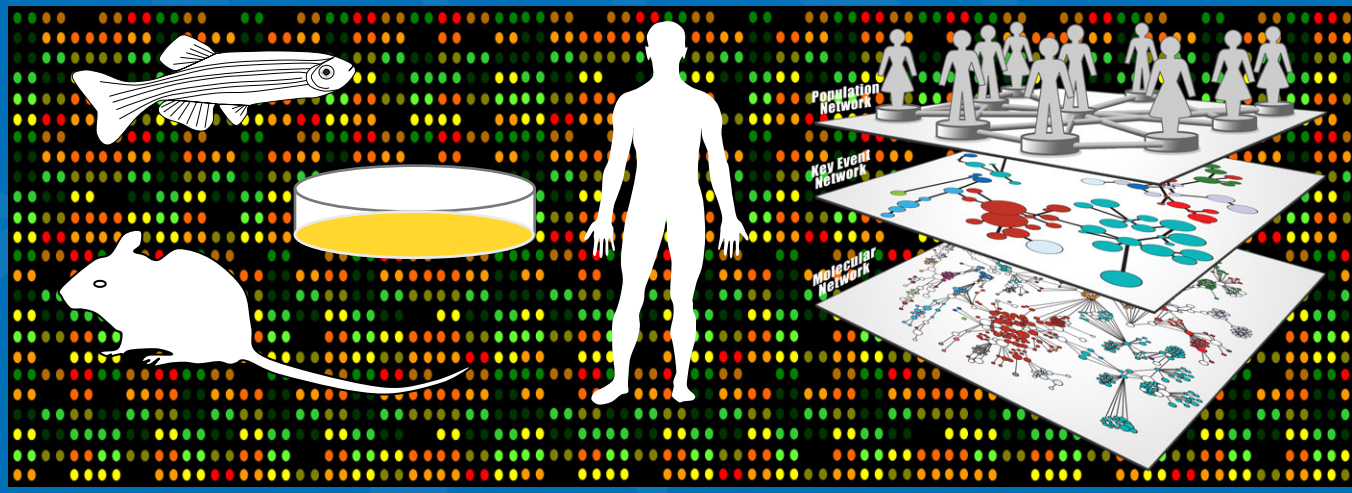
United States Environmental Protection Agency

# AOP Knowledge Base/ Wiki Tool Set

Stephen W. Edwards

Adverse Outcome Pathways: From Research to Regulation

This talk does not necessarily reflect the views of the Environmental Protection Agency.



# Outline

- Why an AOP Knowledgebase?
- Components of the AOP Knowledgebase
- AOP-Wiki
- What's next?

# AOP Timeline

- 2010 AOP development
  - relatively poorly defined *ad hoc* process
- 2012 Launch of OECD AOP Development Programme
  - http://www.oecd.org/chemicalsafety/adverse-outcome-pathways-molecular-screening-and-toxicogenomics.htm
- 2013 OECD Guidance on Developing and Assessing AOPs
  - http://search.oecd.org/officialdocuments/displaydocumentpdf/?cote=env/jm/mono%282013%296&doclanguage=en
- 2014
  - AOP Workshops
    - Part of National Society meetings:  SOT, SETAC, EMGS
    - *Advancing AOPs for Integrated Toxicology and Regulatory Applications* (Somma Lombardo, Italy)
    - *Adverse Outcome Pathways: From Research to Regulation* (Bethesda, MD)
  - Development of an OECD User Handbook as a supplement to the 2013 guidance

