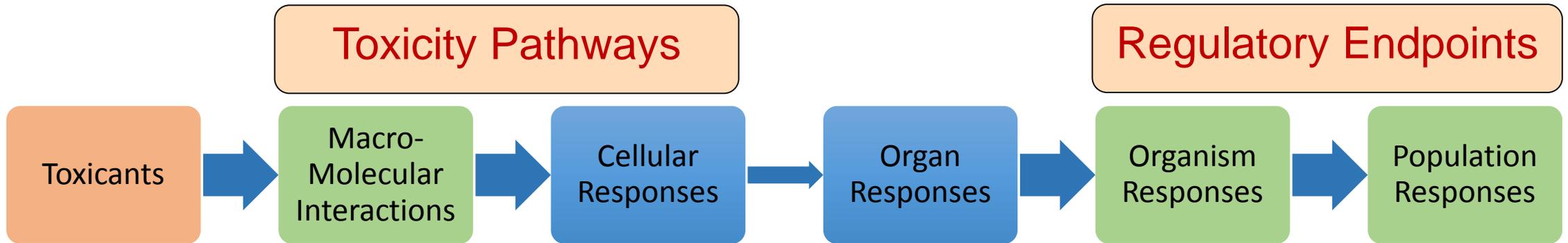
Relationships Among Key Events and the Adverse Outcome

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

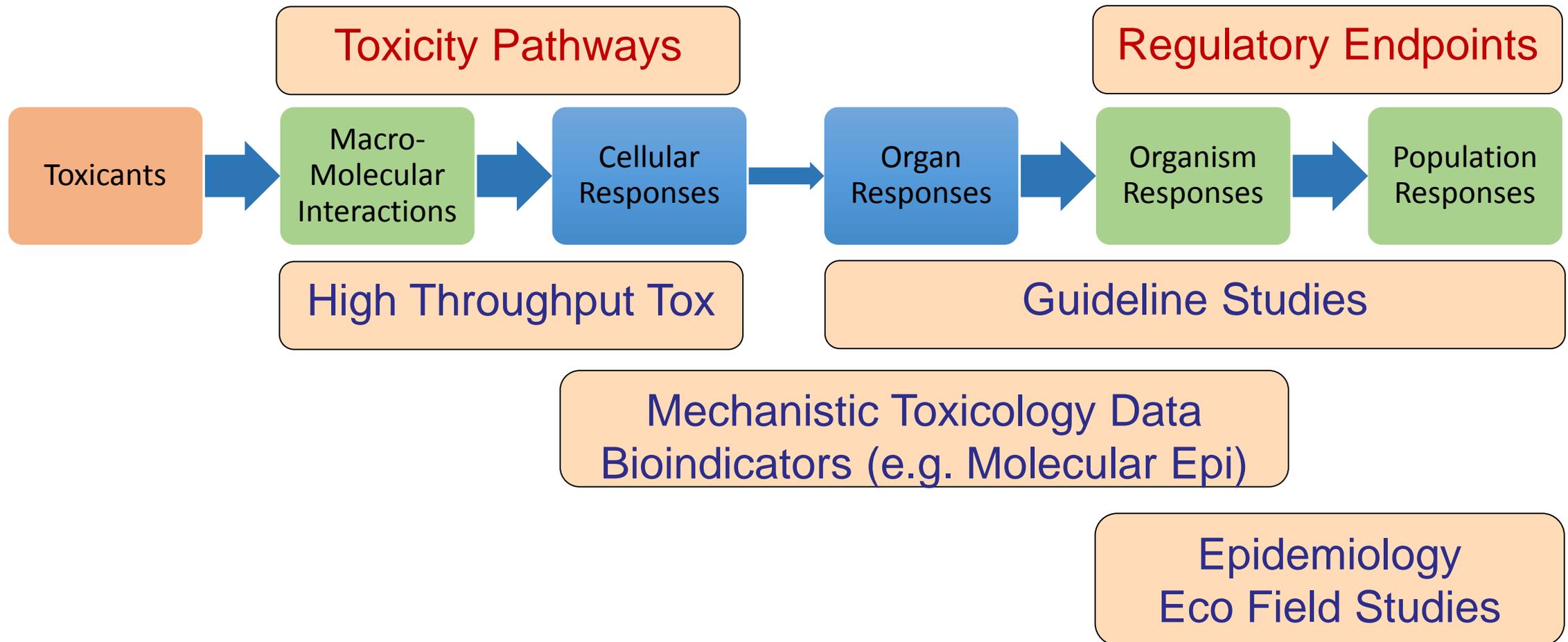
Carole Yauk –

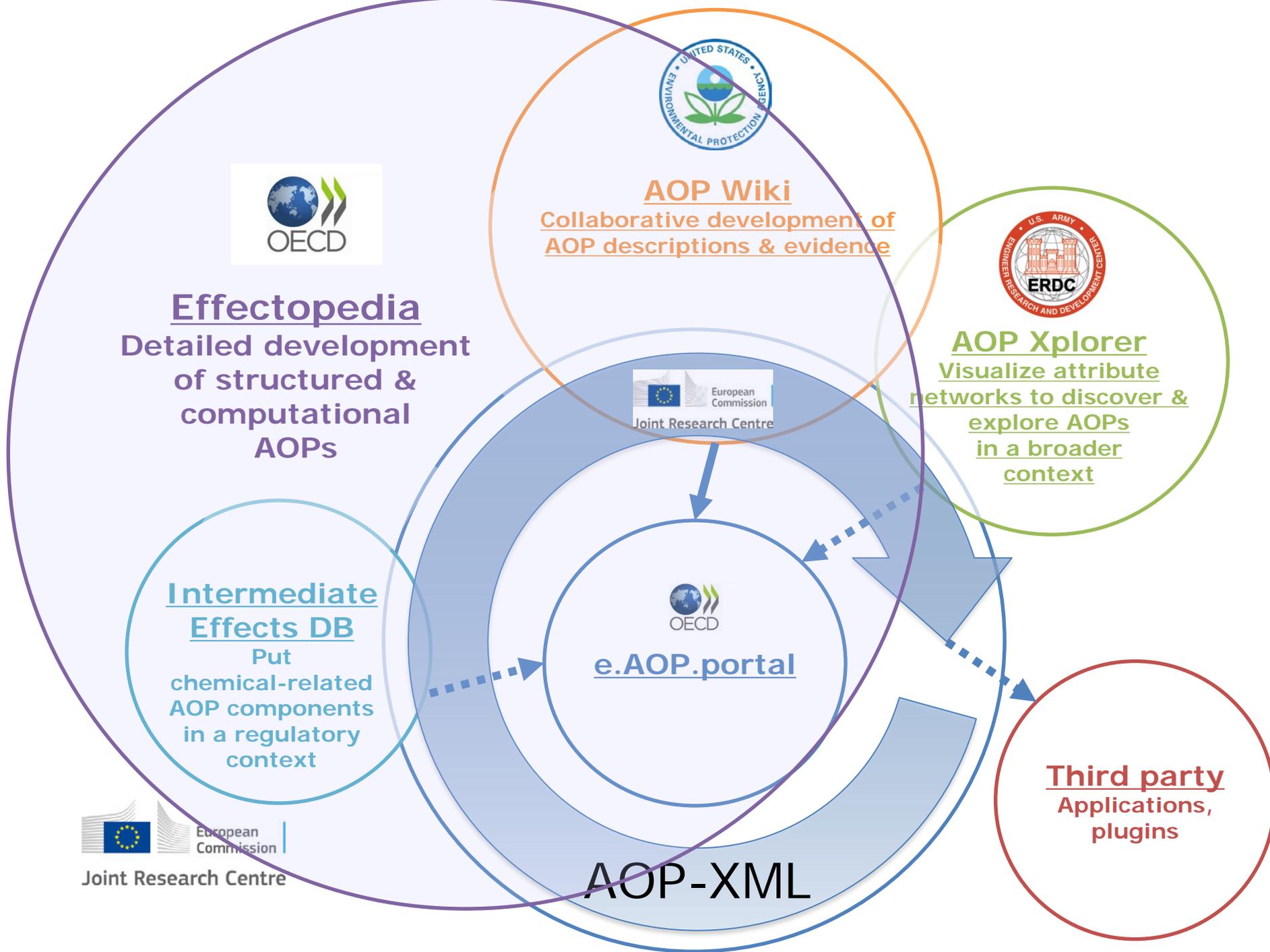
<https://aopwiki.org/wiki/index.php/Aop:15>

