Adverse Outcome Pathway Networks and the AOP Knowledgebase

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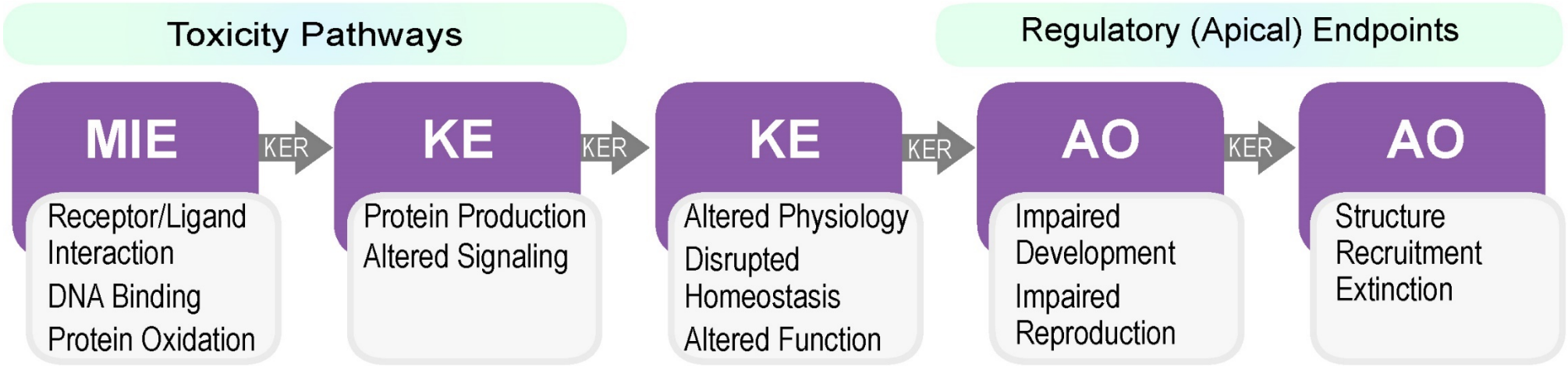
The views expressed in this presentation are those of the presenter, and do not necessarily reflect the views and policies of the Agency.

Outline

- Knowledge management
  - Evidence assembly
  - Data organization
  - Computational modeling
- AOP Networks
  - Automatic assembly by design
  - Basis for decision support tools
  - Challenges and opportunities

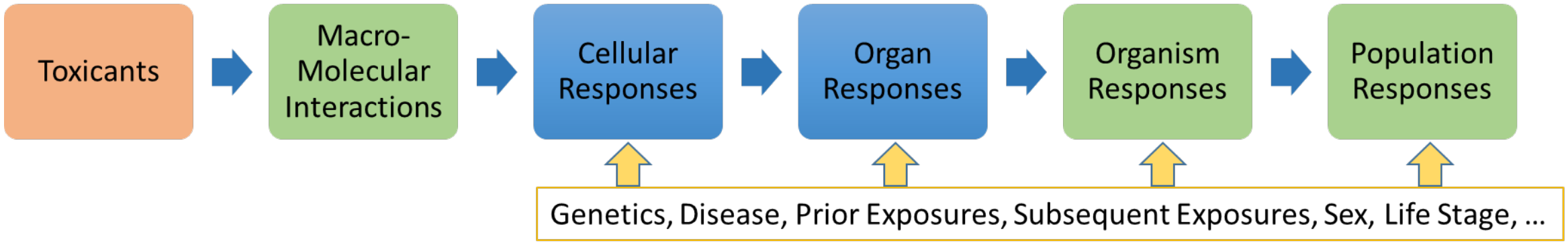
AOPs Connect Toxicity Pathways to Regulatory Endpoints



Predictivity of measurement for AO decreases

Time between exposure and effect increases

Factors Determining Predictivity of Early Key Events

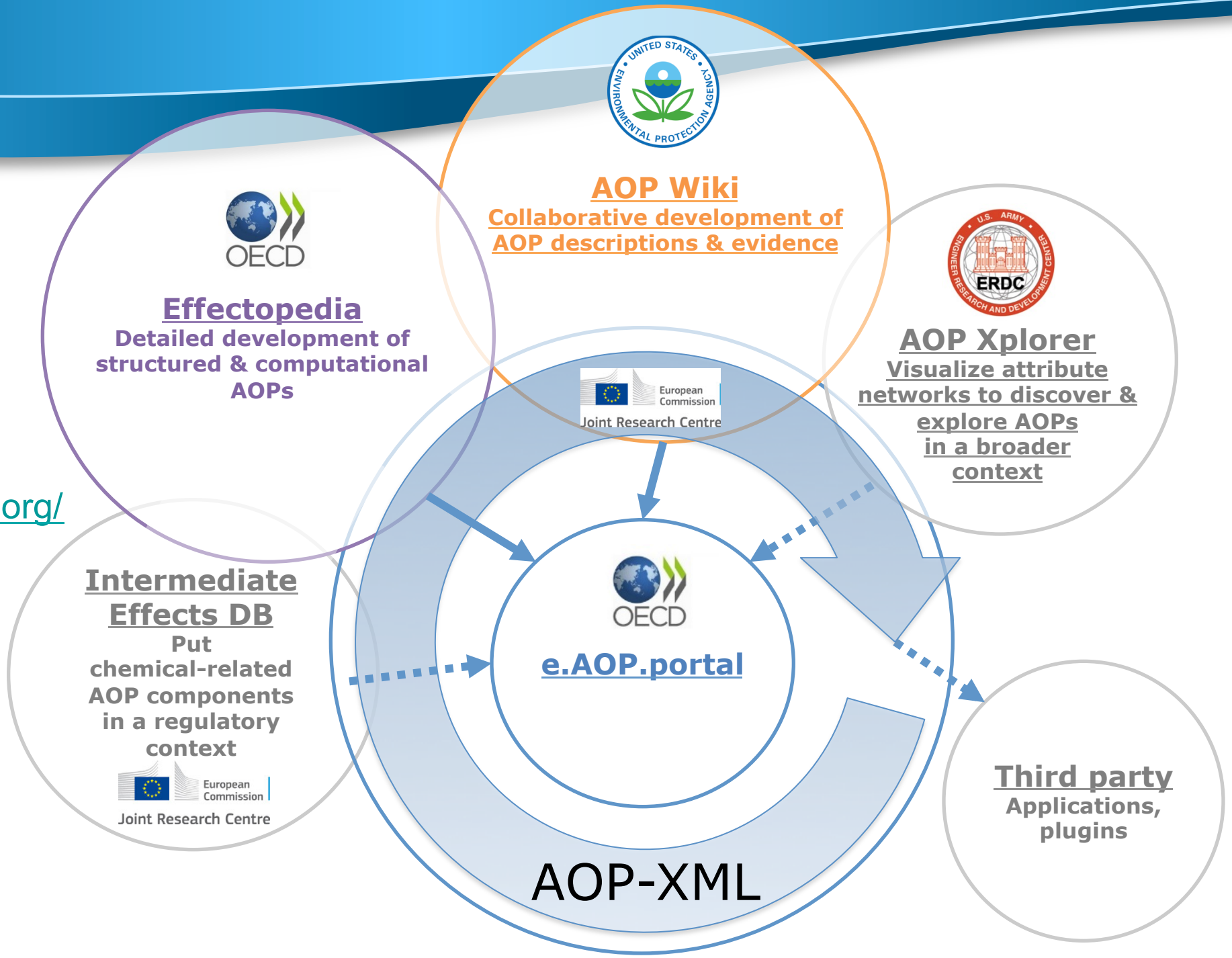


- Evidence supporting the KERs between that KE and the AO
- Quantitative understanding of the downstream KERs
- Modifying factors that influence downstream KEs & KERs

http://aopkb.org/

https://aopwiki.org/

https://www.effectopedia.org/



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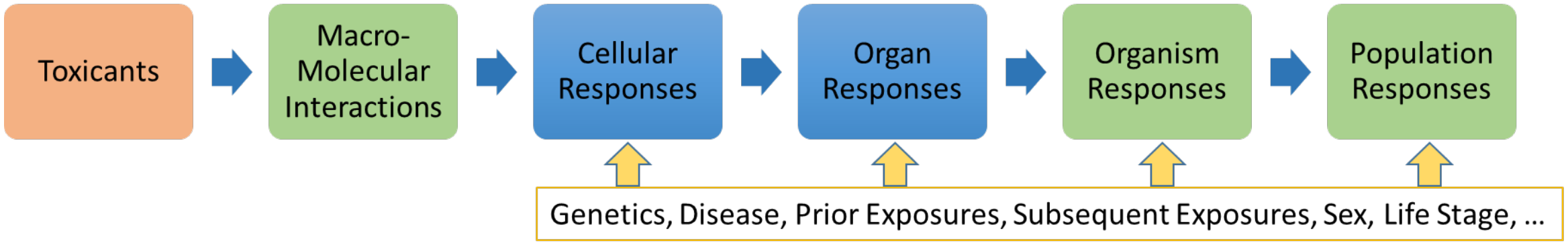