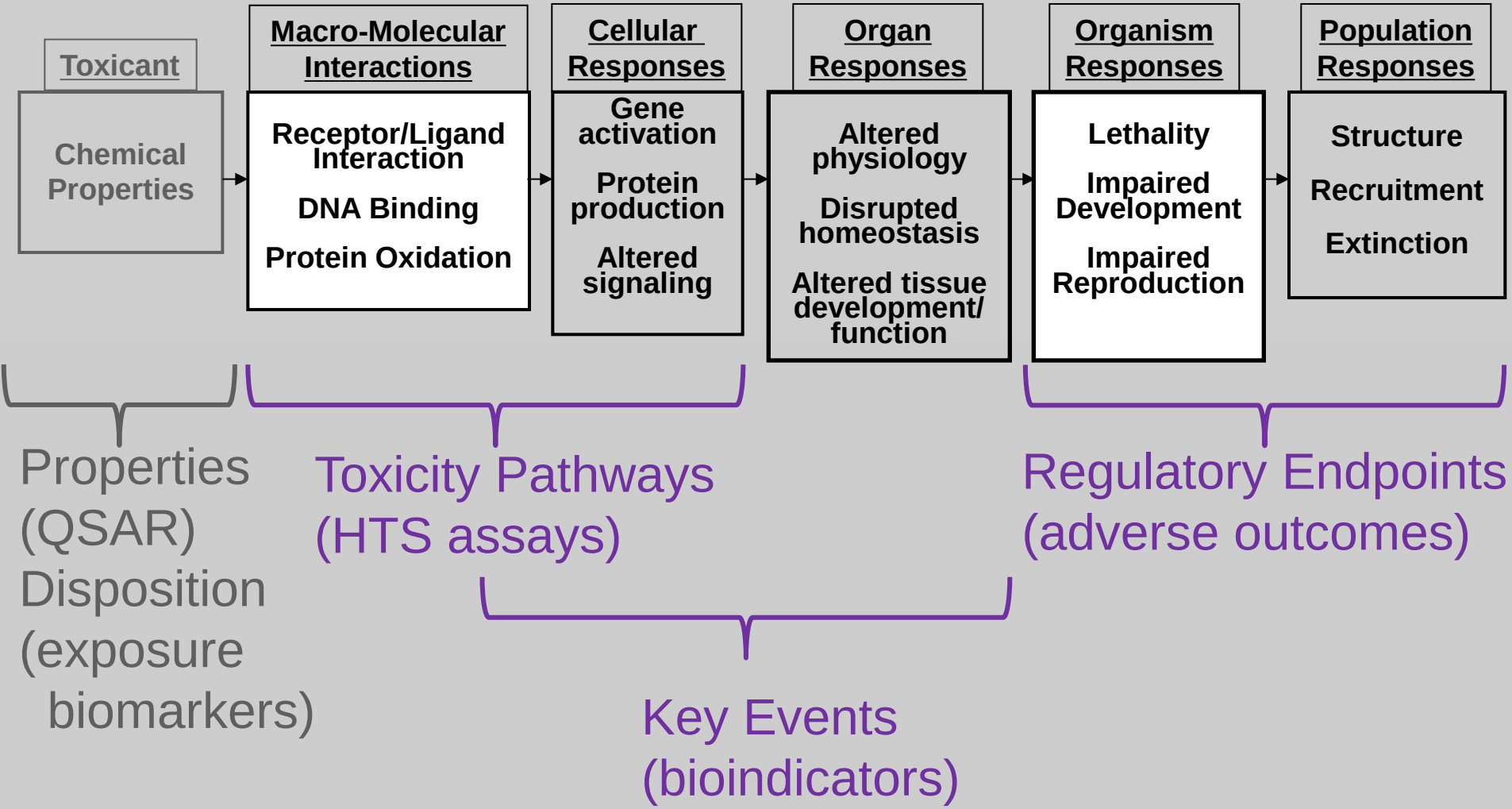
# AOP-KB History

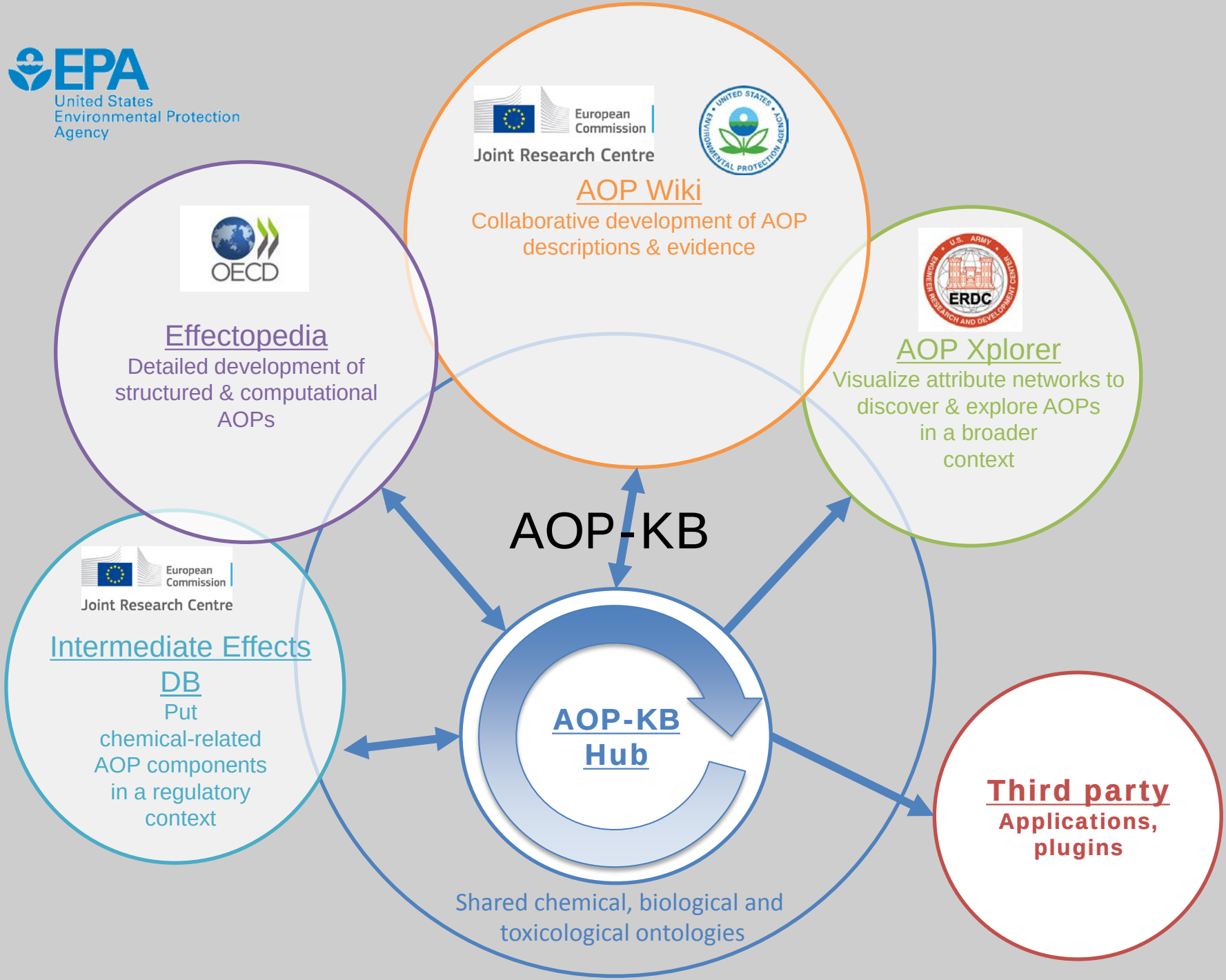
- Effectopedia (International QSAR Foundation)
  - Developed since 2006, alpha releases since 2010
- Chem MOA Wiki (WHO/IPCS) -> AOP Wiki
  - EPA – Fall 2012
- AOP-KB for OECD AOP Programme
  - Joint proposals EPA, JRC, & USACE – March 2013
  - Initial Wiki beta release – July 2013
  - Formal inclusion of OECD (Effectopedia) – Dec. 2013
  - Most recent Wiki release – June 2014