AOP Provides **Understanding** & Scaffold for Data

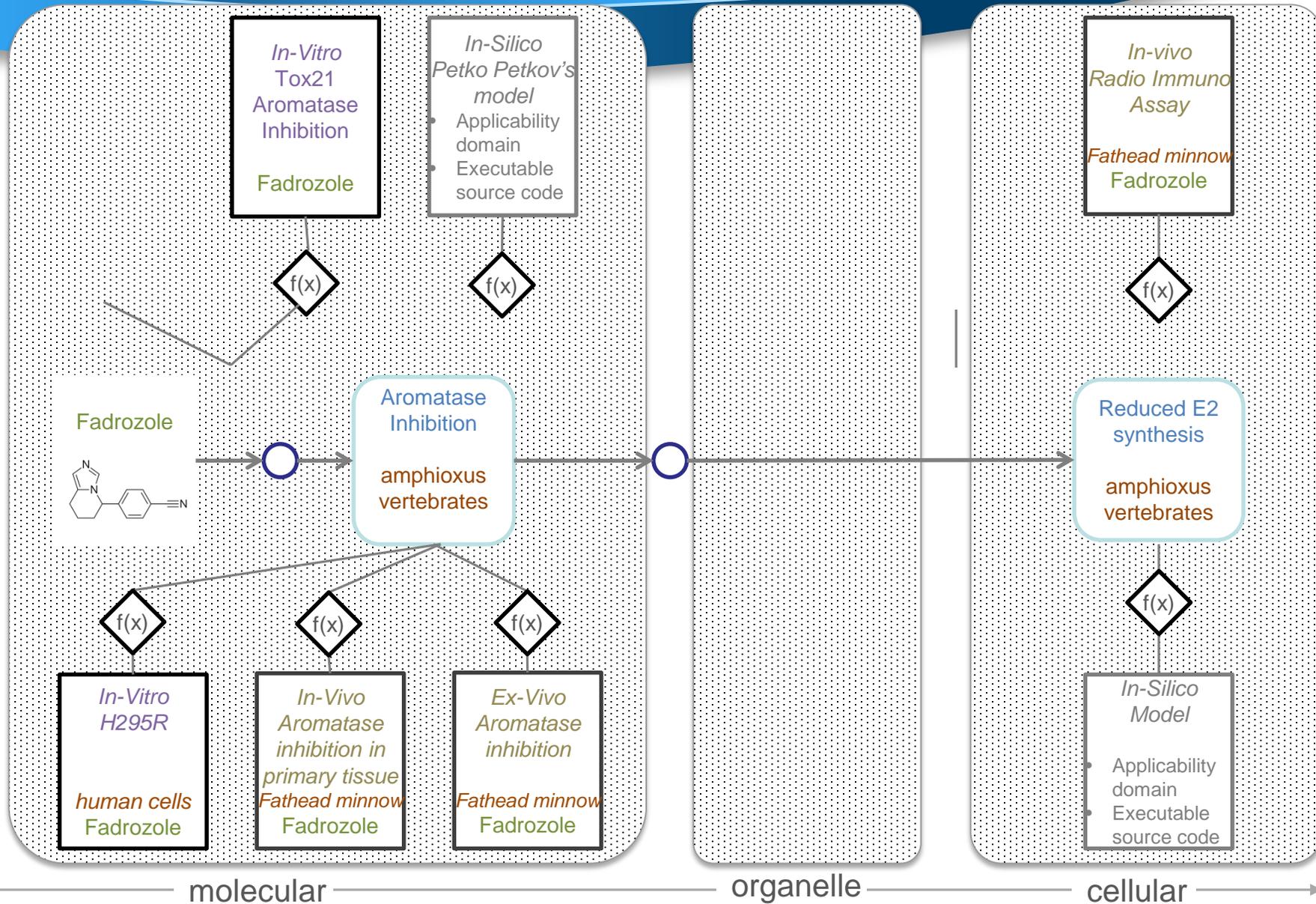


AOP Provides Understanding & **Scaffold** for Data





Sex
mixed

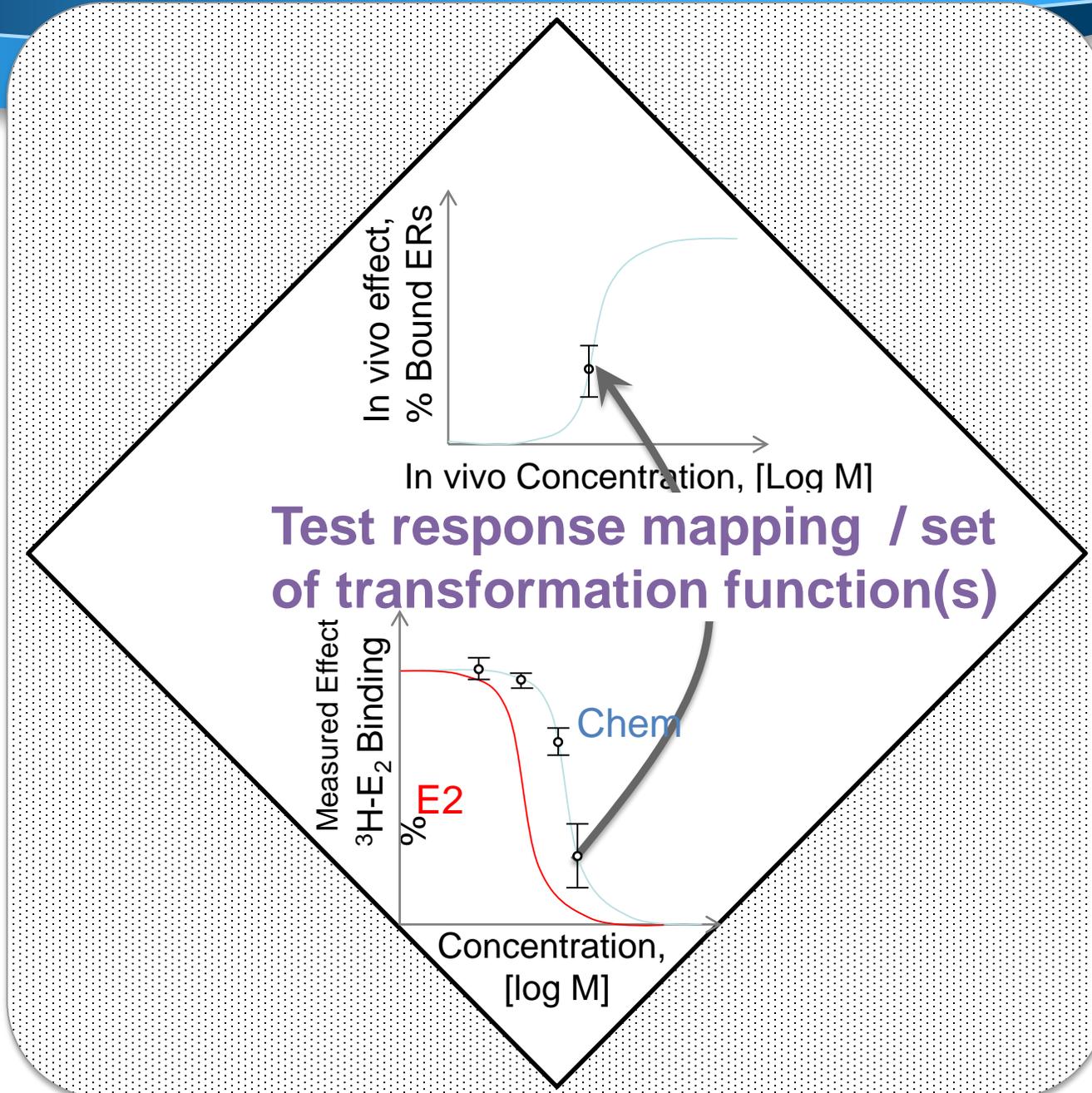


Pathway
Elements and
quantitative
information

Effectopedia
Hristo Aladjov

Level of Biological Organisation

Pathway elements – test response mapping

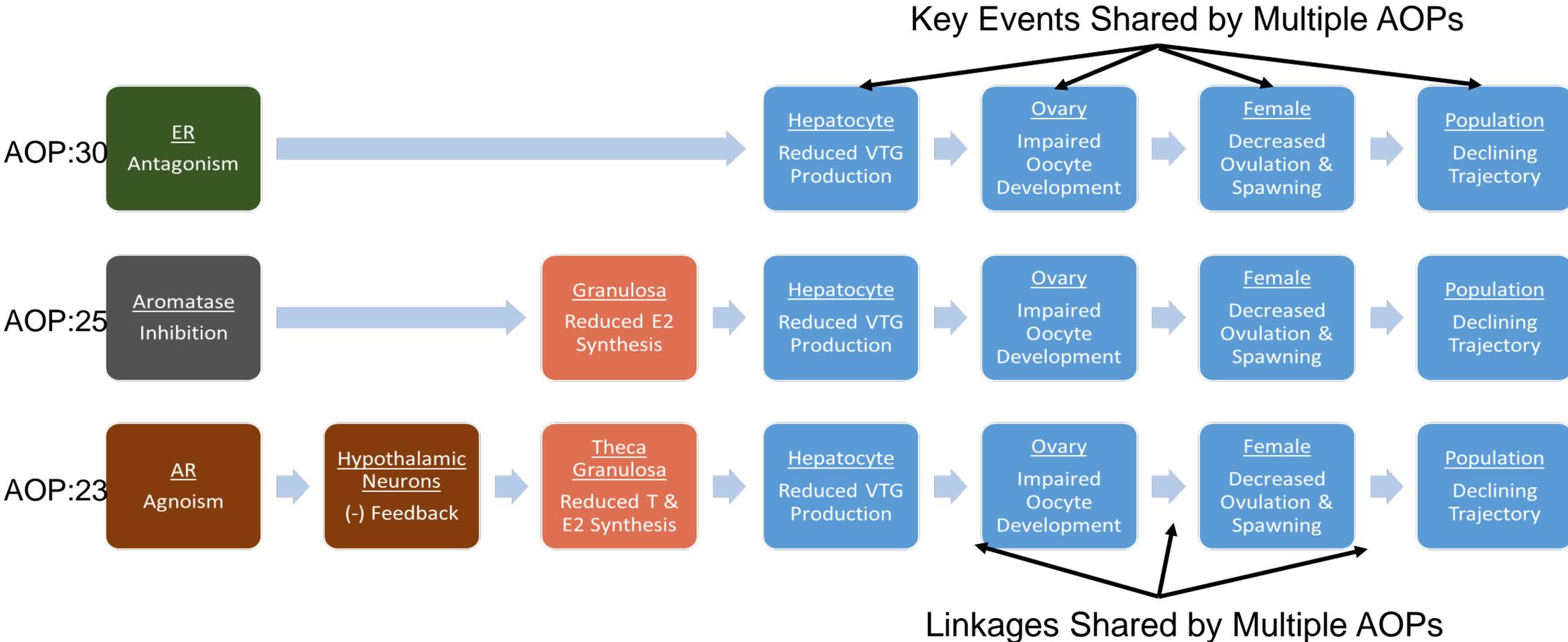


Effectopedia