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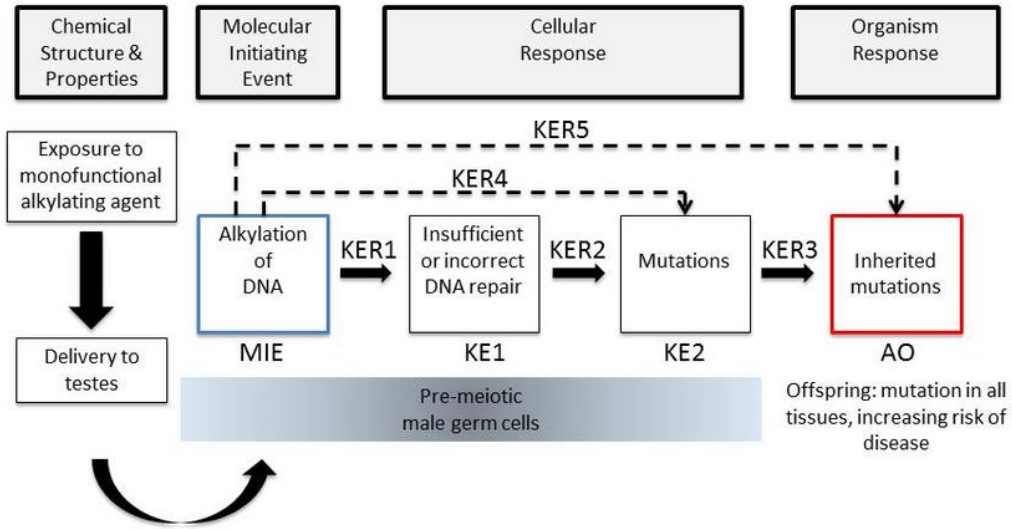
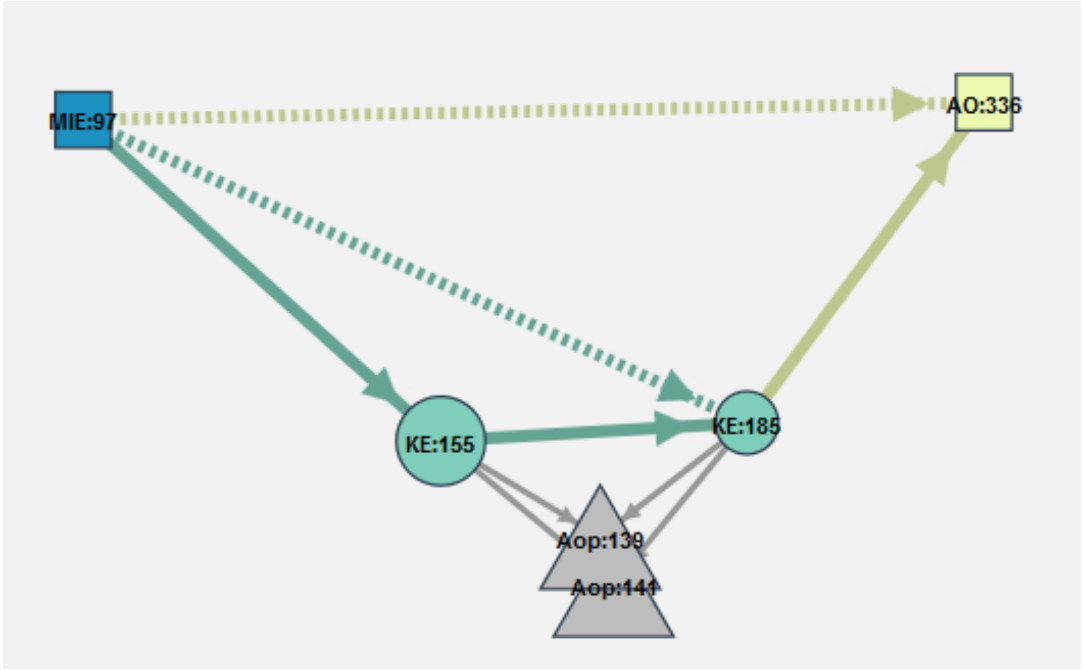
AOP Title

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

Short name: Alkylation of DNA leading to heritable mutations





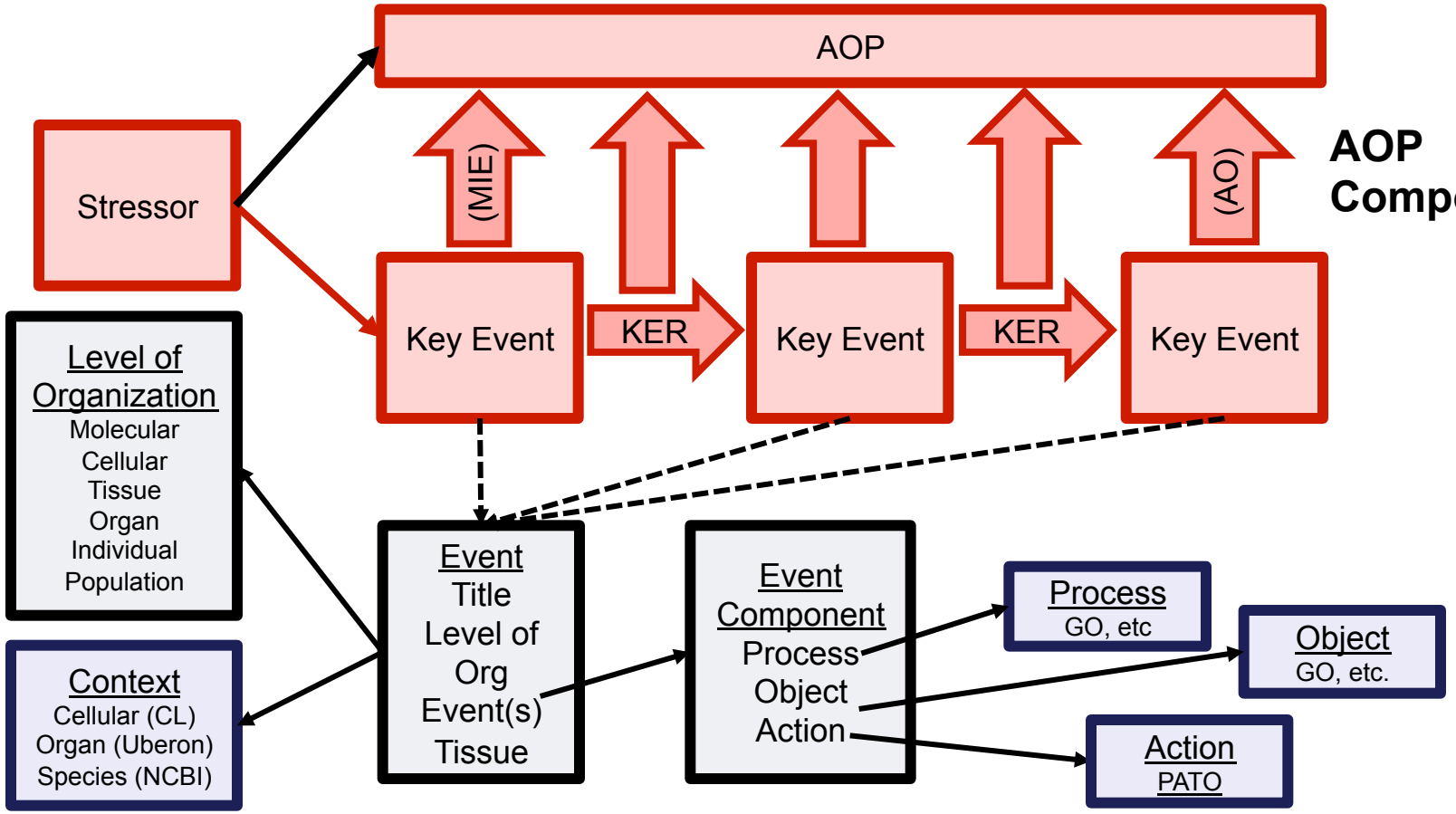
Carole Yauk – https://aopwiki.org/aops/15

Yauk et al., *Environ Mol Mutagen* (2015) **56**:724-50. doi: 10.1002/em.21954.

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

Ontologies that describe key events in existing AOPs



Lyle Burgoon
Cataia Ives

Event components-Definitions

- **Process**

  Biological process, dynamics of the underlying biological system (e.g. receptor signaling). Ideally this represents the normal biology that is perturbed as part of the AOP not the perturbation itself.

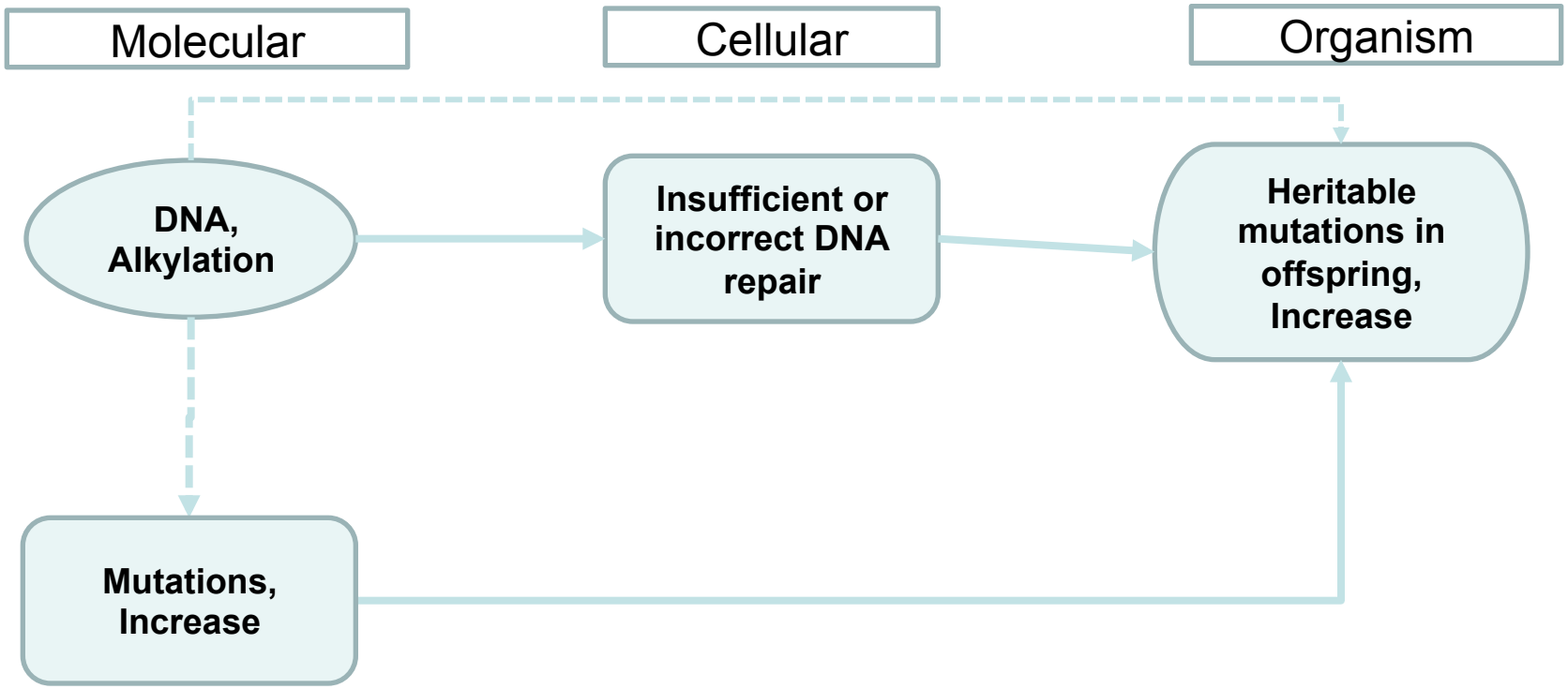
- **Object**

  Biological object (e.g. specific biological receptor that is activated or inhibited). This term again represents the object only and is associated with the normal biology of the system.

- **Action**

  This represents **the perturbation of this system** described by the other two terms that results in this key event (e.g. ‘decreased’ in the case the a receptor is inhibited to indicate a decrease in the signaling by that receptor).