# AOP Key Concepts

- Organize existing knowledge
- Systematic evaluation of evidence
- Avoid duplication of the same key event
- Always expand description to include new science
- **Provide a framework for utilizing 21st century toxicity testing**

# AOP as a Knowledge Bridge

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Shared chemical, biological and
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# AOP-Wiki (http://aopwiki.org)

Sedwar02 Talk Preferences Watchlist Contributions Log out

Adverse Outcome Pathway WIKI

Page Discussion | Read Edit View history | Search

## Main Page

Navigation
- Main page
- AOP List
- Help
- FAQ
- Recent changes
- Release notes

Actions

Feedback

**Contents** [hide]

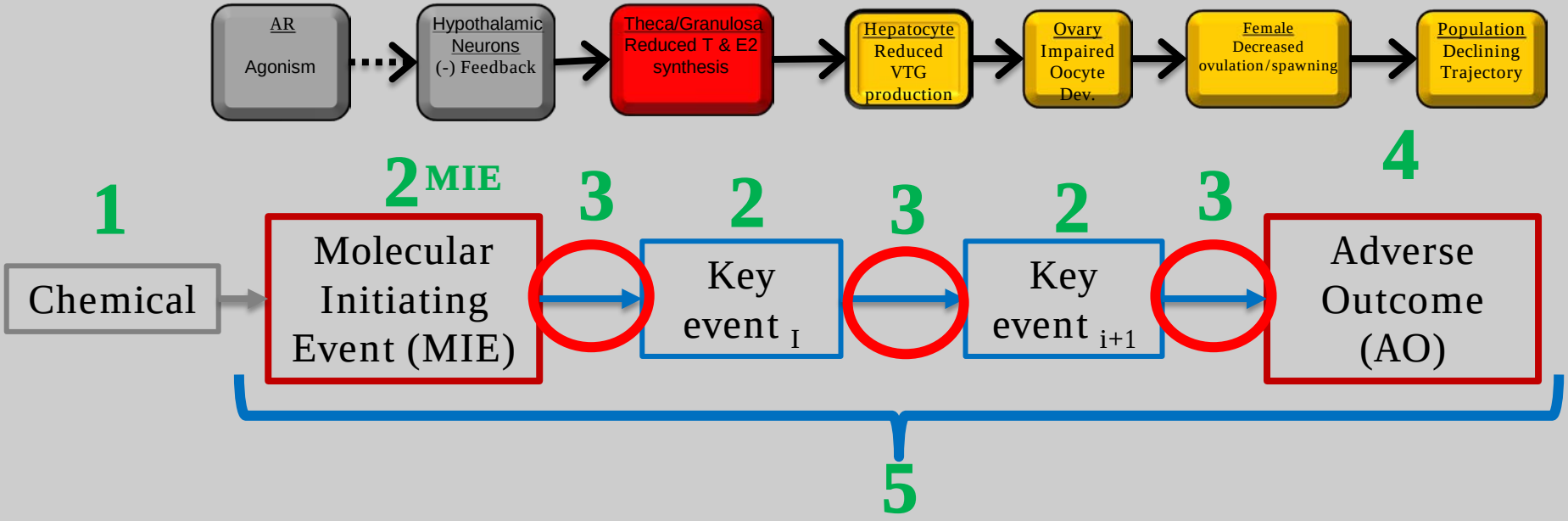


## Welcome to the Collaborative Adverse Outcome Pathway KnowledgeBase (AOP-KB) Wiki [edit]

This wiki represents a joint effort between the European Commission – DG Joint Research Centre and U.S. Environmental Protection Agency. This serves as one component of a larger OECD-sponsored AOP Knowledgebase 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 International QSAR Foundation, and the AOP Network tool, produced by the US Army Corps of Engineers - Engineering Research and Development Center.