Hristo Aladjov

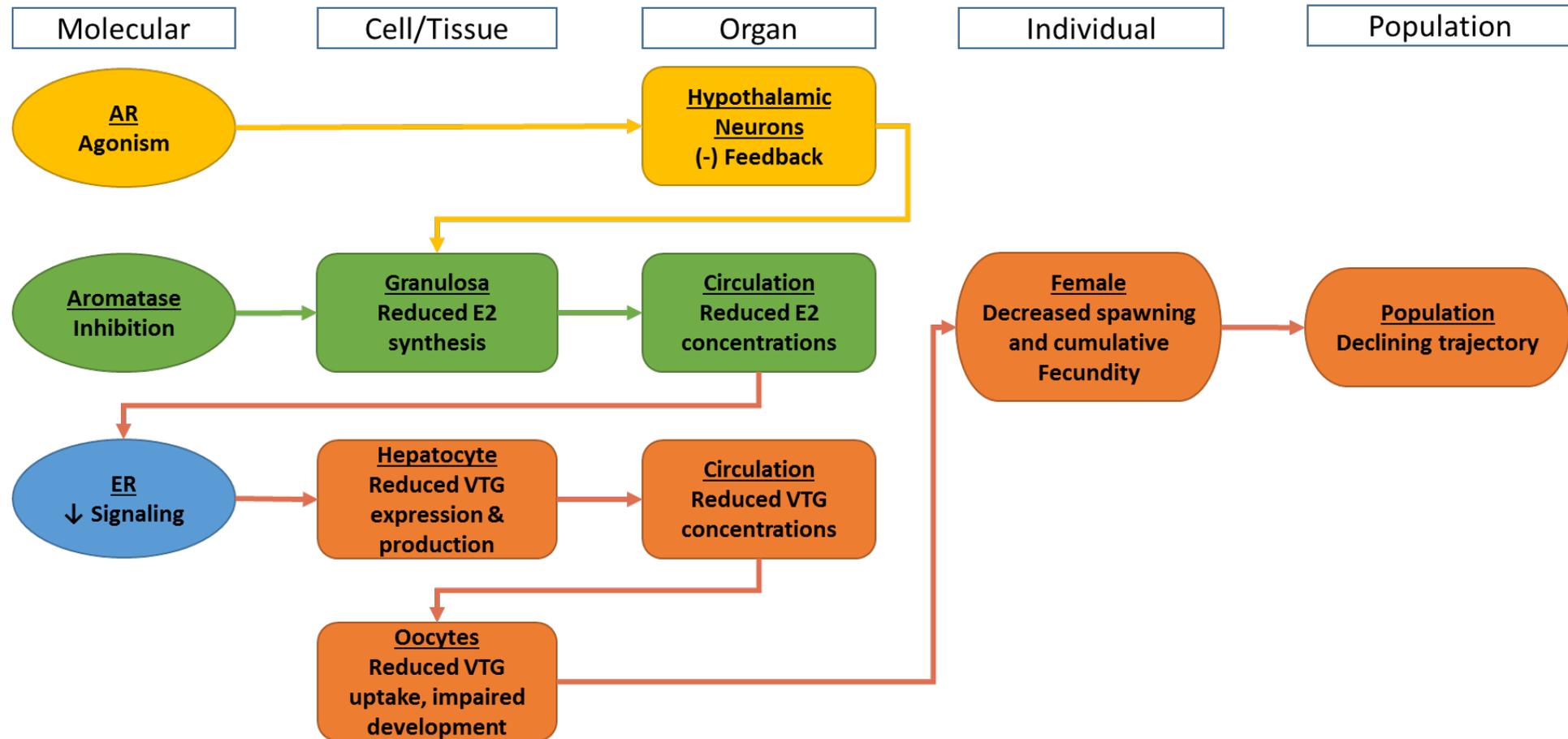
Five Principles of AOP Development

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



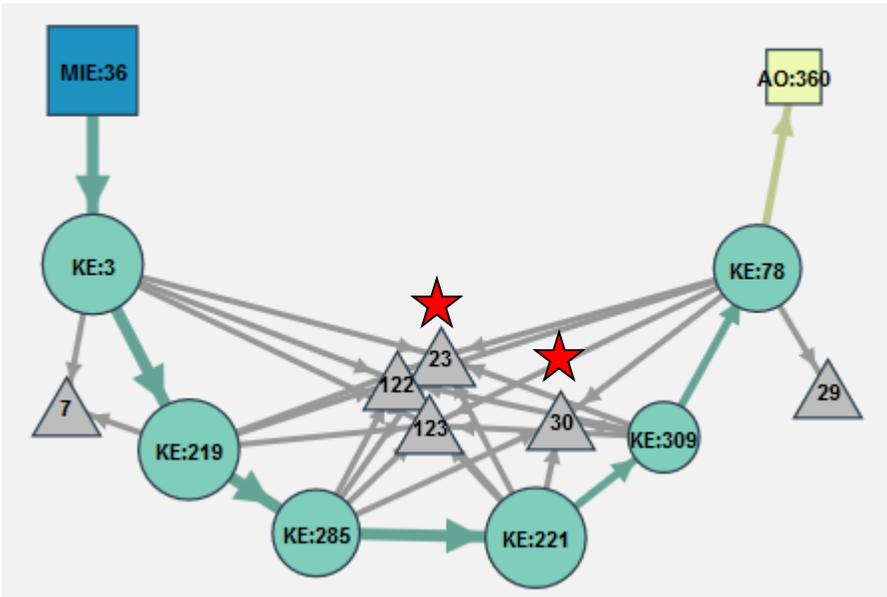
AOP Network as Stored in the AOP-Wiki



Aromatase inhibition leading to reproductive dysfunction (in fish)

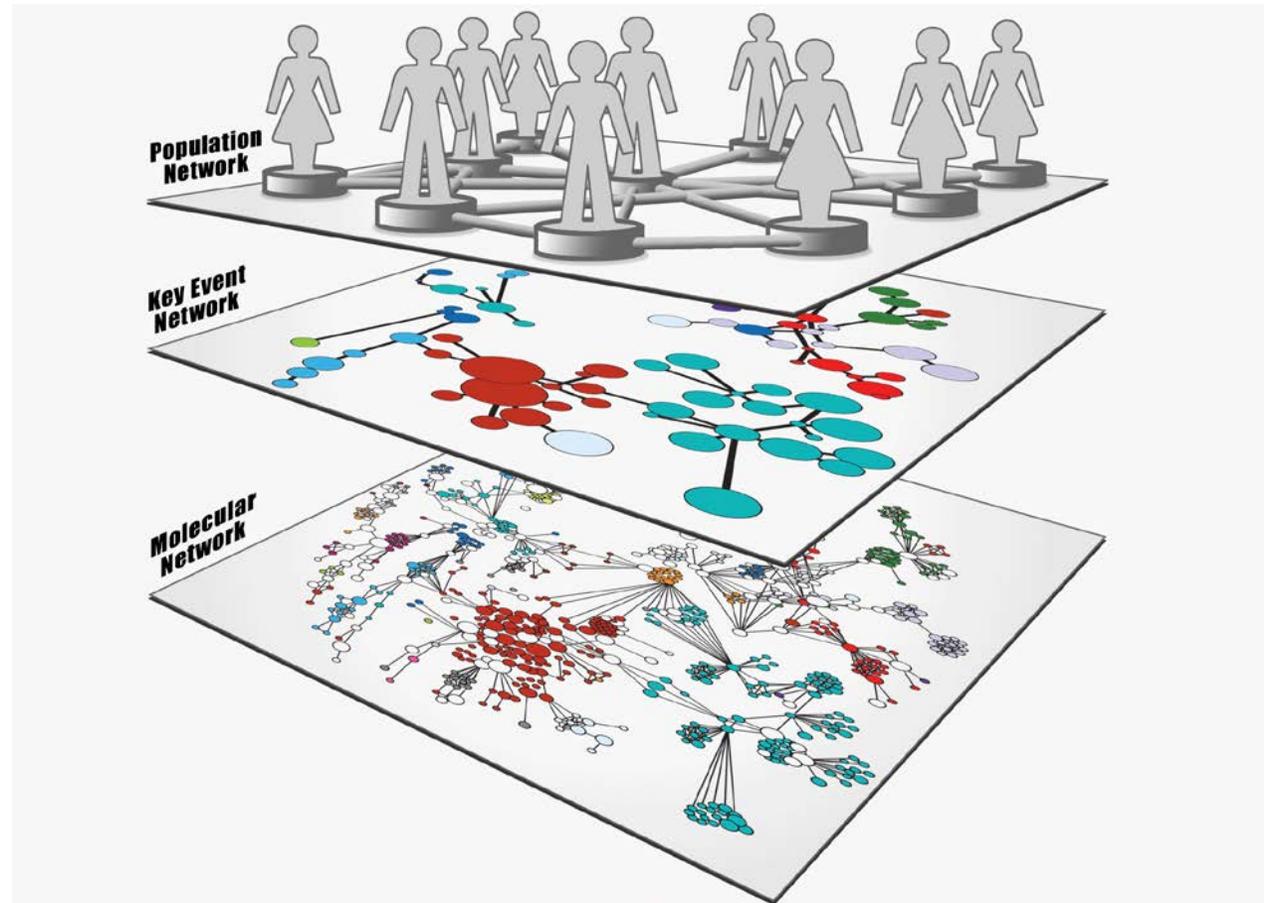
Short name: Aromatase inhibition leading to reproductive dysfunction (in fish)