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



Cataia Ives

https://aopwiki.org/aops/15

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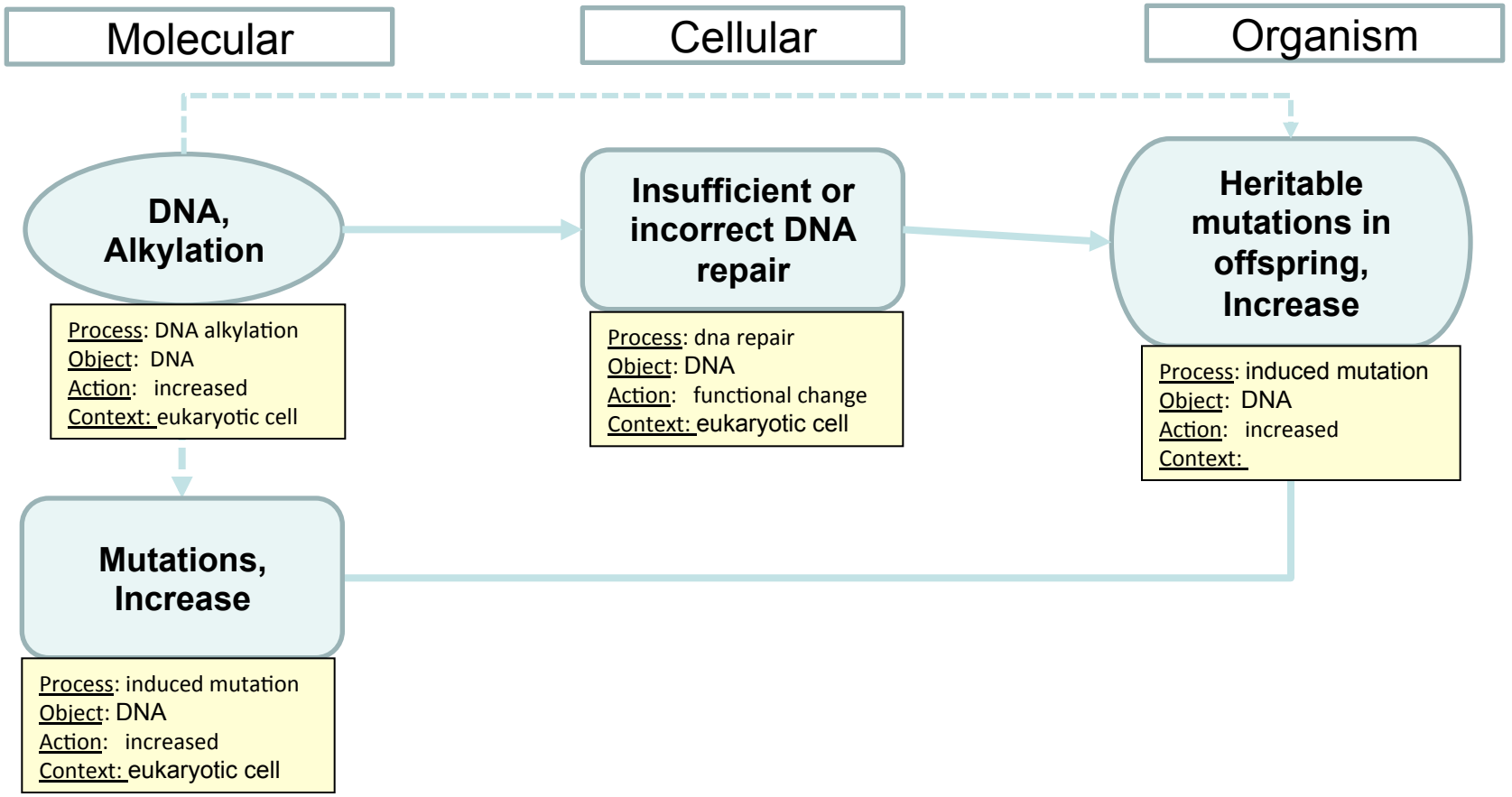


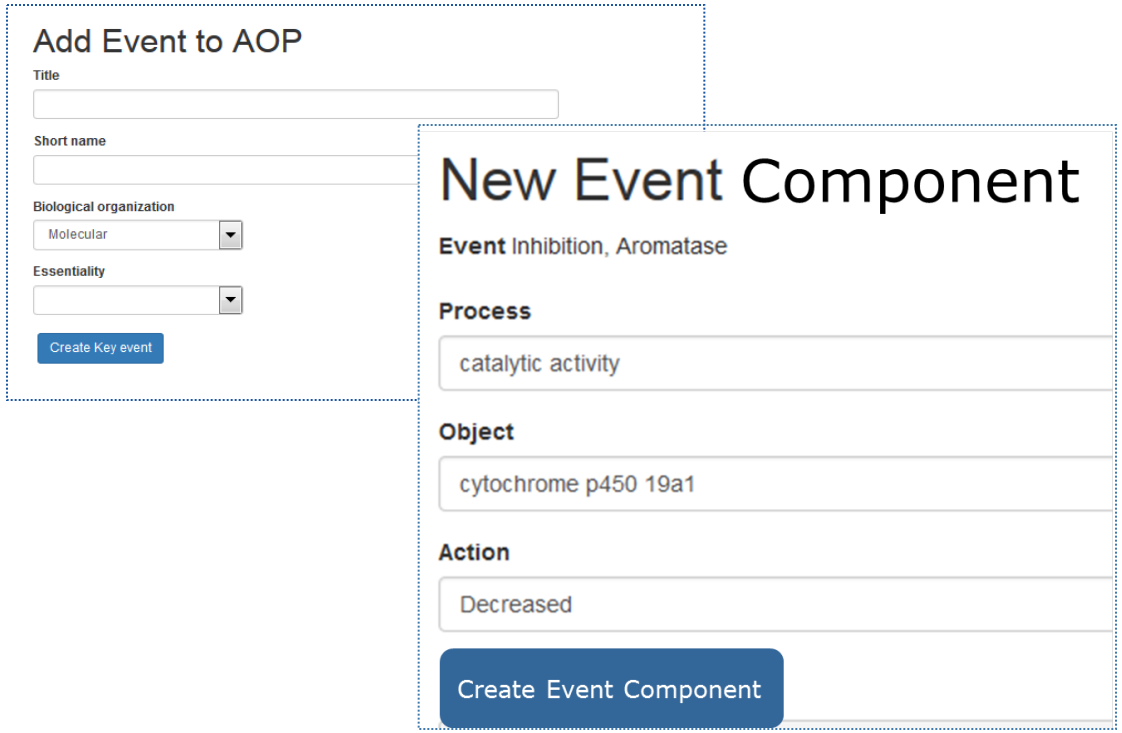
Cataia Ives

https://aopwiki.org/aops/15

What's new in the AOP Wiki

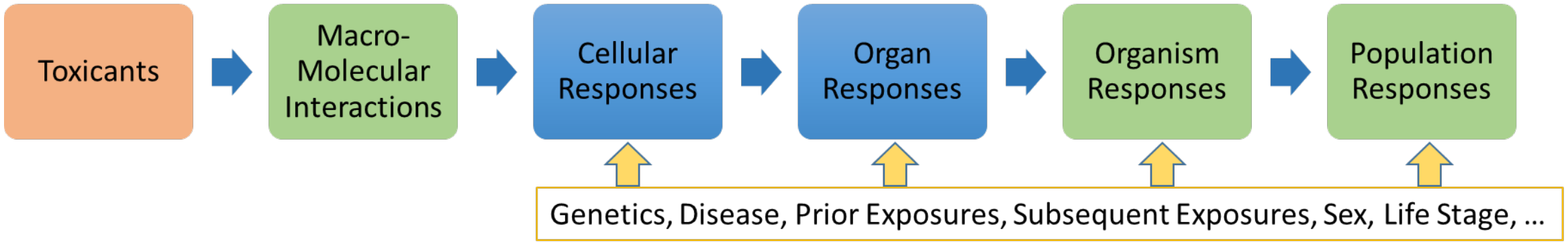
- The AOP Wiki now provides authors the ability to tag AOPs with terms from controlled vocabularies and ontologies.

- In order to harmonize the tagging of existing AOPs in the Wiki, we worked with authors to annotate all AOPs in the AOP-Wiki as of December 4, 2016.
- Currently working on instructions for authors to annotate their own AOPs in the future.