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

# Structuring and Storing AOP Information



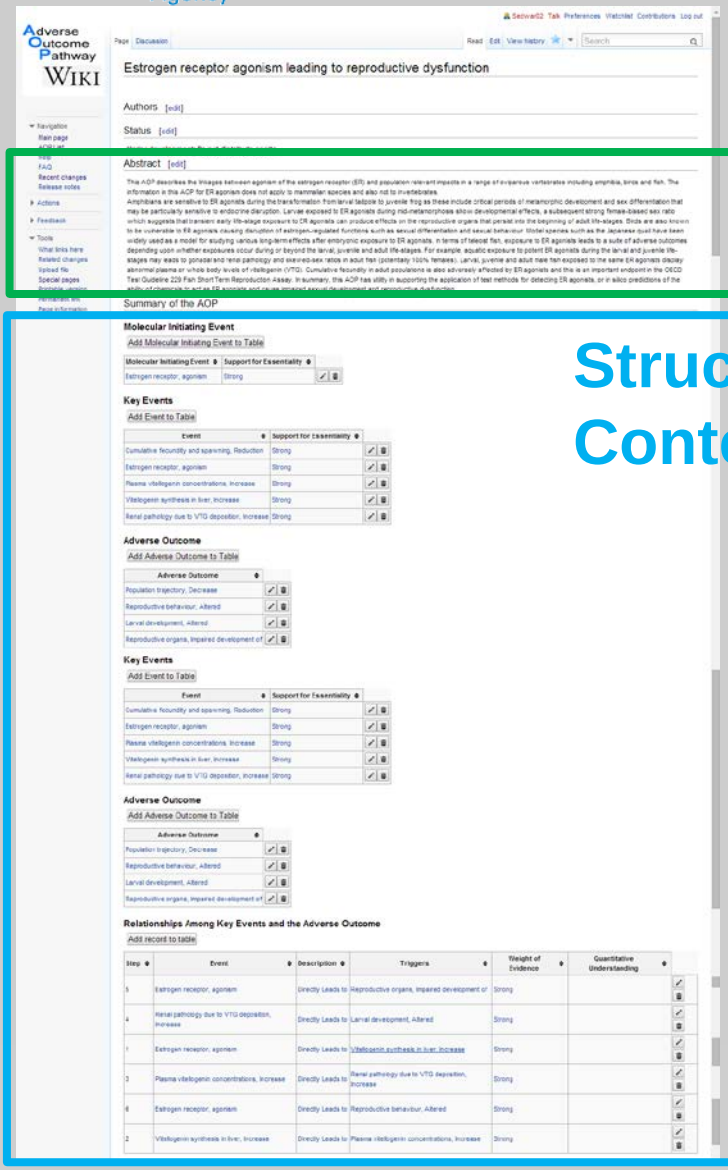

**AOP Components are mapped to specific entities in the KB**

1. Chemical initiator
2. Key event (including MIE; node)
3. KE Relationship (linkage; edge)
4. Adverse Outcome
5. AOP

# AOP Page in Wiki

Free Text

Structured Content

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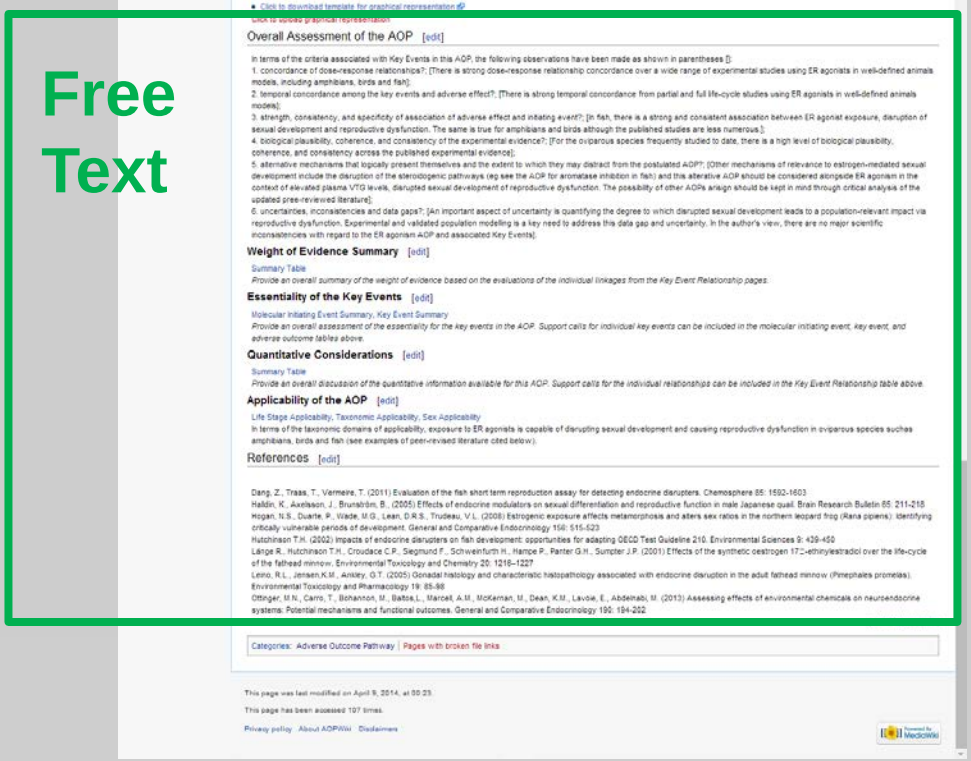
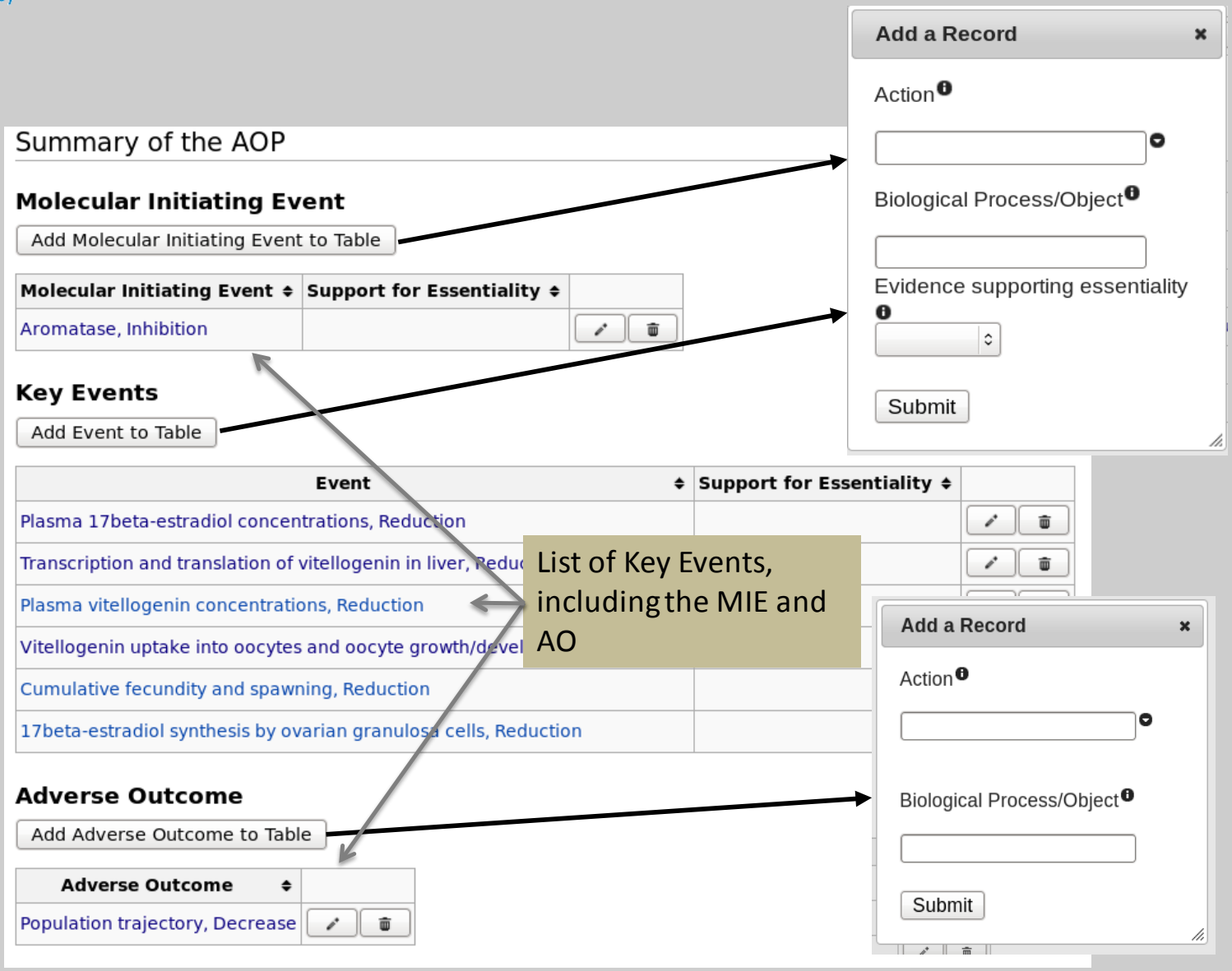