Relationships Among Key Events and the Adverse Outcome

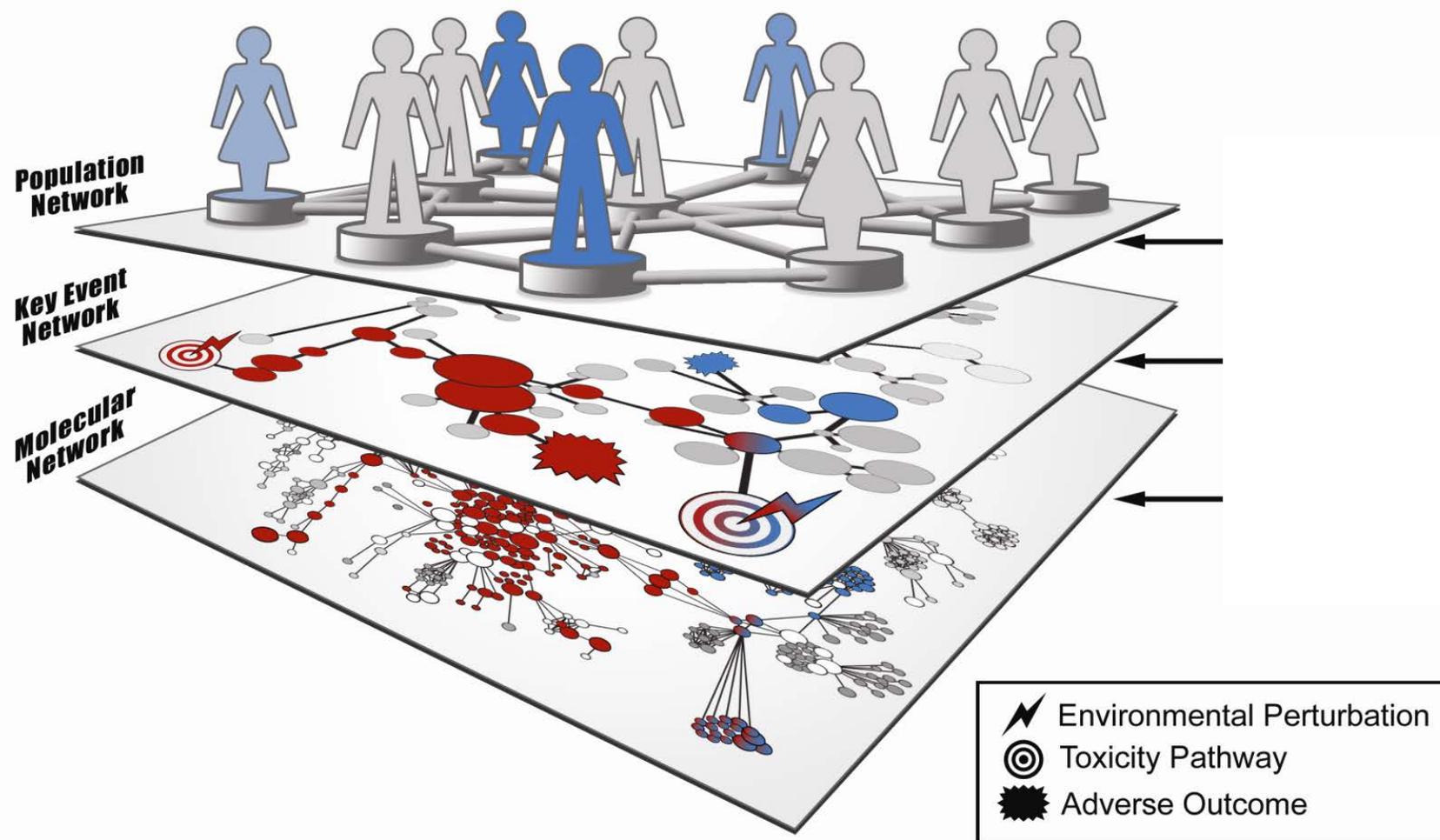


Event	Description	Triggers	Weight of Evidence	Quantitative Understanding
Aromatase, Inhibition	Directly Leads to	17beta-estradiol synthesis by ovarian granulosa cells, Reduction	Strong	Moderate
17beta-estradiol synthesis by ovarian granulosa cells, Reduction	Directly Leads to	Plasma 17beta-estradiol 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

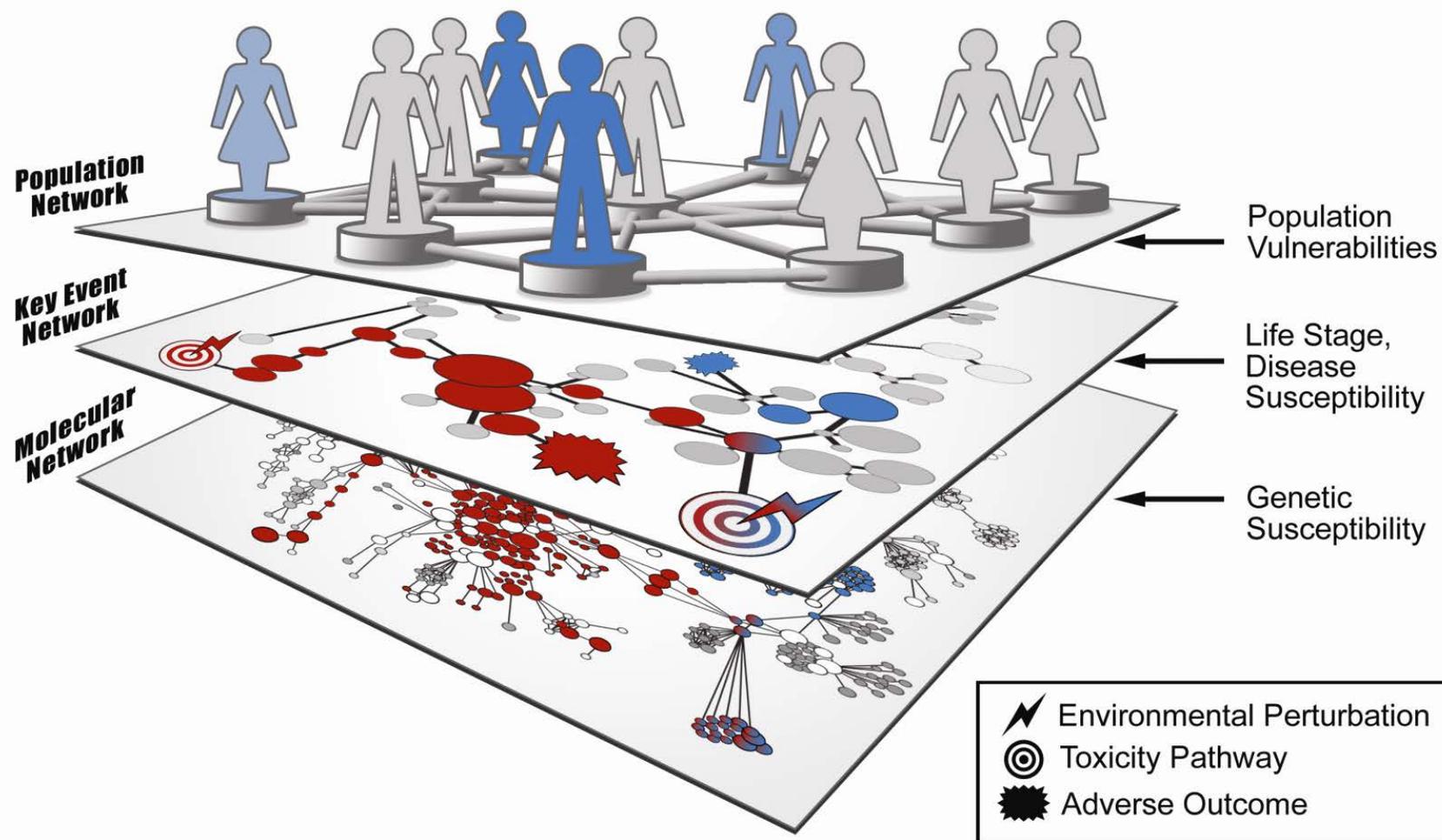
AOPs in a Systems Biology Context



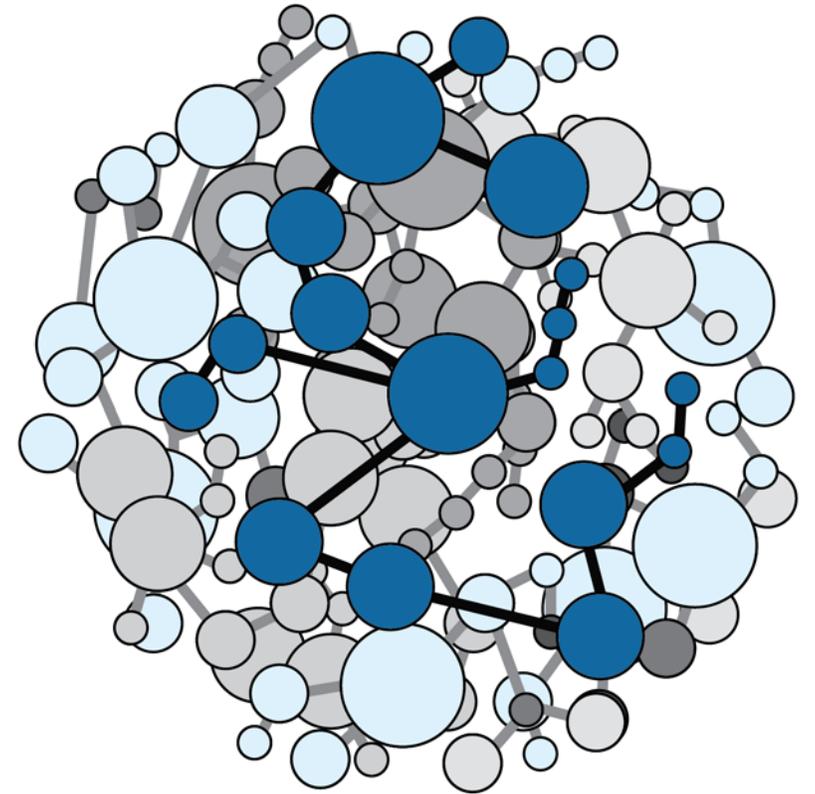
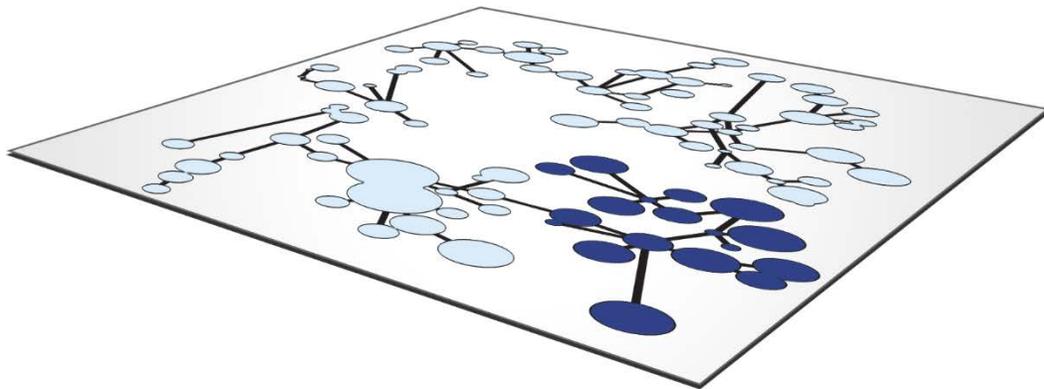
Chemical Interactions Emerge from AOP Networks