Ivana Campia

Factors Determining Predictivity of Early Key Events



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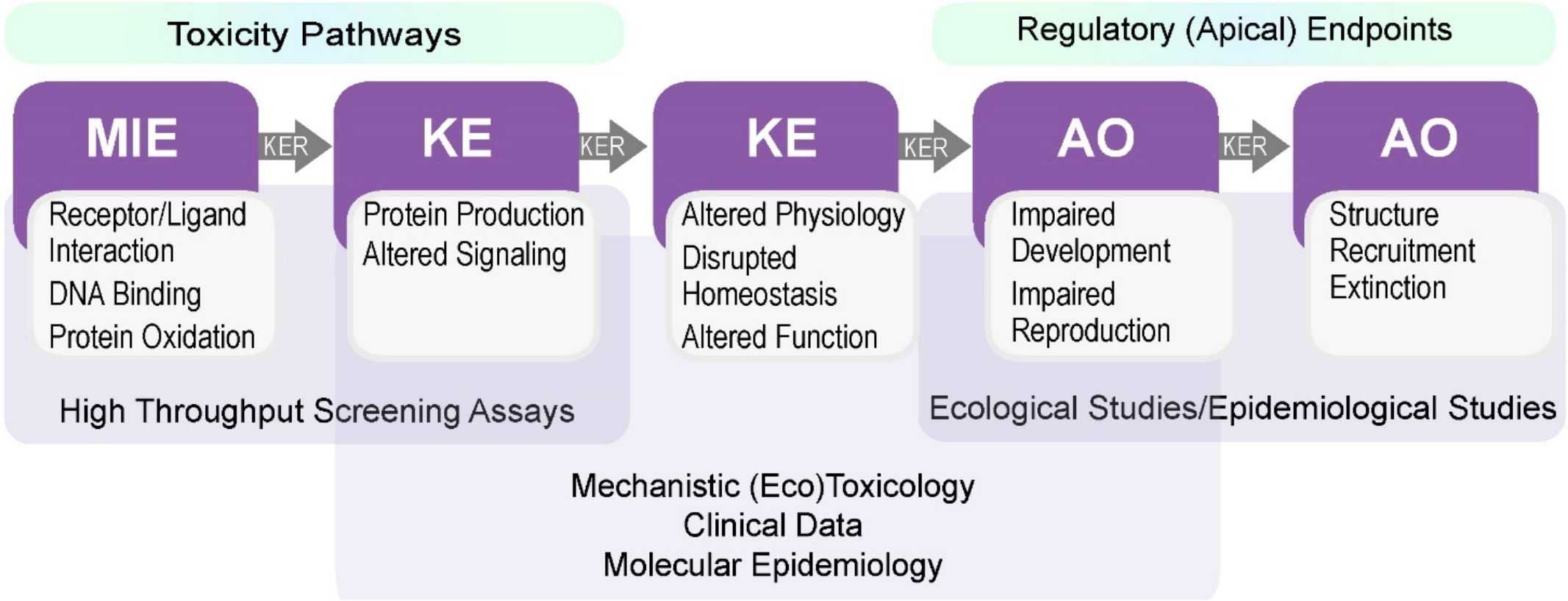
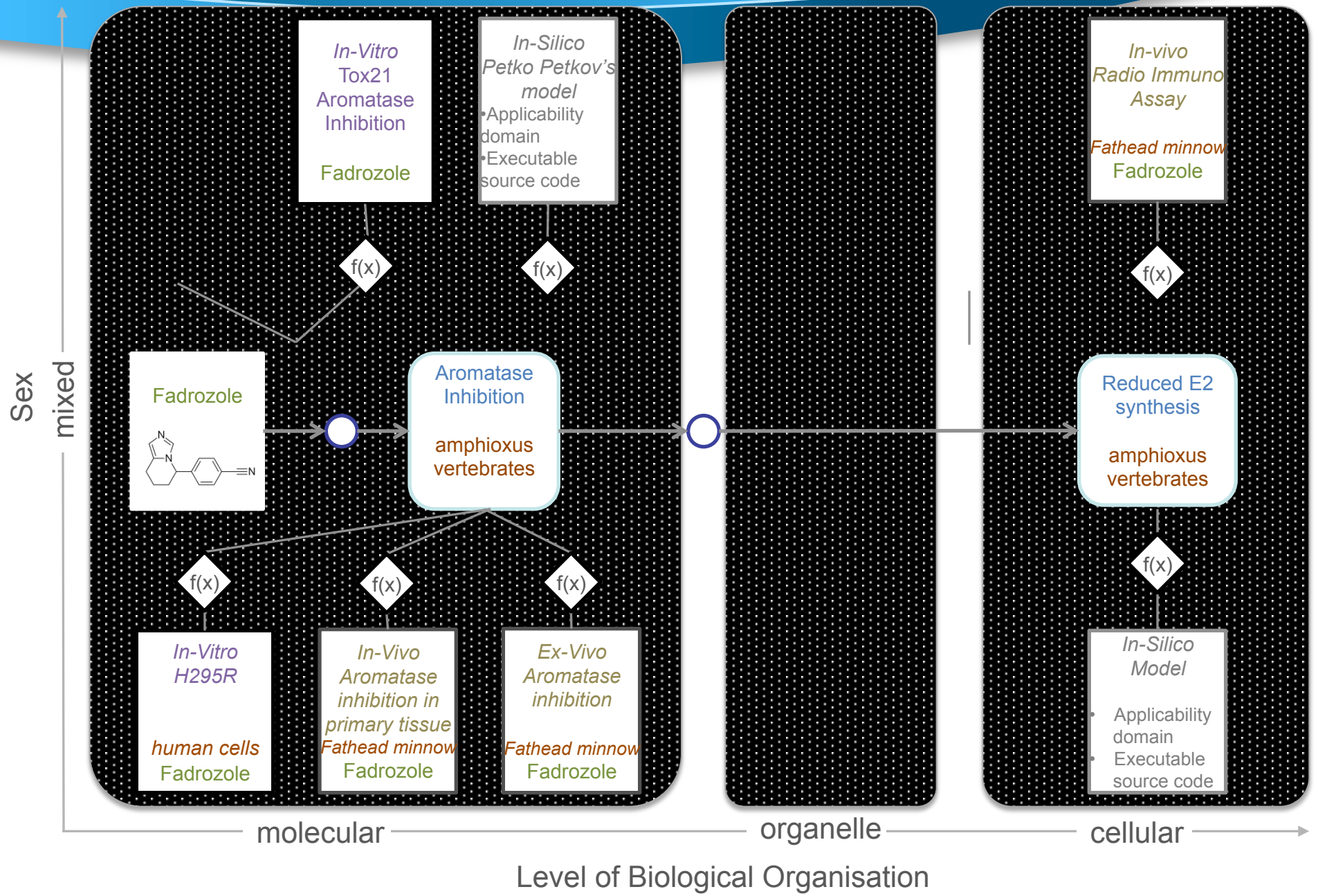
AOP Provides Understanding & Scaffold for Data

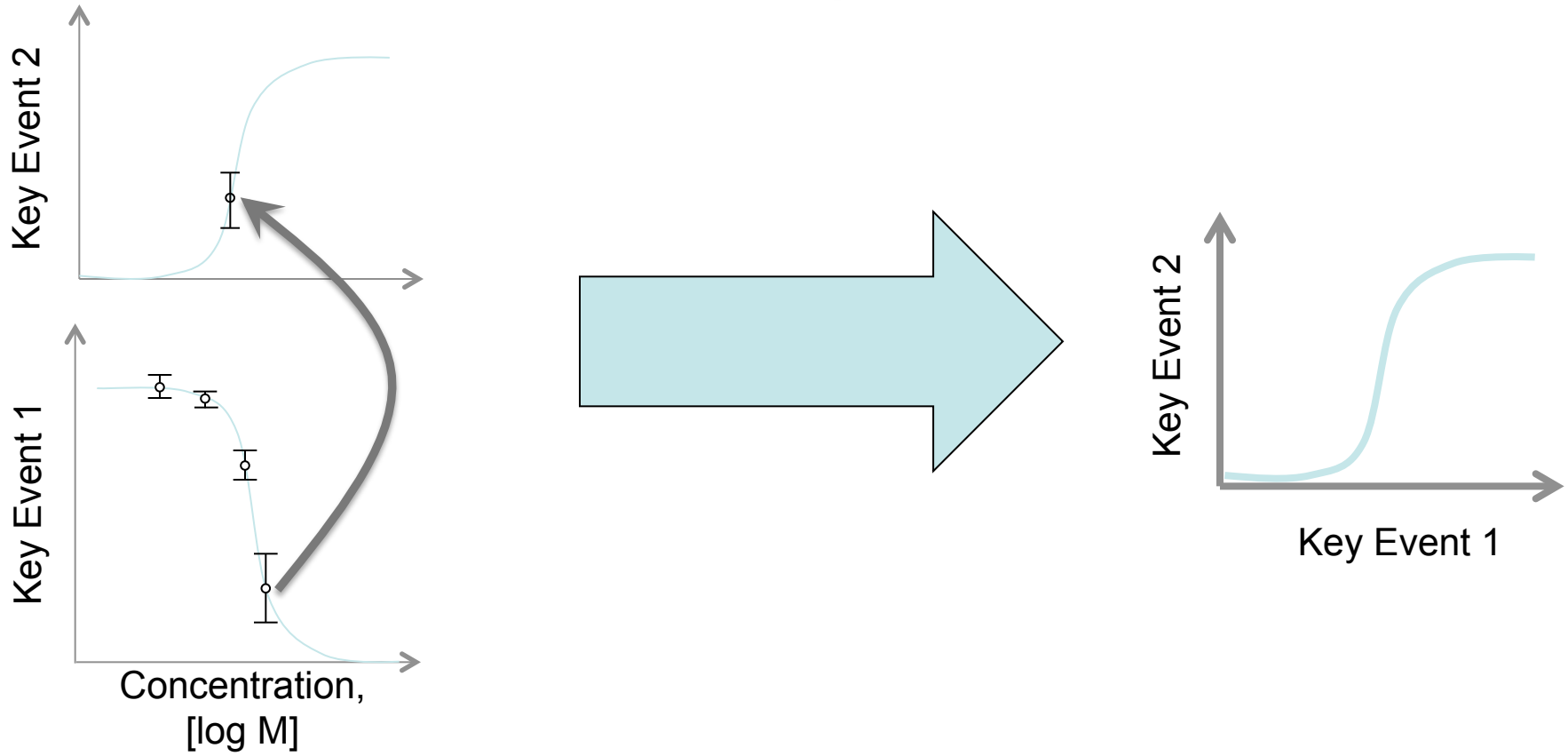




Pathway Elements and quantitative information

Effectopedia
Hristo Aladjov

Transformation of Dose-Response to Response-Response



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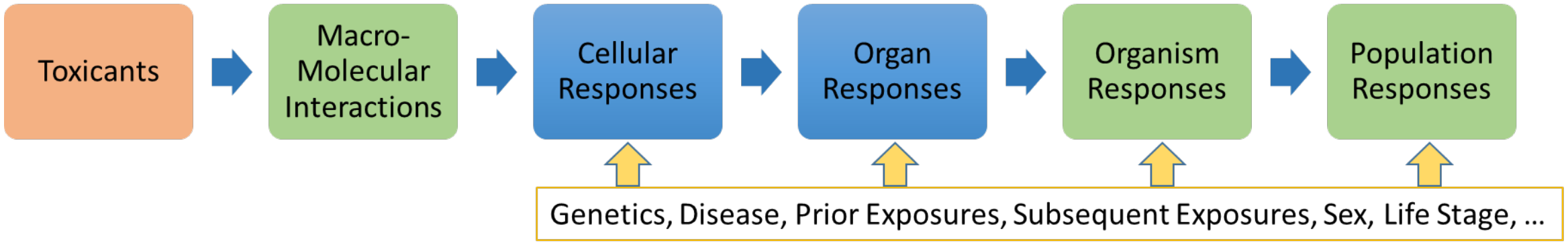