# Widgets Facilitate Data Entry



# Wiki Matches OECD Guidance & Handbook

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## AOP Page

**Section 1 – Title**

**Section 2 – Authors**

**Section 3 - Status**

**Section 4 – Abstract**
Background (Optional)

**Section 5a – Summary of the AOP**

- MIE
- KEs
- AO

Linkage table

- Key Event Relationships

Applicability domain(s) of the AOP

- Life-stage
- Taxonomic
- Sex

**Section 7 – Overall Assessment of the AOP**

- Modified Bradford Hill Considerations

**Section 8 – Considerations for Potential Applications of the AOP**

**Section 5b – MIE, KE, and AO descriptions**

### MIE Page

*Chemical initiator(s)*

- Description
- Measurement/ detection
- Taxonomic applicability
- *Evidence for chemical initiation*

### KE Pages

- Description
- Measurement/ detection
- Taxonomic applicability

### AO Page

- Description
- Measurement/ detection
- Taxonomic applicability
- *Regulatory relevance*

**Section 6 – Scientific evidence supporting the linkages in the AOP**

### KER Pages

- Title
- Description
- Biological plausibility
- Empirical support
- Inconsistencies and uncertainties
- Quantitative understanding

# AOP Snapshot from the AOP-Wiki

AOP Title

**Androgen receptor agonism leading to reproductive dysfunction**

Authors

Dan Villeneuve, U

Status

**Alert: The Weig these tables.**

**Under developn**

Abstract

This adverse outc reduced cumulati Assay. The OECI variables known t receptor binding

Summary o

**Molecular In**

| Molecular Initia |
|---|
| Androgen recept |

**Androgen re**

**How this Key I**

| Level of Biolog |
|---|

**Site of action**: T

**Responses at th** facilitates dissoci Homodimerizatio (Claessens et al. Tindall 2007).

**How it is Meas**

*Methods that hav established in th directly or indirec*

**Measurement/d** testosterone or D based transcriptic to screen chemic responsive protei

In fish, phenotypi tubercles, a dors 2006; Ankley et a activation (Raut e

**Evidence Sup**

| Common Name |
|---|
| Fathead minnow |
| Medaka |

**Taxonomic appl** Therefore, this MI

## Key Events

| Event |
|---|
| Gonadotropins, circulating concentrations, Red |
| Testosterone synthesis by ovarian theca cells, |
| Plasma 17beta-estradiol concentrations, Reduc |
| Transcription and translation of vitellogenin in li |
| Plasma vitellogenin concentrations, Reduction |
| Vitellogenin uptake into oocytes and oocyte gr |
| Cumulative fecundity and spawning, Reduction |
| 17beta-estradiol synthesis by ovarian granulosa |