Modifying Factors Emerge from AOP Networks

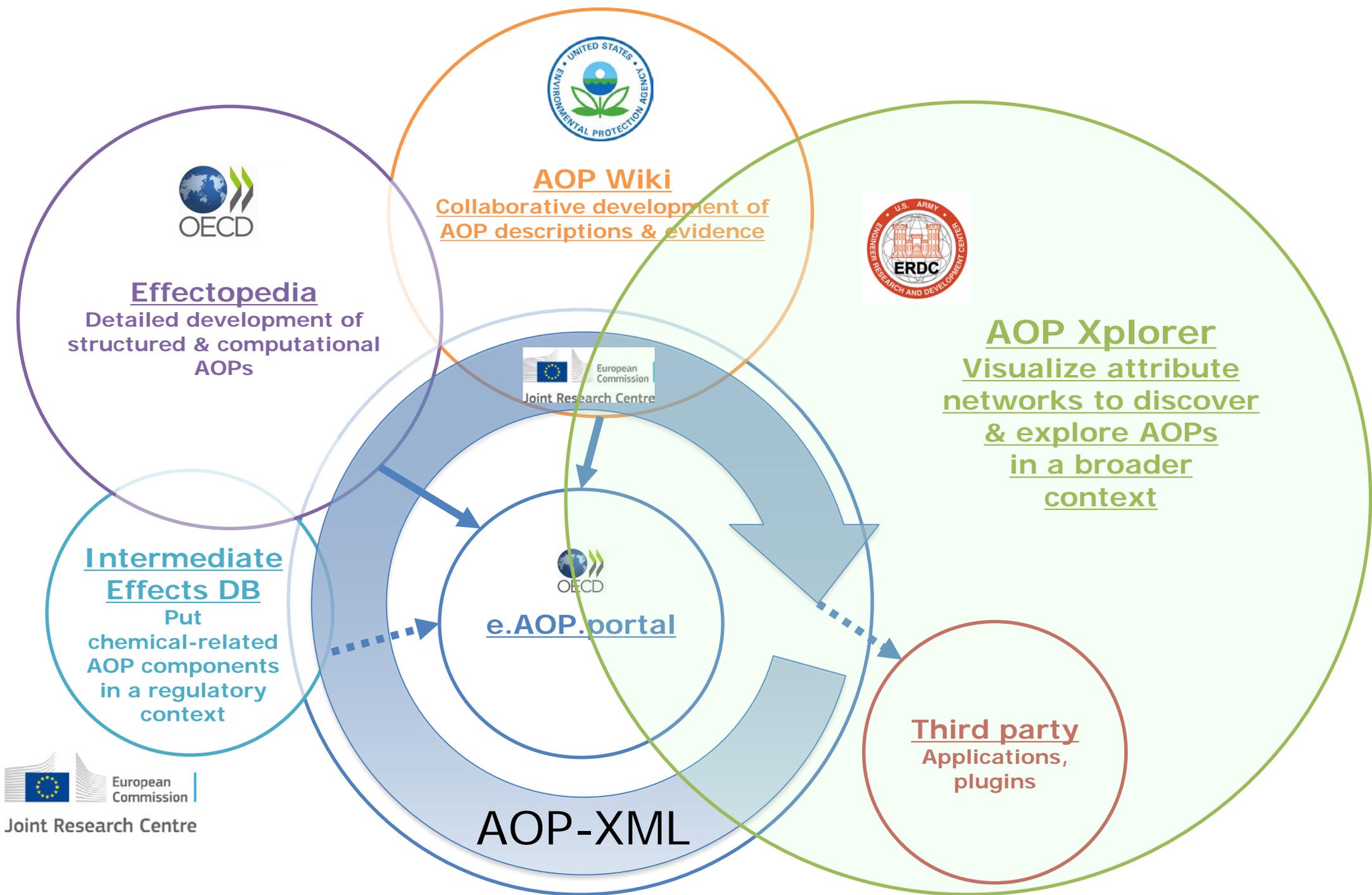


Too many AOPs, too little time...

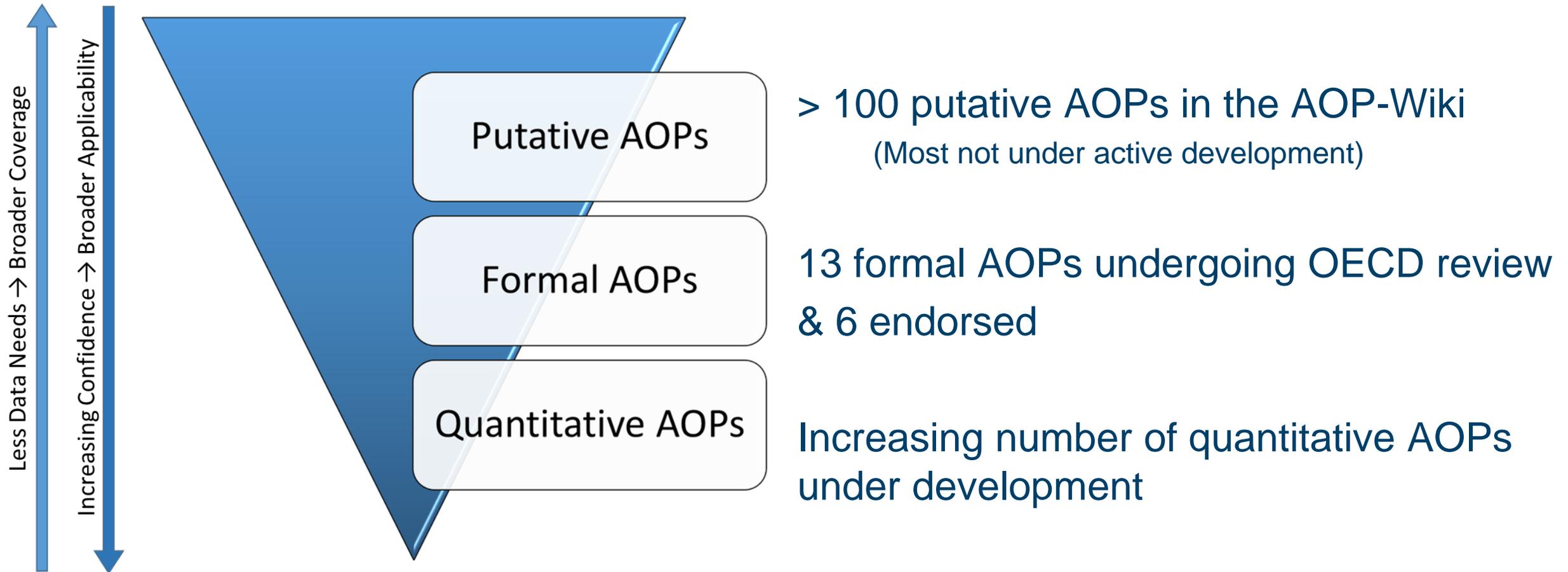


Accelerating AOP Development

Associations
derived from public
data sources



Current Status of AOP 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

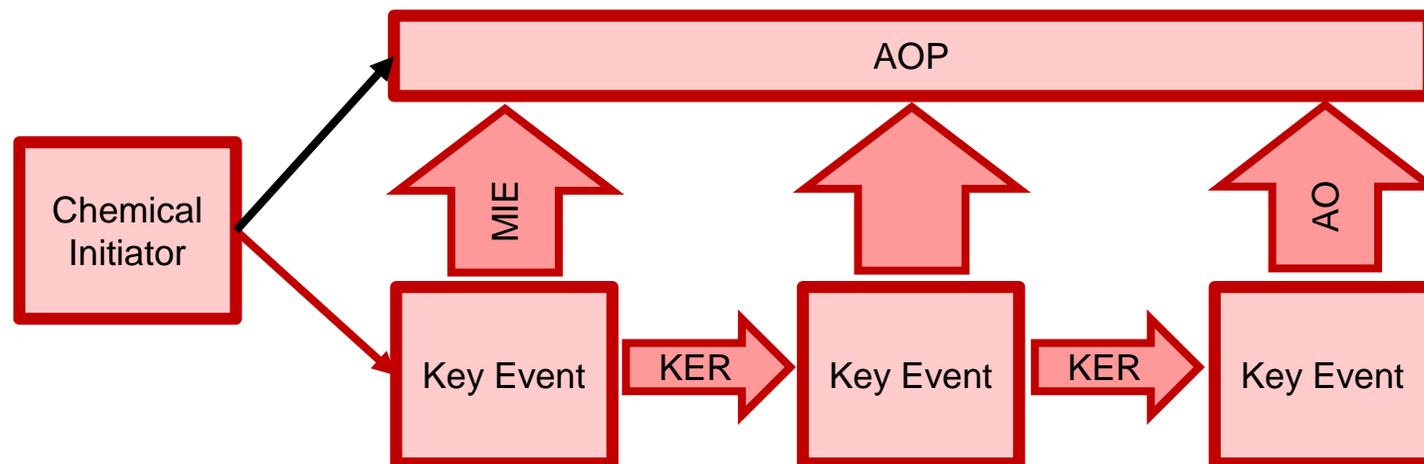
- Collaborative Partners
 - OECD External Advisory Group on Molecular Screening & Toxicogenomics
 - IPCS/WHO Mode of Action Steering Committee