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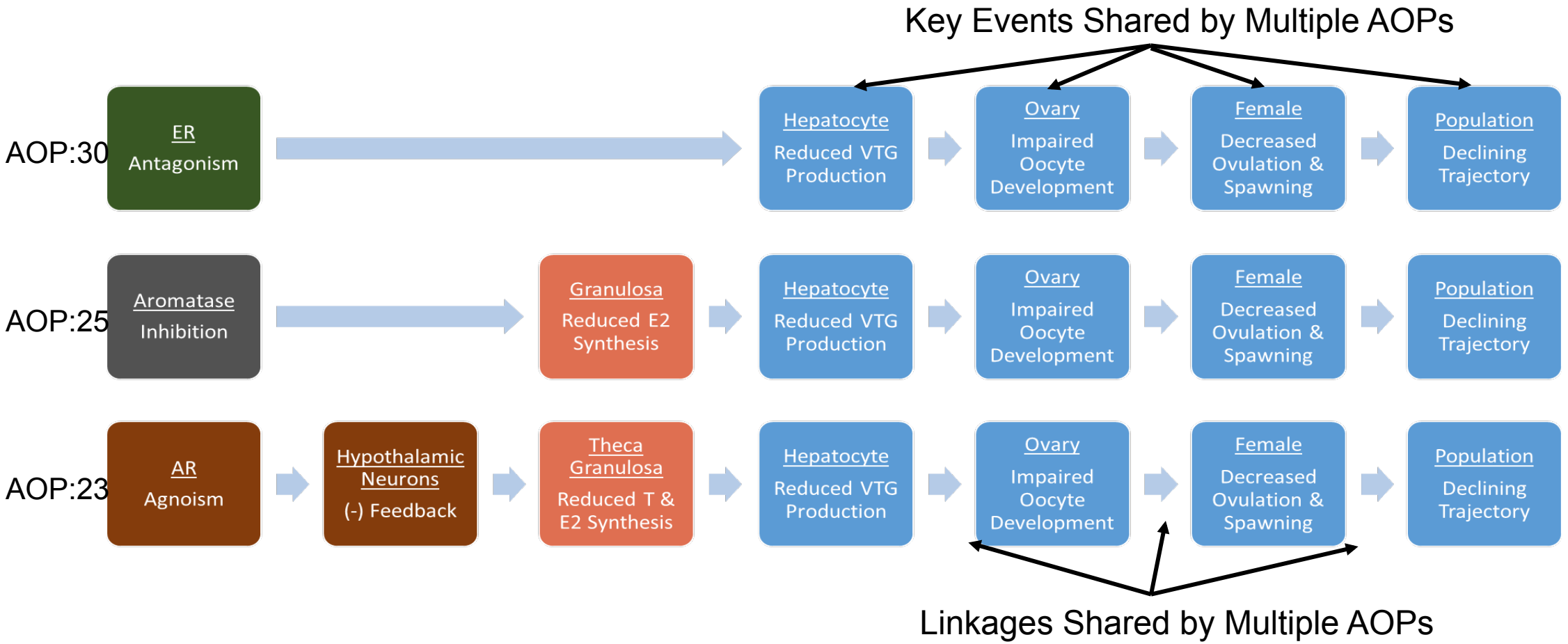
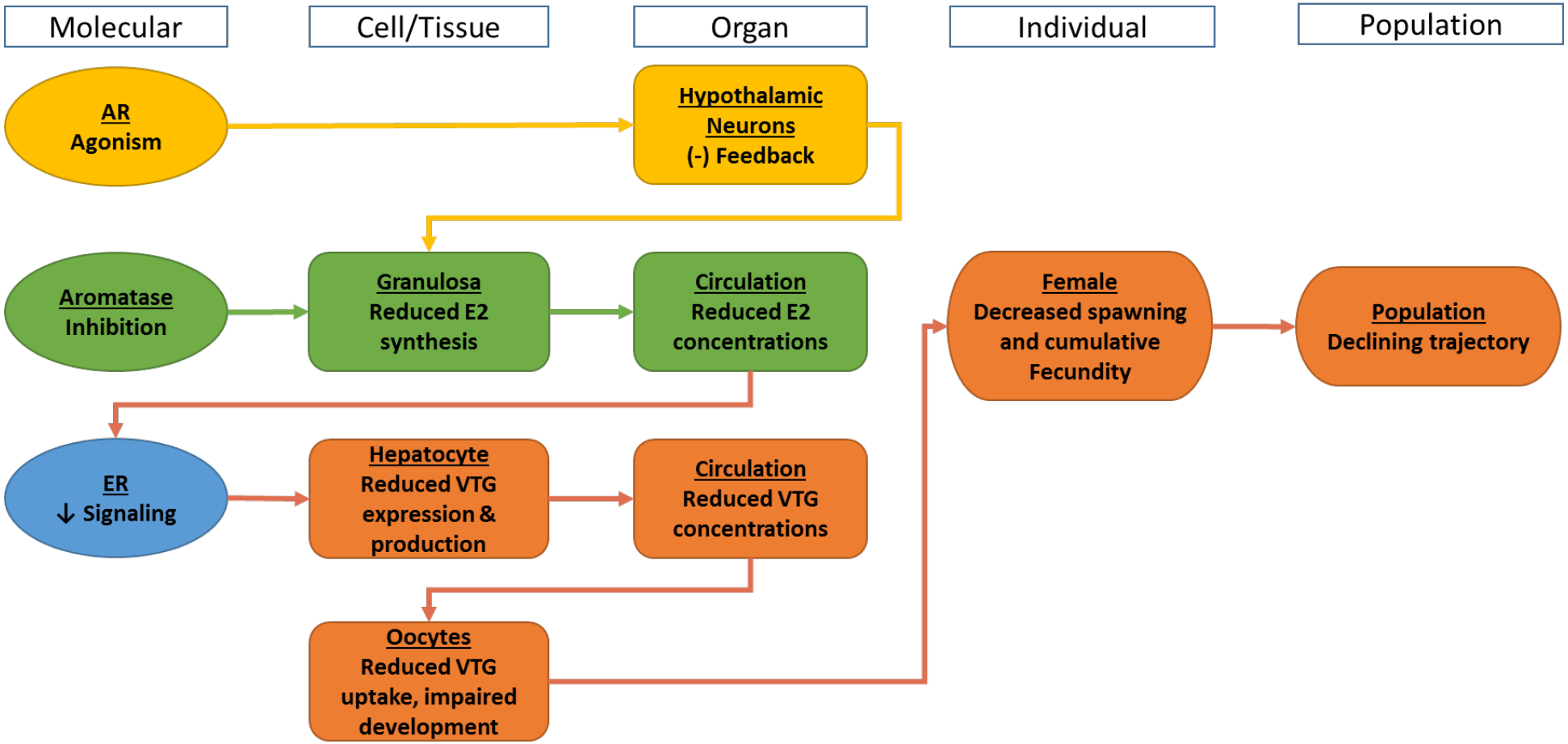
AOP networks emerge as AOPs are entered into the AOP-Wiki



Courtesy of Dan Villeneuve

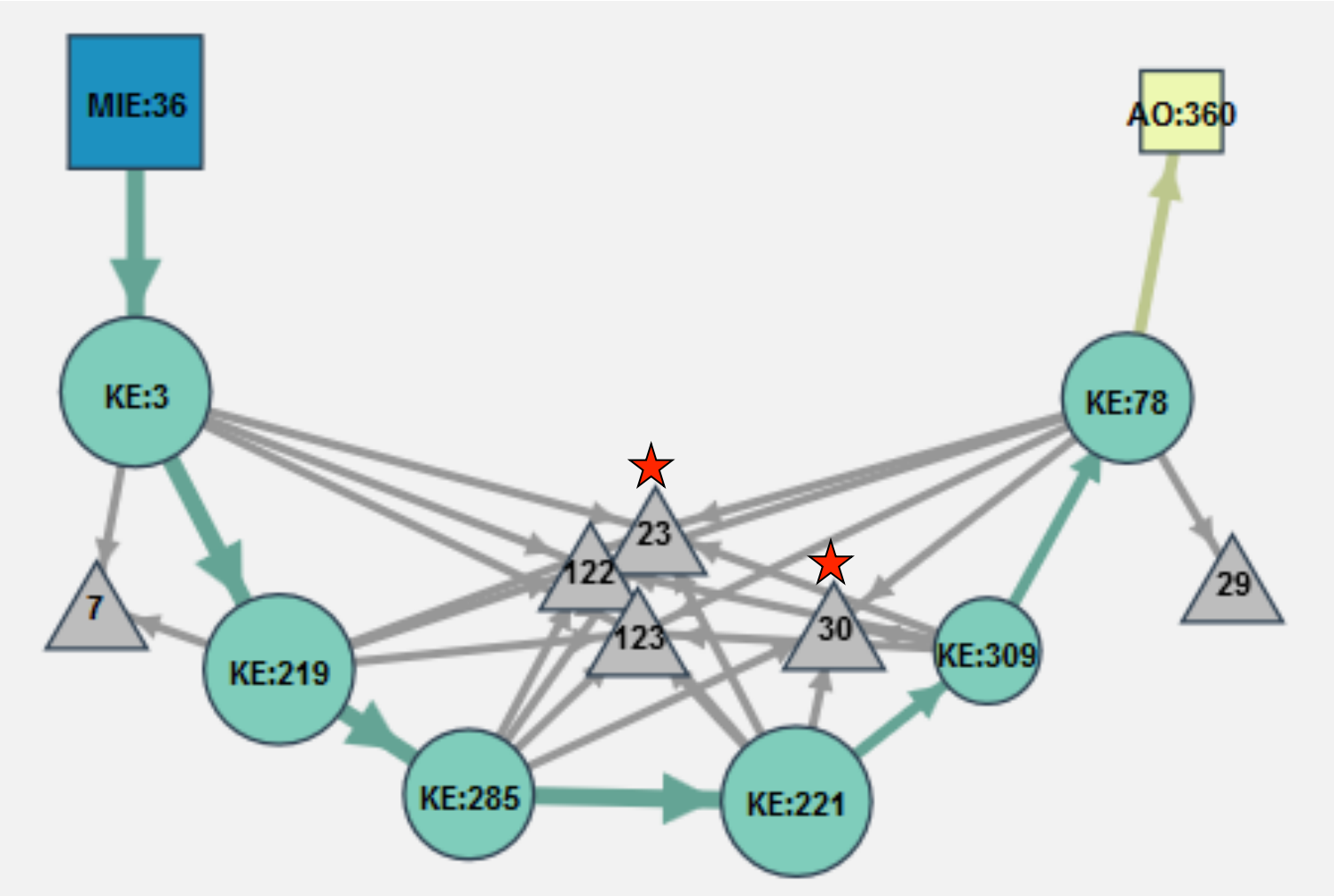
AOP Network as Stored in the AOP-Wiki



AOP Title [edit]

Aromatase inhibition leading to reproductive dysfunction (in fish)