### Gonadotropins, circulating concer

**How this Key Event works**

| Level of Biological Organization |
|---|

Gonadotropin (luteinizing hormone [LH] and follic heterodimeric glycoproteins composed of a horr and stored in secretory vesicles. Gonadotropin s of gonadotropin expression (e.g., activin, follistat

**How it is Measured or Detected**

Circulating concentrations of gonadotropins in h commercial or custom immunoassays (e.g., EL (Govoroun et al. 1998; Amano et al. 2000; Kah limited number of species, primarily salmonids ( beta subunit (fshb) tend to fluctuate in parallel in (Levavi-Sivan et al. 2010). Consequently, the two volumes relative to the sensitivity of the available

**Evidence Supporting Taxonomic Applic**

| Common Name | Scientific Name | Evidence |
|---|---|---|

A functional hypothalamic-pituitary-gonadal axis taxonomic applicability of this key event is limit

**References**


- Norris DO. 2007. Vertebrate Endocrinology. I
- Habibi HR, Huggard DL. 1998. Testosterone endocrinology 119(3): 339-344.
- Trudeau VL, Spanswick D, Fraser EJ, Lariviè fish. Biochemistry and Cell Biology 78: 241-
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- Cheng GF, Yuen CW, Ge W. 2007. Evidence gonadal steroids. The Journal of endocrinolo
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- Amano M, Iigo M, Ikuta K, Kitamura S, Yam and comparative endocrinology 120(2): 190-
- Kah O, Pontet A, Nunez Rodriguez J, Calas 41(1): 68-73.
- Prat F, Sumpter JP, Tyler CR. 1996. Validatio reproductivecycle in male and female rainbo
- Levavi-Sivan B, Bogerd J, Mananos EL, Gom 412-437.
- Sower SA, Freamat M, Kavanaugh SI. 2009. new insights from lampreys. General and co


## Scientific evidence supporting the linkages in the AOP

| Step | Event |
|---|---|
| 2 | Testosterone synthesis by ovarian theca cells, Reduction |
| 3 | Gonadotropins, circulating concentrations, Reduction |
| 4 | 17beta-estradiol synthesis by ovarian granulosa cells, Reduction |
| 5 | Plasma 17beta-estradiol concentrations, Reduction |
| 6 | Transcription and translation of vitellogenin in liver, Reduction |
| 8 | Vitellogenin uptake into oocytes and oocyte growth/development, Reduction |
| 9 | Cumulative fecundity and spawning, Reduction |
| 10 | Androgen receptor, agonism |
| 11 | Plasma vitellogenin concentrations, Reduction |

### Testosterone synthesis by ovarian theca cells, Reduction I Reduction

**How Does This Key Event Relationship Work**

**Biological Plausibility**

Theca cell-derived androgens (e.g., testosterone, androstenedione) are precursors are aromatized to estrogens in the ovarian granulosa cells. Consequently, reducti synthesis by the ovarian granulosa cells (Payne and Hales 2004; Miller 1988; Nap

**Empirical Support for Linkage**

*Include consideration of temporal concordance here*

- Ex vivo T production by ovary tissue collected from female fathead minnows ex exposure (Ekman et al. 2011). Reductions in ex vivo T production preceded si
- Ketoconazole is a fungicide thought to inhibit CYP11A and CYP17 (both involv (Villeneuve et al. 2007). Ex vivo E2 and T production were significantly reduce

**Quantitative Understanding of the Linkage**

*Is it known how much change in the first event is needed to impact the second? extrapolation approaches that help describe those relationships?* At present we a indirect measure of theca cell T synthesis) and ex vivo E2 production (as an indire support the development of such a relationship. Additionally, there are a number c adaptable to support a quantitative understanding of this linkage (Breen et al. 200

**Uncertainties or Inconsistencies**

**Evidence Supporting Taxonomic Applicability**

| Common Name | Scientific Name | Evidence | Links |
|---|---|---|---|

**References**


- Payne AH, Hales DB. 2004. Overview of steroidogenic enzymes in the pathwa
- Miller WL. 1988. Molecular biology of steroid hormone synthesis. Endocrine r
- Nagahama Y, Yoshikumi M, Yamashita M, Sakai N, Tanaka M. 1993. Molecul 3-14.
- Ekman DR, Villeneuve DL, Teng Q, Ralston-Hooper KJ, Martinovic-Weigelt D, exposure and effects assessment of the model androgen 17beta-trenbolone in
- Villeneuve DL, Ankley GT, Makynen EA, Blake LS, Greene KJ, Higley EB, et assays for identifying endocrine-active chemicals. Ecotoxicol Environ Saf 68(1


## Overall Assessment of the AOP

**Overall Assessment of the AOP:**

**Biological Plausibility**

- The biochemistry of steroidogenesis and the predominant
- Similarly, the role of E2 as the major regulator of hepatic v concentrations in the plasma and reduced uptake into ooc
- The direct connection between reduced VTG uptake and impaired VTG uptake limits oocyte growth and failure to re oocyte from the surrounding follicles. In at least one expe vitellogenic oocytes was observed (R. Johnson, personal cumulative fecundity are best supported by the correlation initiating events (Miller et al. 2007).
- At present, negative feedback is the most biologically plau vitro exposure of fathead minnow ovary tissue to 17β-trenb those that produce significant responses in vivo (i.e., at no any known reports of 17β-trenbolone directly inhibiting ste trenbolone caused a concentration-dependent increase in concurrent with increased transcription of CYP19 (aromat enzyme activity, negative feedback is currently the most li exact mechanisms through which an exogenous, non-aro