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>

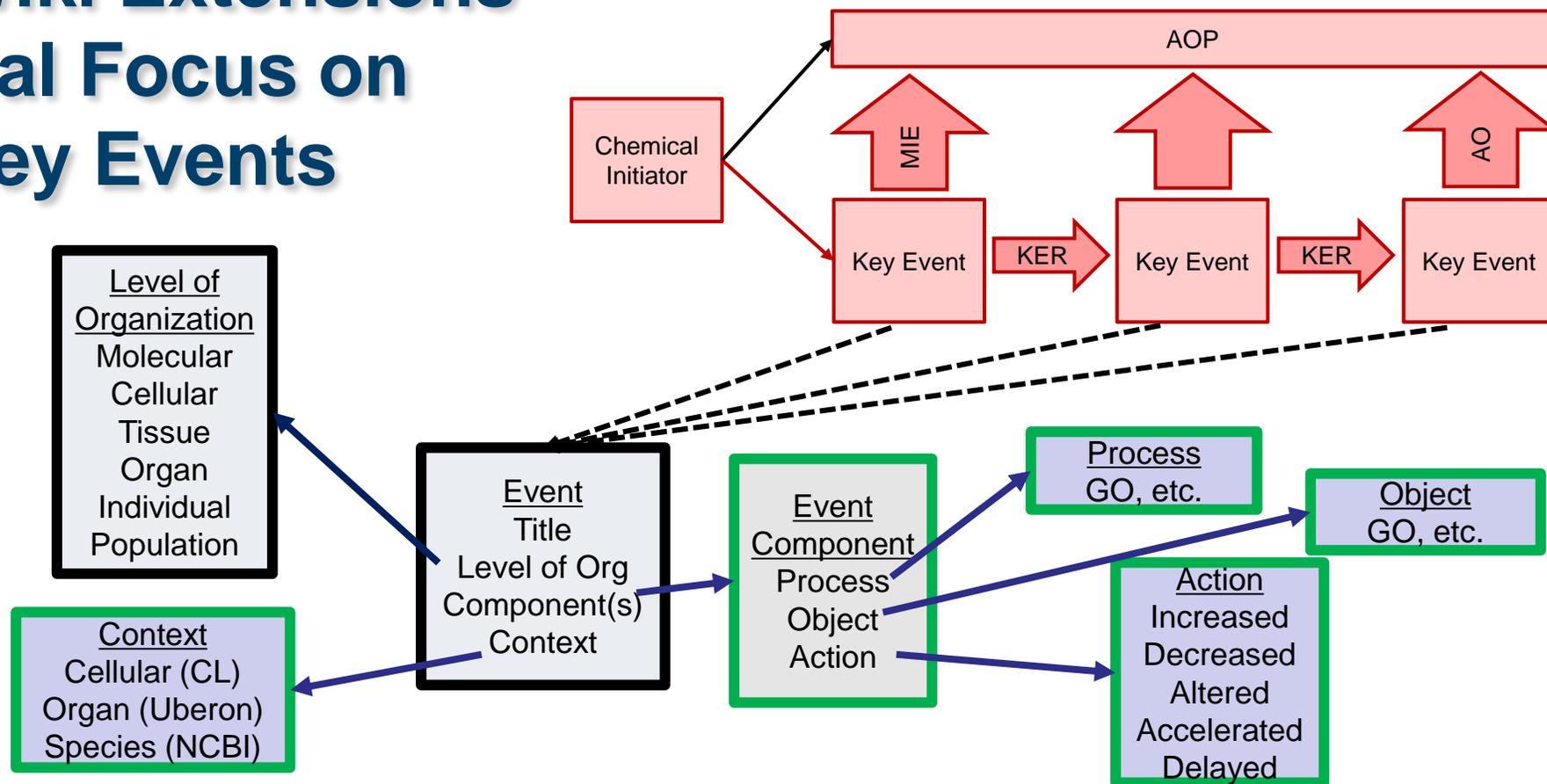
Lyle Burgoon
Kyle Painter

Extending the Core AOP Ontology

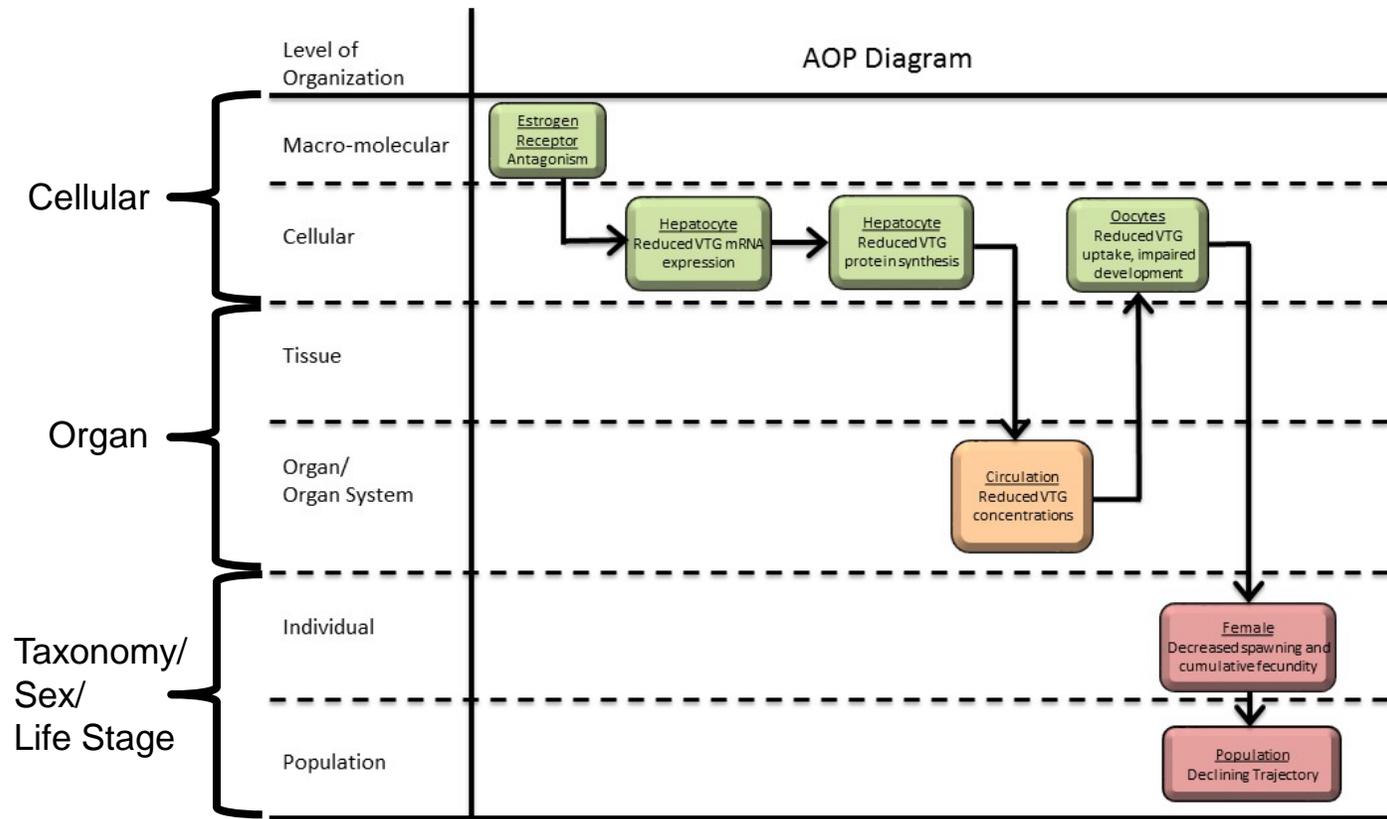
- Core AOP Ontology is extended by incorporating existing chemical and biological ontologies
- US ACE – Extending core ontology to illustrate proof of concept for reasoners in risk assessment
- **US EPA – Extending core ontology to capture AOP-Wiki information**
- EC JRC – Extending core ontology to 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

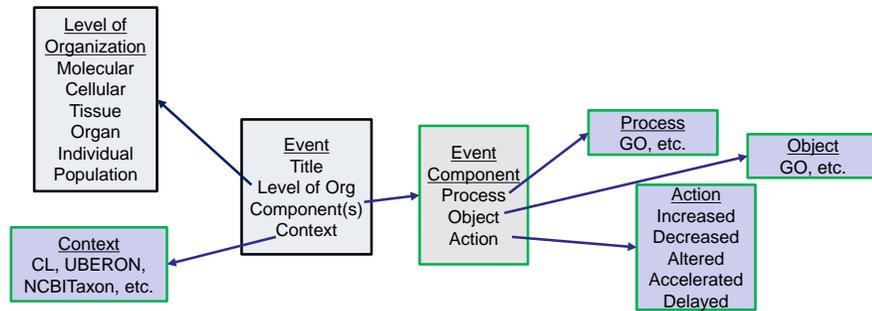
Initial Focus on Key Events



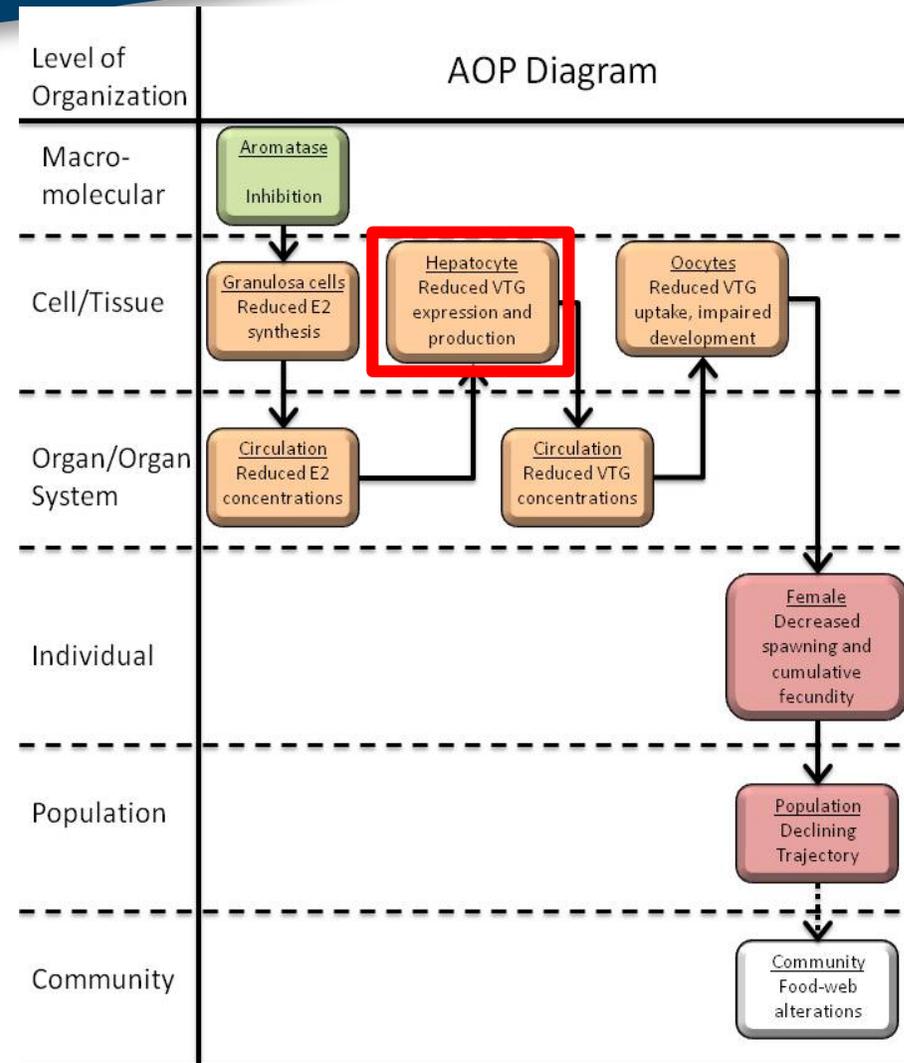
Context changes across levels of biological organization