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

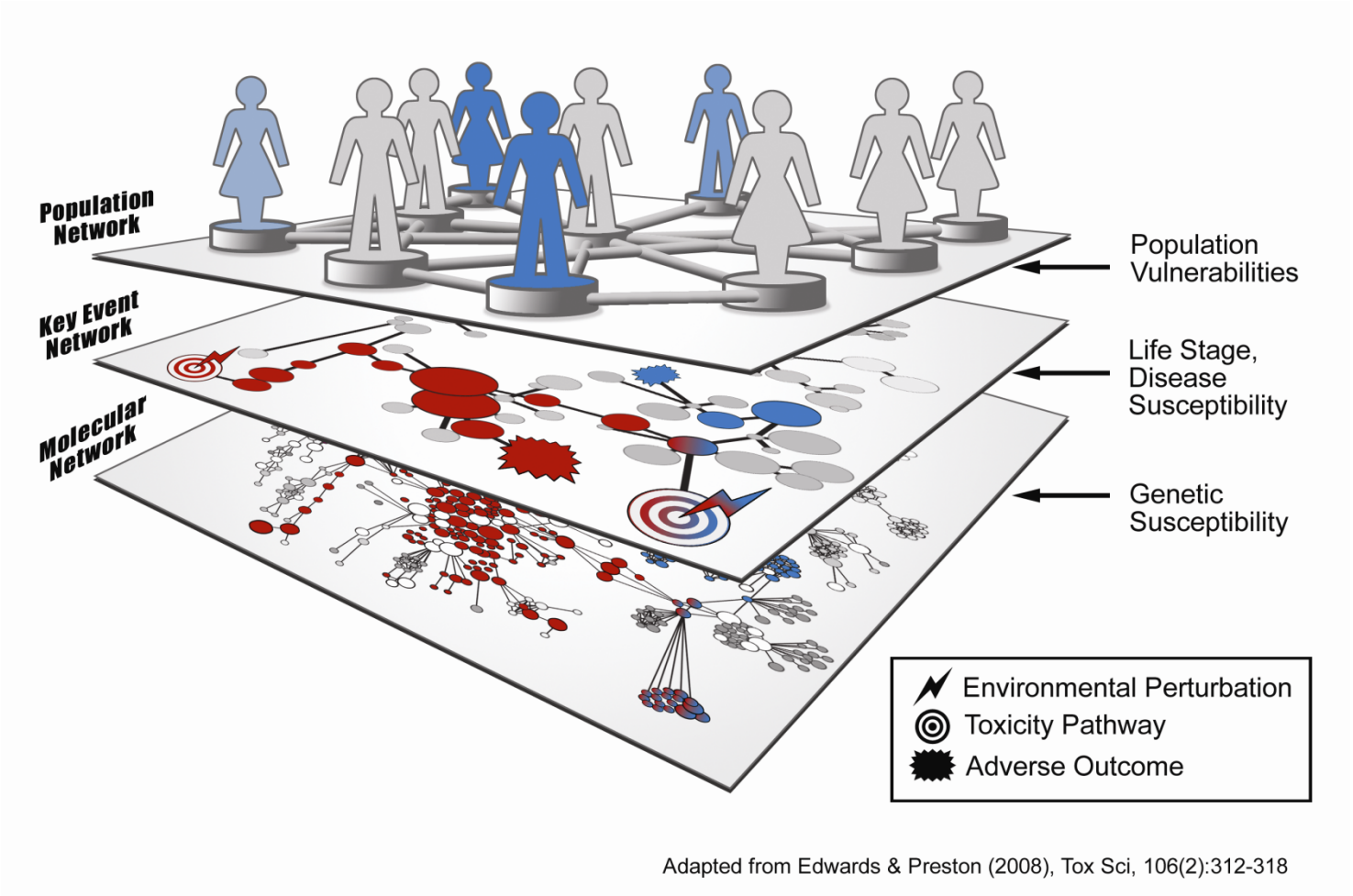


Dan Villeneuve –
https://aopwiki.org/aops/25

Chemical Interactions Emerge from AOP Networks

Nelms, M.D., et al. (2017) in *Chemical Mixtures and Combined Chemical and Nonchemical Stressors: Exposure, Toxicity, Analysis and Risk*

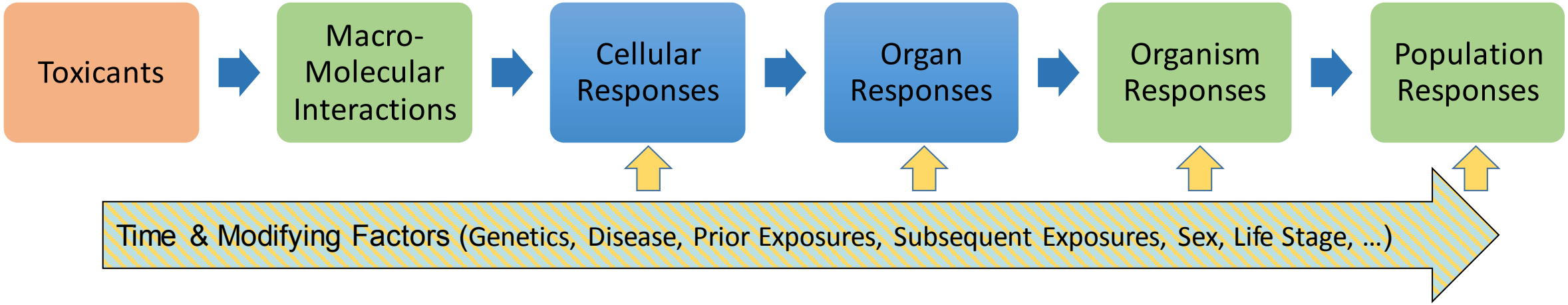
AOP Networks Incorporate "Effect Modifiers"



Adapted from Edwards & Preston (2008), Tox Sci, 106(2):312-318

Gallagher, et al., (2010) in "Biomarkers in Medicine, Drug Discovery and Environmental Health"

Factors Determining Predictivity of Early Key Events



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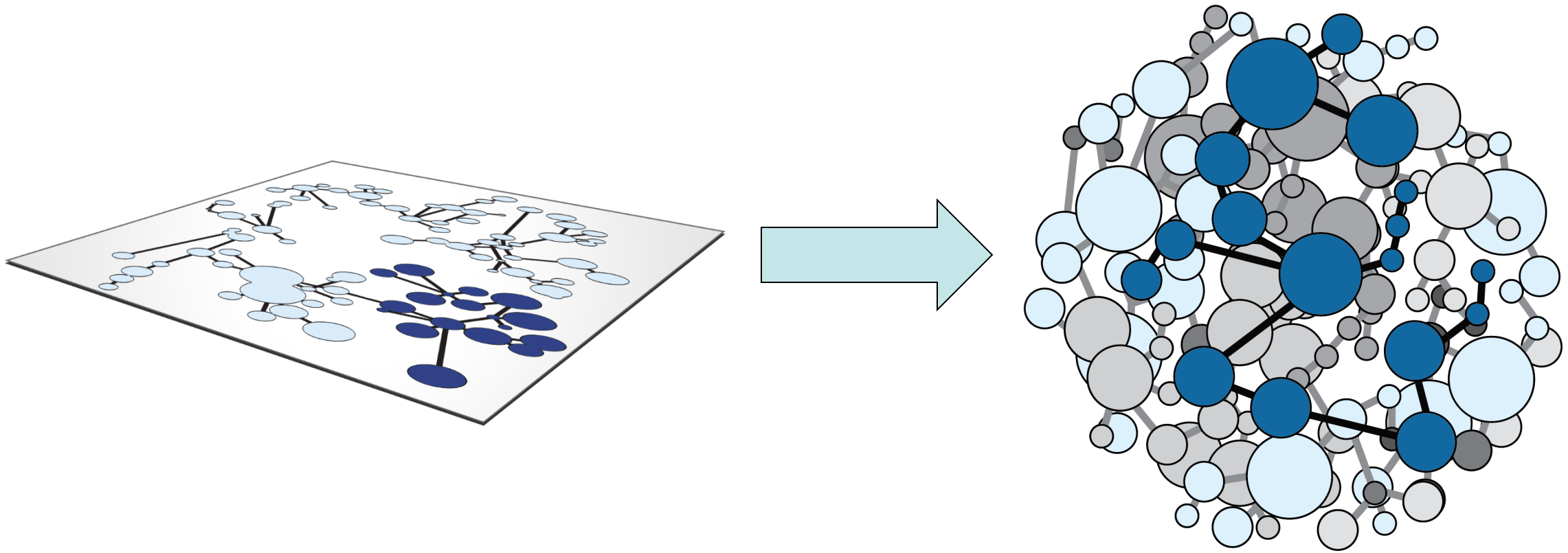
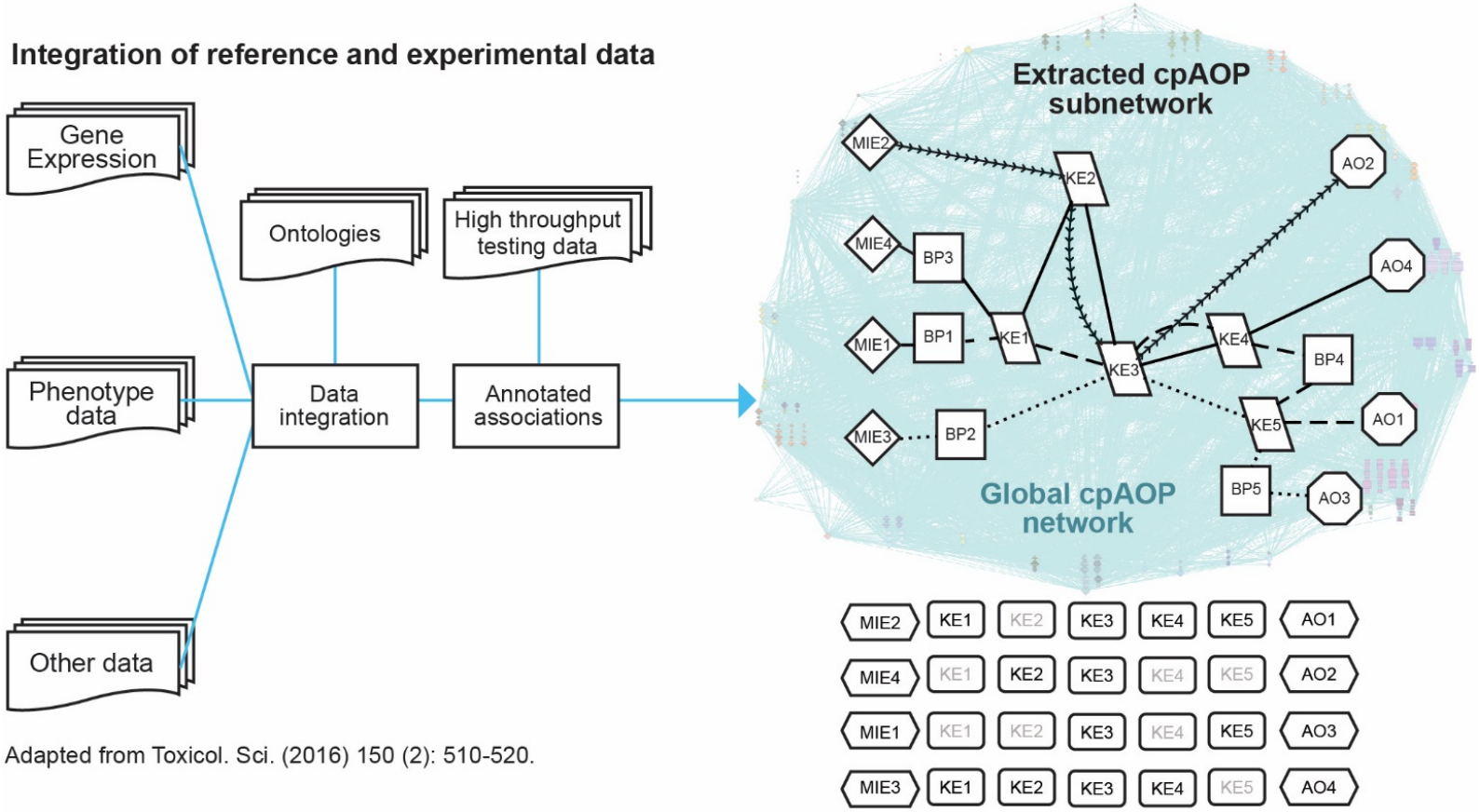
Too many AOPs, too little time…





Adapted from Toxicol. Sci. (2016) 150 (2): 510-520.