**Concordance of dose-response relationships:** The dependence o starting at and down-stream of reduced T synthesis. However, to dat exposure to non-endogenous AR agonists (e.g., xenobiotics, pharm

- Exposure of female fathead minnows to the AR agonist 17 concentrations over a range from 0.005 to 0.5 µg/L. The c indicate concentration-dependent differences in the feedbu gonad stage were evident, although the concentration-resp biochemical level, concentration-dependent reductions in causing phenotypic masculinization in female fish.
- Jensen et al. (2006) also demonstrated concentration-dep et al. 2006).
- In a time-course experiment in which female fathead minn showed concentration-dependent reductions that were co
- Exposure of female fathead minnows to spironolactone, a cumulative fecundity, plasma VTG and VTG mRNA expres accumulation, and increased oocyte atresia was concentr
- Exposure of female medaka to spironolactone caused cor hormone concentrations were not measured). Spironolact

**Temporal concordance among the key events and adverse** negative feedback response resulting in decreased gonadotropin biosynthesis and proceeding through reductions in plasma vitello vitellogenin has not been established, in large part due to discon reproductive toxicity testing can spawn anywhere from once daily evaluate cumulative fecundity at a time scale shorter than roughly exposure, lack of impact on cumulative fecundity before the othe concordance can reasonably be evaluated based on currently ava

**Consistency**: We are aware of no cases where the pattern of key variability in the cumulative fecundity endpoint and potential com Ekman et al. 2012), the cumulative fecundity endpoint can be les of the final adverse outcome when the other key events are obse this AOP overlap with AOPs linking other molecular initiating eve

- In general, there is a consistent body of evidence linking and cumulative fecundity in female fish. For example, the replicated in over a dozen independent experiments (Ekm 2006; Brockmeier et al. 2013). However, relatively few exo (Lalone et al. 2013), we are not aware of the profile of resp

**Uncertainties, inconsistencies, and data gaps**: There are two as to the specific mechanism(s) through which AR agonism elici data gap relative to establishing that exposure to an AR agonist l major uncertainty in this AOP relates to whether there is a direct fecundity. Plausible biological connections have been hypothesiz

## Weight of Evidence Summary

| Step | Event | Description | Triggers | Weight of Evidence |
|---|---|---|---|---|
| 2 | Testosterone synthesis by ovarian theca cells, Reduction | Directly Leads to | 17beta-estradiol synthesis by ovarian granulosa cells, Reduction | Strong |
| 3 | Gonadotropins, circulating concentrations, Reduction | Directly Leads to | Testosterone synthesis by ovarian theca cells, Reduction | Strong |
| 4 | 17beta-estradiol synthesis by ovarian granulosa cells, Reduction | Directly Leads to | Plasma 17beta-estradiol concentrations, Reduction | Strong |
| 5 | Plasma 17beta-estradiol concentrations, Reduction | Directly Leads to | Transcription and translation of vitellogenin in liver, Reduction | Strong |
| 6 | Transcription and translation of vitellogenin in liver, Reduction | Directly Leads to | Plasma vitellogenin concentrations, Reduction | Strong |
| 8 | Vitellogenin uptake into oocytes and oocyte growth/development, Reduction | Directly Leads to | Cumulative fecundity and spawning, Reduction | Moderate |
| 9 | Cumulative fecundity and spawning, Reduction | Directly Leads to | Population trajectory, Decrease | Moderate |
| 10 | Androgen receptor, agonism | Directly Leads to | Gonadotropins, circulating concentrations, Reduction | Weak |
| 11 | Plasma vitellogenin concentrations, Reduction | Directly Leads to | Vitellogenin uptake into oocytes and oocyte growth/development, Reduction | Moderate |

### Essentiality of the Key Events

| Molecular Initiating Event | Support for Essentiality |
|---|---|
| Androgen receptor, agonism | |

| Key Event | Support for Essentiality |
|---|---|
| Gonadotropins, circulating concentrations, Reduction | |
| Testosterone synthesis by ovarian theca cells, Reduction | |
| Plasma 17beta-estradiol concentrations, Reduction | |
| Transcription and translation of vitellogenin in liver, Reduction | |
| Plasma vitellogenin concentrations, Reduction | |
| Vitellogenin uptake into oocytes and oocyte growth/development, Reduction | |
| Cumulative fecundity and spawning, Reduction | |
| 17beta-estradiol synthesis by ovarian granulosa cells, Reduction | |

- In general, few studies have directly addressed the essentiality of the proposed sequence of key events.
- Ekman et al. 2011 provide evidence that in fathead minnow, cessation of trenbolone exposure resulted in recovery of plasma E2 and VTG concentrations which were depressed by continuous exposure to 17beta trenbolone. This provides some support for the essentiality of these two key events.
- Essentiality of the proposed negative feedback key event is supported by experimental work that evaluated the ability of AR agonists to reduce T or E2 production in vitro. In vitro exposure of fathead minnow ovary tissue to 17β-trenbolone or spironolactone does not cause reductions in T or E2 synthesis at concentrations comparable to those that produce significant responses in vivo (i.e., at non-cytotoxic concentrations; D.L. Villeneuve, unpublished data; C.A. LaLone unpublished data), nor are there any known reports of 17β-trenbolone directly inhibiting steroid biosynthesis. When tested in an in vitro steroidogenesis assay using H295R adrenal carcinoma cells, trenbolone caused a concentration-dependent increase in estradiol production, as opposed to any reductions in steroid hormone concentrations, an effect that was concurrent with increased transcription of CYP19 (aromatase) in the cell line (Gracia et al. 2007).