Using ontology to tag existing wiki entry

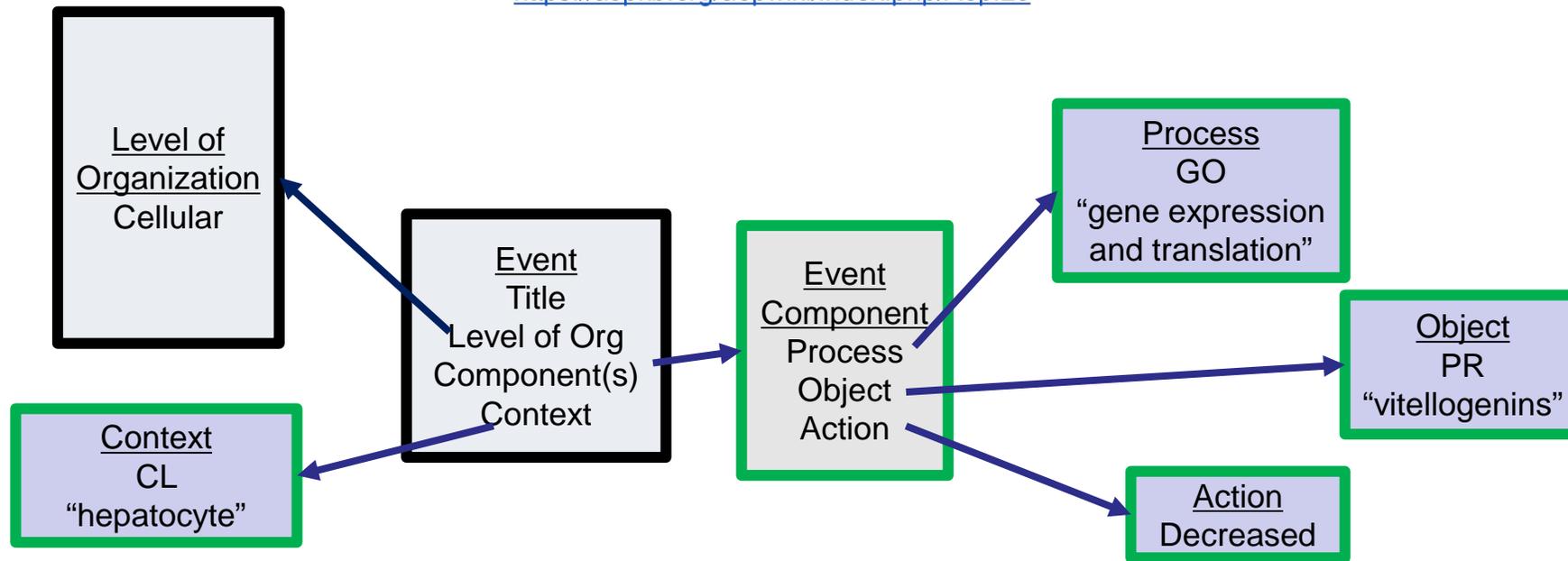


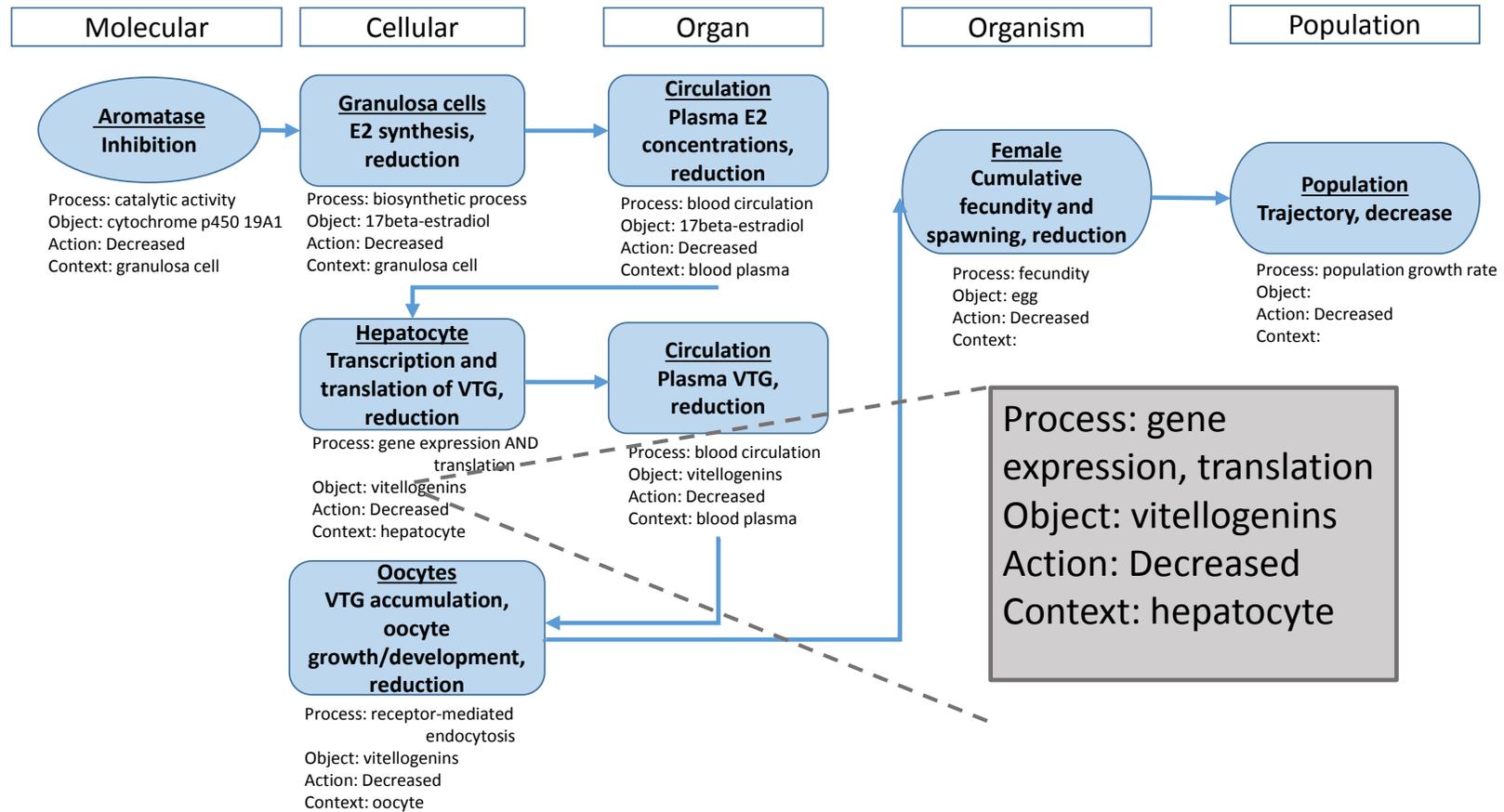
<https://aopkb.org/aopwiki/index.php/Aop:25>



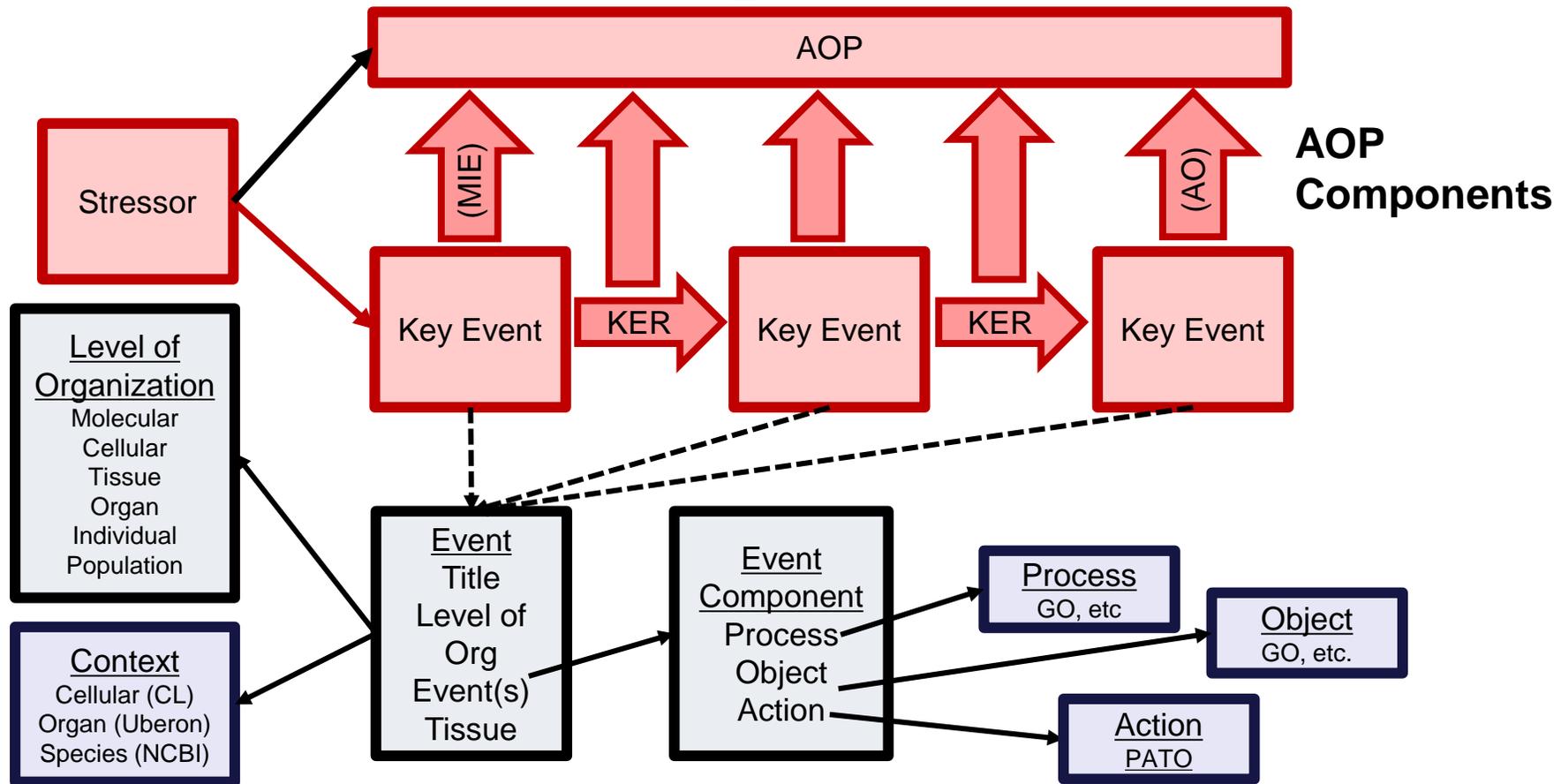
AOP: “Aromatase inhibition leading to reproductive dysfunction (in fish)”
KE: Title “Transcription and Translation of Vitellogenin in Liver, Reduction”

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





Ontologies that describe key events in existing AOPs



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 Jeliaskova
- Olga Tcheremenskaia

- AOP-KB Representatives

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

Main Page

Main Page

Contents [hide]

- 1 Announcements
- 2 Welcome to the Collaborative Adverse Outcome Pathway Wiki (AOP-Wiki)
 - 2.1 Disclaimer
- 3 How to add a new AOP
 - 3.1 Before You Start
 - 3.2 OECD User Handbook
 - 3.3 Commenting on AOPs
 - 3.4 To create a new AOP
 - 3.5 To edit AOP wiki pages
 - 3.6 To edit other wiki pages (key events, MIE's, etc.)