Noffisat Oki, Shannon Bell

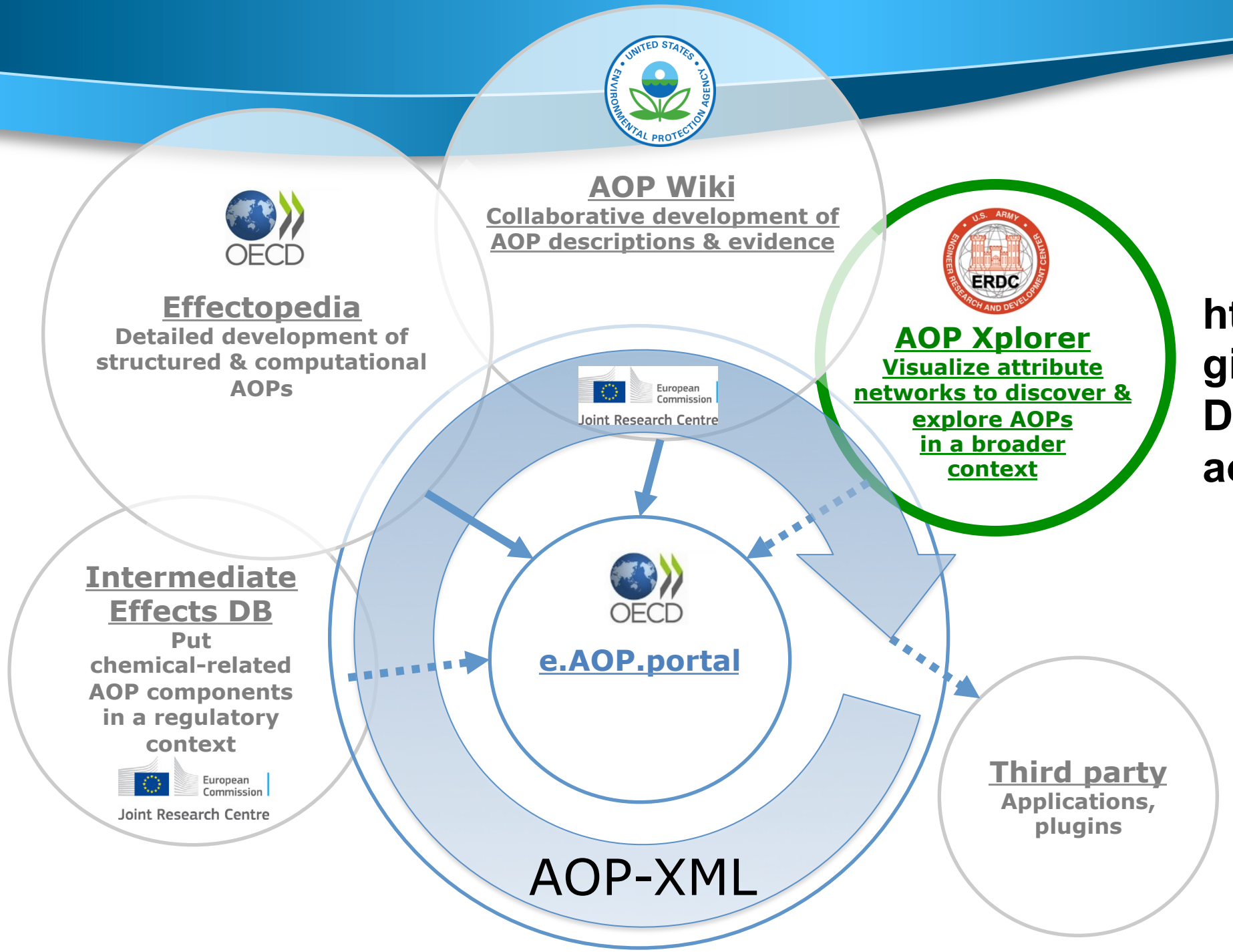
Bell et al. (2016)
Toxicol. Sci., **150**:510-520
doi:10.1093/toxsci/kfw017

Oki & Edwards (2016)
Toxicology, **350–352**:49–61
doi:10.1016/j.tox.2016.04.004

Oki et al. (2016)
Current Environmental Health Reports,
3(1):53-63
doi:10.1007/s40572-016-0079-y

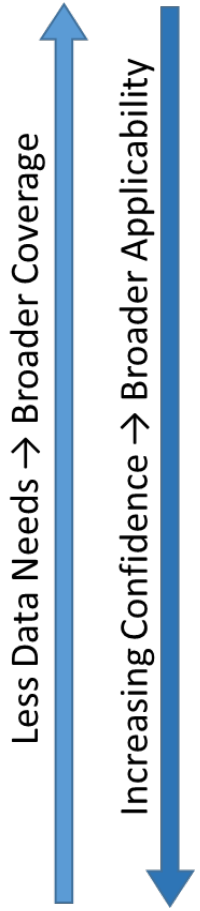
Accelerating AOP Development

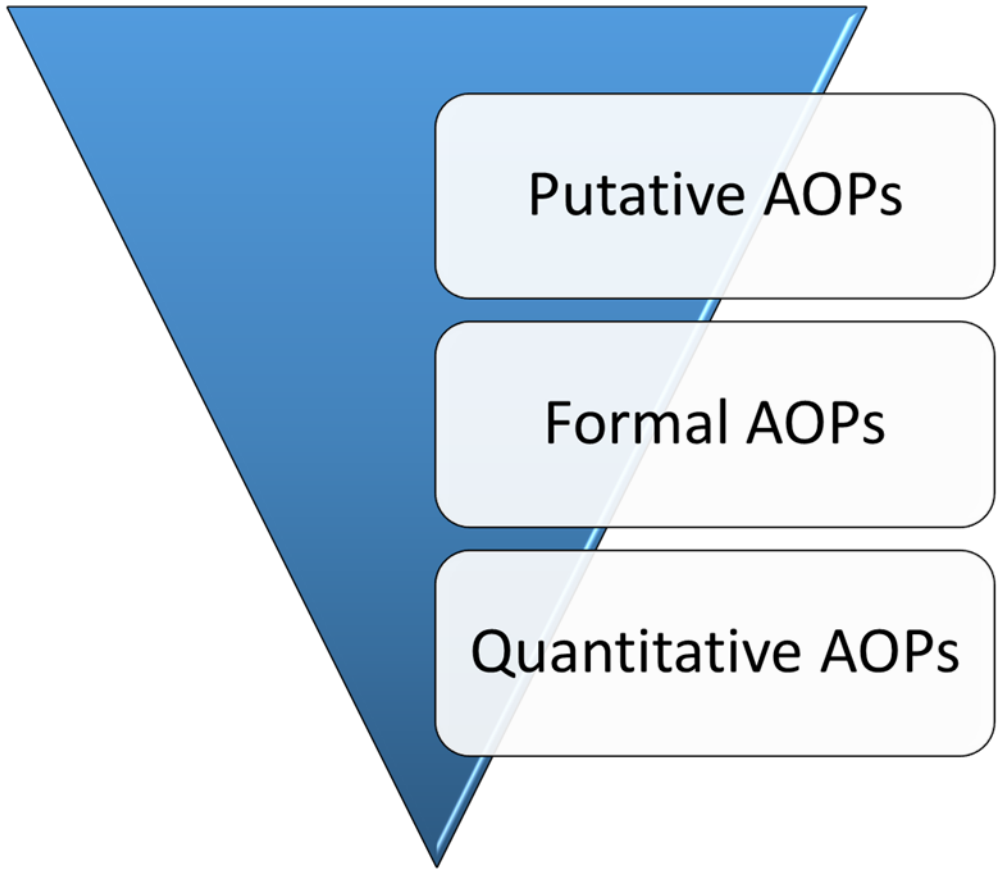
Associations derived from public data sources



https://github.com/DataSciBurgoon/aop_networks

OECD AOP-KB (http://aopkb.org/) Supports All Stages of Development





AOP-Xplorer –http://apps.cytoscape.org/apps/aopxplorer

AOP-Wiki –https://aopwiki.org/

Effectopedia –http://effectopedia.org/

The Adverse Outcome Pathway (AOP) Portal on WikiPathways

edit

Welcome to the Adverse Outcome Pathway Portal!

This Adverse Outcome Pathway (AOP) portal for WikiPathways is created to highlight the molecular basis of AOPs or events in AOPS. In general, AOPs start with a Molecular Initiating Event (MIE) caused by a stressor, followed by Key Events (KEs), that lead to an Adverse Outcome (AO). These AOPs are intended specifically for regulatory decision making and are typically stored in the AOP Knowledge Base (AOPKB). Because AOPs are simplified explanations of biological effects after the effect of a stressor they are not useful to describe and understand the molecular basis of the AOPs and not suited to do data analysis. Such analysis is needed especially for in silico risk analysis that is intended to lower animal use in toxicology studies. This portal was created to present the molecular level of the AOPs and getting more into detail on the biological processes involved in them. The development of these molecular AOPS is relevant for the European research projects on toxicology EU-ToxRisk and OpenRiskNet that also fundedn part of the work.

News

edit

2017-08-14 - Proposed AOP list added to the Mission section

2017-05-19 - The first AOP based on descriptive text from aopwiki.org on liver fibrosis is added to the portal.

2017-03-29 - The first AOPs that are added into this portal on pulmonary fibrosis, are results of the eNanoMapper project.

2017-03-29 - This portal was created

Mission

edit

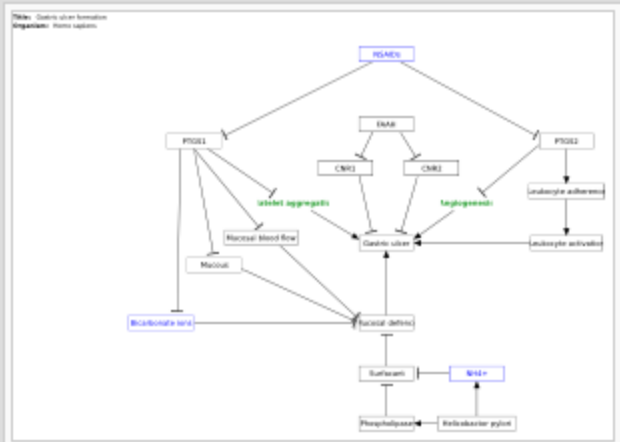
The purpose of this portal is to create a collection of AOPs on the molecular level for the AOPs that are, or will be created for the EU-ToxRisk program, in which Open PHACTS Foundation (OPF) is responsible for AOP creation. The subjects of the first AOPs are linked to the use cases of the EU-ToxRisk program, and there will be a team of experts involved in the creation of each AOP.