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

- Navigation
 - Main page
 - AOP List
 - AOP Table
 - EAGMST Approved AOPs
- Help
 - FAQ
 - Recent changes
 - Release notes
- Actions
 - Create new AOP

Feedback

- Tools
 - What links here
 - Related changes
 - Special pages
 - Printable version
 - Permanent link
 - Page information

[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 confirming 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, please 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](#)

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[add](#)

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 1. [OECD User Handbook](#)
 2. [Commenting on AOPs](#)
2. [AOP Welcome](#)
 1. [Welcome to the Collaborative Adverse Outcome Pathway Wiki \(AOP-Wiki\)](#)
 2. [Disclaimer](#)
3. [How to add a new AOP](#)
 1. [For more detailed instructions, please see the main HELP page.](#)
 2. [Before you start](#)
 3. [To create a new AOP](#)
 4. [To edit AOP pages](#)
 5. [To edit other pages \(key events, MIE's, etc.\)](#)

API

Links to OECD & SAAOP AOP Pages:

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	TFHAWNT Endorsed	1.11	<input type="button" value="Edit status"/> <input type="button" value="Destroy"/>
Alkylation of DNA leading to cancer	Arthur Author	Under development: Not open for comment. Do not cite	Under Development	DNA alkylation	cancer			<input type="button" value="Edit status"/> <input type="button" value="Destroy"/>
Alkylation of DNA leading to cancer	Arthur Author	Not under active development	Archived	DNA alkylation	cancer			<input type="button" value="Edit status"/> <input type="button" value="Destroy"/>
Protein Alkylation leading to Liver Fibrosis	Arthur Author	Open for citation & comment	Included in OECD work plan	Protein alkylation	liver fibrosis	TFHAWNT Endorsed	1.14	<input type="button" value="Edit status"/> <input type="button" value="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

[TFHA/WNT Endorsed](#)

Open for citation & comment

[EAGMST Approved](#)

Open for citation & comment

[EAGMST Under Review](#)

Open for citation & comment

[Under Development](#)

Under development: Not open for comment. Do not cite

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 uroporphyrin	Arthur Author	AhR	uroporphyrin	Edit

Contents

[Under Development](#)

Under development: Not open for comment. Do not cite

[Archived](#)

Not under active development

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

-
- admin
 - author
 - gardener

set roles

- admin
- author
- gardener

set roles

- admin
- author
- gardener

set roles

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

Authors

You Song¹ and Knut Erik Tollefsen^{1,2}

¹ Norwegian Institute for Water Research (NIVA), Section of Ecotoxicology and Risk Assessment
Gaustadalléen 21, N-0349 Oslo, Norway

² Norwegian University of Life Sciences (NMBU), Faculty of Environmental Science and Techno
Department of Environmental Sciences (IMV). P.O. Box 5003, N-1432 Ås, Norway

Contact:

Corresponding Author Arthur Author

[Change](#)

Contributors

[Add Contributor](#)

[Arthur Author](#)

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)	Authors & Gardeners	Edit Destroy
Reduction, 17beta-estradiol concentrations	17beta-estradiol concentrations	Gardeners Only	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

Editing Aop

Title

Aromatase inhibition leading to reproductive dysfunction (in fist)

Short name

Aromatase inhibition leading to reproductive dysfunction (in fist)

Corresponding author

Undefined

Authors

WYSIWYG Easily create tables and add images



Source [Clipboard icons] [Undo] [Redo] [Search] [ABC] [List icons] [Table icon] [Image icon] [Omega icon] Styles Normal Font Size A A

Dan Villeneuve, US EPA Mid-Continent Ecology Division (villeneuve.dan@epa.gov)

body p strong

Save changes to all sections with one click

Edit all text sections from a single page

Back to AOP Snaps All AOPs Watch

Comment

Update AOP

- 1. Abstract
 - 1. Background
- 2. Overall Assessment of the AOP
 - 1. Domain of Applicability
 - 2. Essentiality of the Key Events
 - 3. Weight of Evidence Summary
 - 4. Quantitative Considerations
- 3. Considerations for Potential Applications of the AOP
- 4. References

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

New Event Sub Event

Event Inhibition, Aromatase

Process

catalytic activity

Object

cytochrome p450 19a1

Action

Decreased

Create Event sub event

Comments

- Modern look & feel
- Allows comments on comments

Comments for Event:2

Cataia Ives

On June 08, 2016 09:26

Cute comment

Reply

Edit

Destroy

Cataia Ives

On June 08, 2016 09:26

I agree

Edit

Destroy

New Comment

Versions of Aop:154

Aop as of:	Created By	from to
June 07, 2016 10:30	Cataia Ives	<input type="radio"/> <input checked="" type="radio"/>
May 20, 2016 16:10	Cataia Ives	<input checked="" type="radio"/> <input type="radio"/>
May 20, 2016 15:45	Cataia Ives	<input type="radio"/> <input type="radio"/>
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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

Title

nothing to show

Short Name

nothing to show

Authors

nothing to show

Abstract

nothing to show

Aop:154 as of June 07, 2016 10:30

nothing to show

nothing to show

```
<p>Great author</p>
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<p>This AOP is concise</p>
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Acknowledgements

OECD AOP-KB Working Group



- Stephen Edwards
- Dan Villeneuve
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- Robert Kavlock

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- Evgeniia Kazymova



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- Brigitte Landesmann
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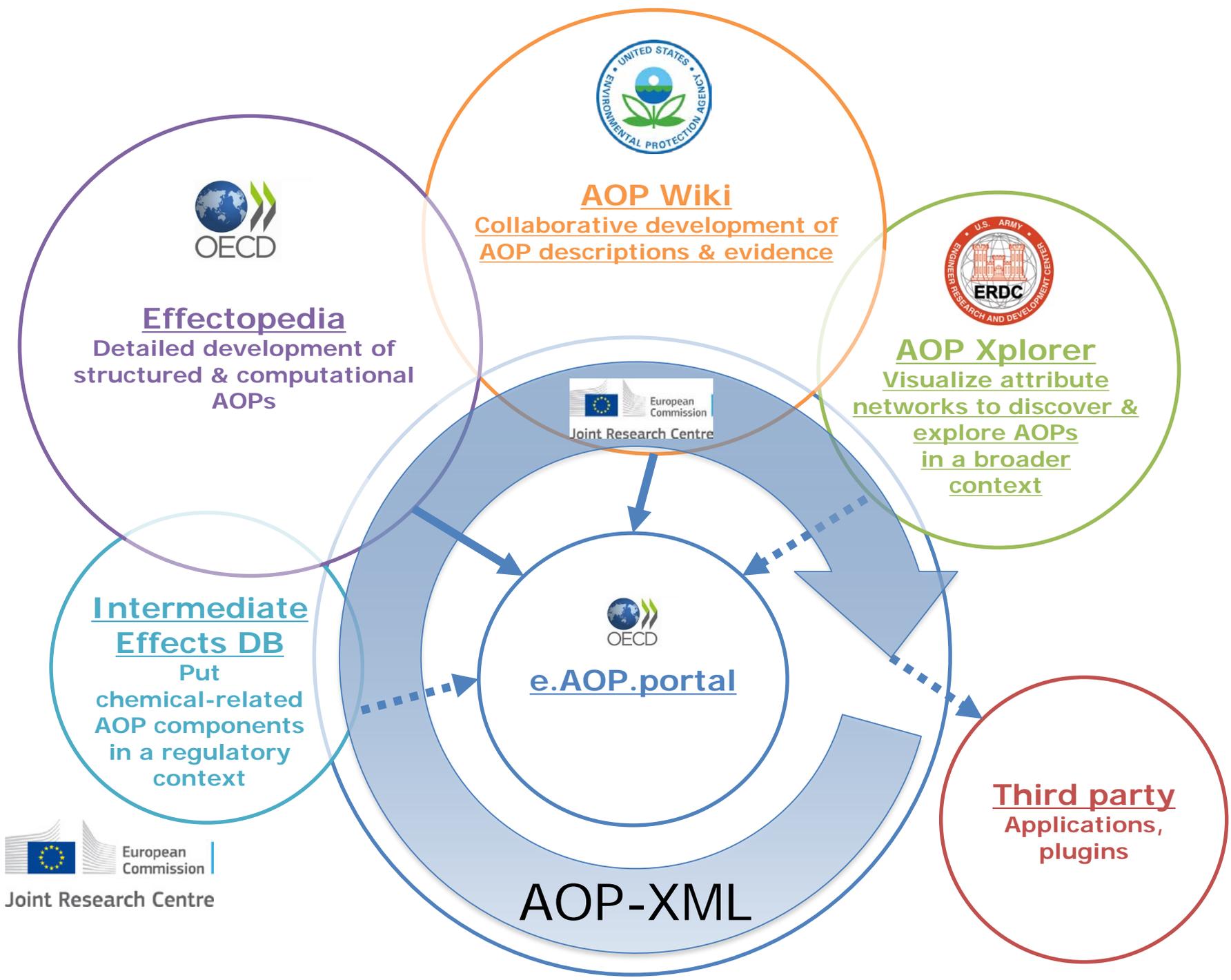
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- Magda Sachana
- Joop DeKnecht



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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



Questions?