The proposed list of the first set of AOPs to be created, some are more defined than others:

Featured Pathway

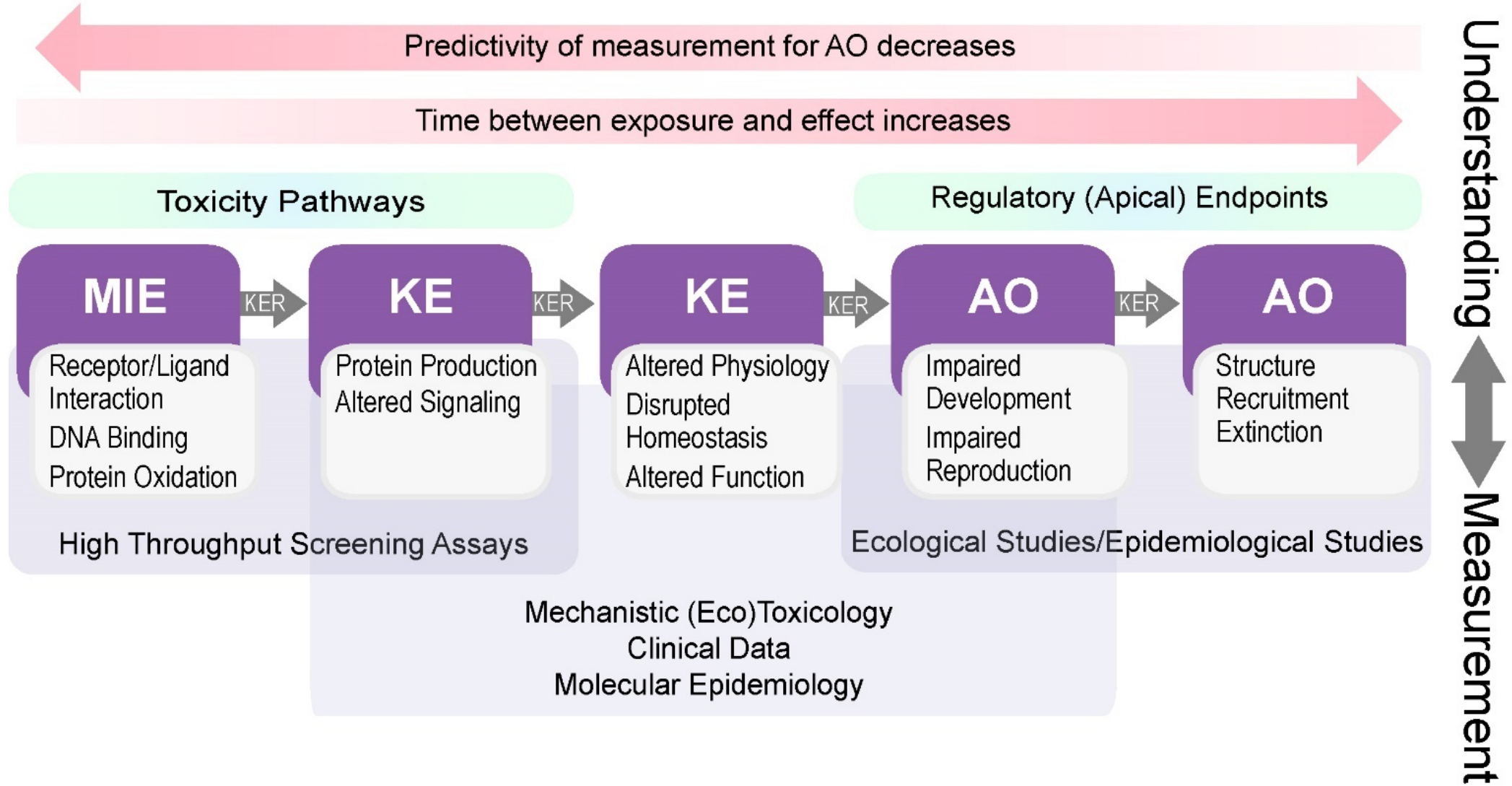
edit

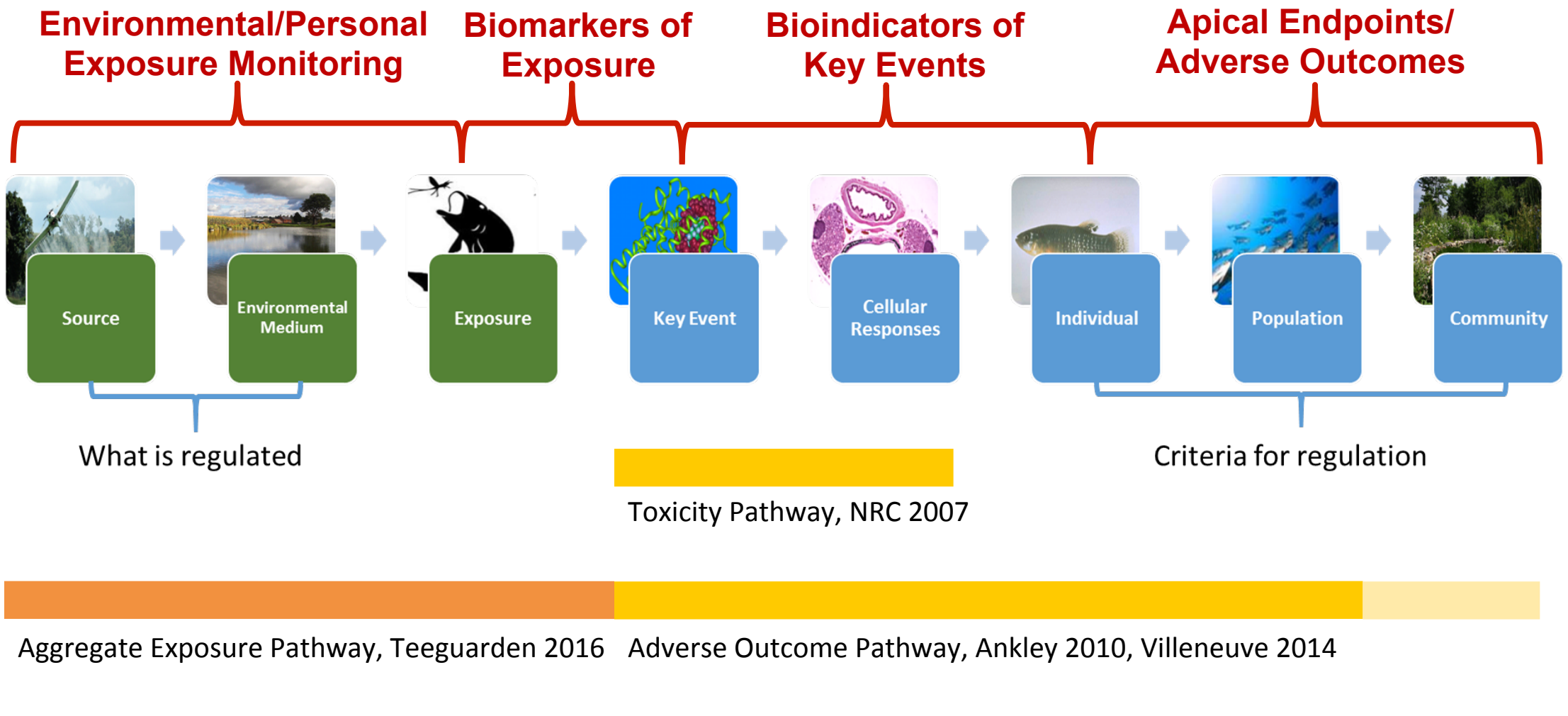
Gastric ulcer formation (Homo sapiens)



Gastric ulcer formation

View all Featured Pathways for this Portal


Predictivity of measurement for AO decreases
Time between exposure and effect increases
Toxicity Pathways
Regulatory (Apical) Endpoints
MIE
KER
KE
KER
KE
KER
AO
KER
AO
Receptor/Ligand Interaction
DNA Binding
Protein Oxidation
Protein Production
Altered Signaling
Altered Physiology
Disrupted Homeostasis
Altered Function
Impaired Development
Impaired Reproduction
Structure
Recruitment
Extinction
High Throughput Screening Assays
Ecological Studies/Epidemiological Studies
Mechanistic (Eco)Toxicology
Clinical Data
Molecular Epidemiology
Understanding
Measurement


Environmental/Personal Exposure Monitoring
Biomarkers of Exposure
Bioindicators of Key Events
Apical Endpoints/ Adverse Outcomes
Source
Environmental Medium
Exposure
Key Event
Cellular Responses
Individual
Population
Community
What is regulated
Criteria for regulation
Toxicity Pathway, NRC 2007
Aggregate Exposure Pathway, Teeguarden 2016
Adverse Outcome Pathway, Ankley 2010, Villeneuve 2014
Measurement
Understanding

Acknowledgements

OECD AOP-KB Working Group

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

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

- Ed Perkins
- Lyle Burgoon
- Natalia Garcia Reyero

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

- Hristo Aladjov
- Magda Sachana
- Joop DeKnecht

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

CSS AOP Discovery & Development Project Team

- Cataia Ives
- Ivana Campia
- Clemens Wittwehr

- Rong-Lin Wang

- Lyle Burgoon
- Kyle Painter

OECD AOP Ontology Efforts

- AOP-KB Ontology Effort
  - Stephen Edwards
  - Cataia Ives
  - Clemens Wittwehr
  - Ivana Campia
  - Brigitte Landesmann
  - Hristo Aladjov
  - Magda Sachana
  - Lyle Burgoon

- OECD Ontology WG
  - Richard Currie (chair)
  - Ahmed Abdelaziz
  - Annamaria Colacci
  - George Fotakis
  - Ignacio Tripodi
  - Nikolai Georgiev Nikolov
  - Nina Jeliazkova
  - Olga Tcheremenskaia
  - AOP-KB Representatives

Additional Information Available Online

- Reference
  - https://www.epa.gov/chemical-research/adverse-outcome-pathway-aop-research-brief
  - http://www.oecd.org/chemicalsafety/testing/adverse-outcome-pathways-molecular-screening-and-toxicogenomics.htm
  - http://www.saaop.org/workshops/somma.html
  - http://www.saaop.org/workshops/pellston2017.html
- Training
  - https://aopwiki.org/training/
  - https://humantoxicologyproject.org/about-pathways-2/
  - http://setac.sclivelearningcenter.com/index.aspx?PID=9484&SID=215605