### Quantitative Considerations

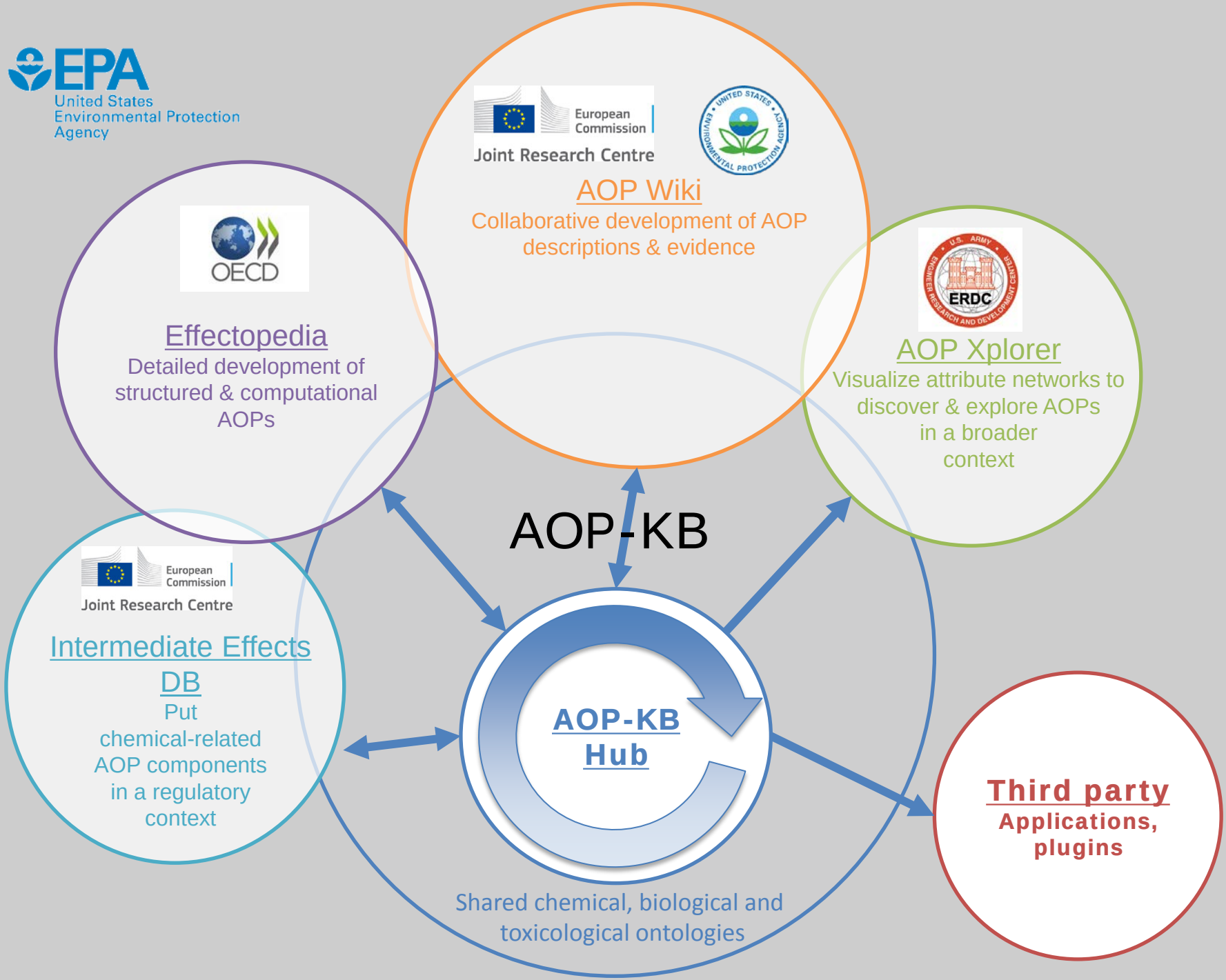
| Step | Event | Description | Triggers | Quantitative Understanding |
|---|---|---|---|---|
| 2 | Testosterone synthesis by ovarian theca cells, Reduction | Directly Leads to | 17beta-estradiol synthesis by ovarian granulosa cells, Reduction | |
| 3 | Gonadotropins, circulating concentrations, Reduction | Directly Leads to | Testosterone synthesis by ovarian theca cells, Reduction | |
| 4 | 17beta-estradiol synthesis by ovarian granulosa cells, Reduction | Directly Leads to | Plasma 17beta-estradiol concentrations, Reduction | |

# AOP-Wiki Status

- 41 AOPs as of September 1, 2014
  - 8* with documented evaluation of evidence
  - 4 with descriptions of all/most components
  - 22* with components defined
  - 8 stubs

- New code & template release September 2014
  - Will be consistent with updated AOP Handbook

- Public access starting September 25, 2014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Shared chemical, biological and
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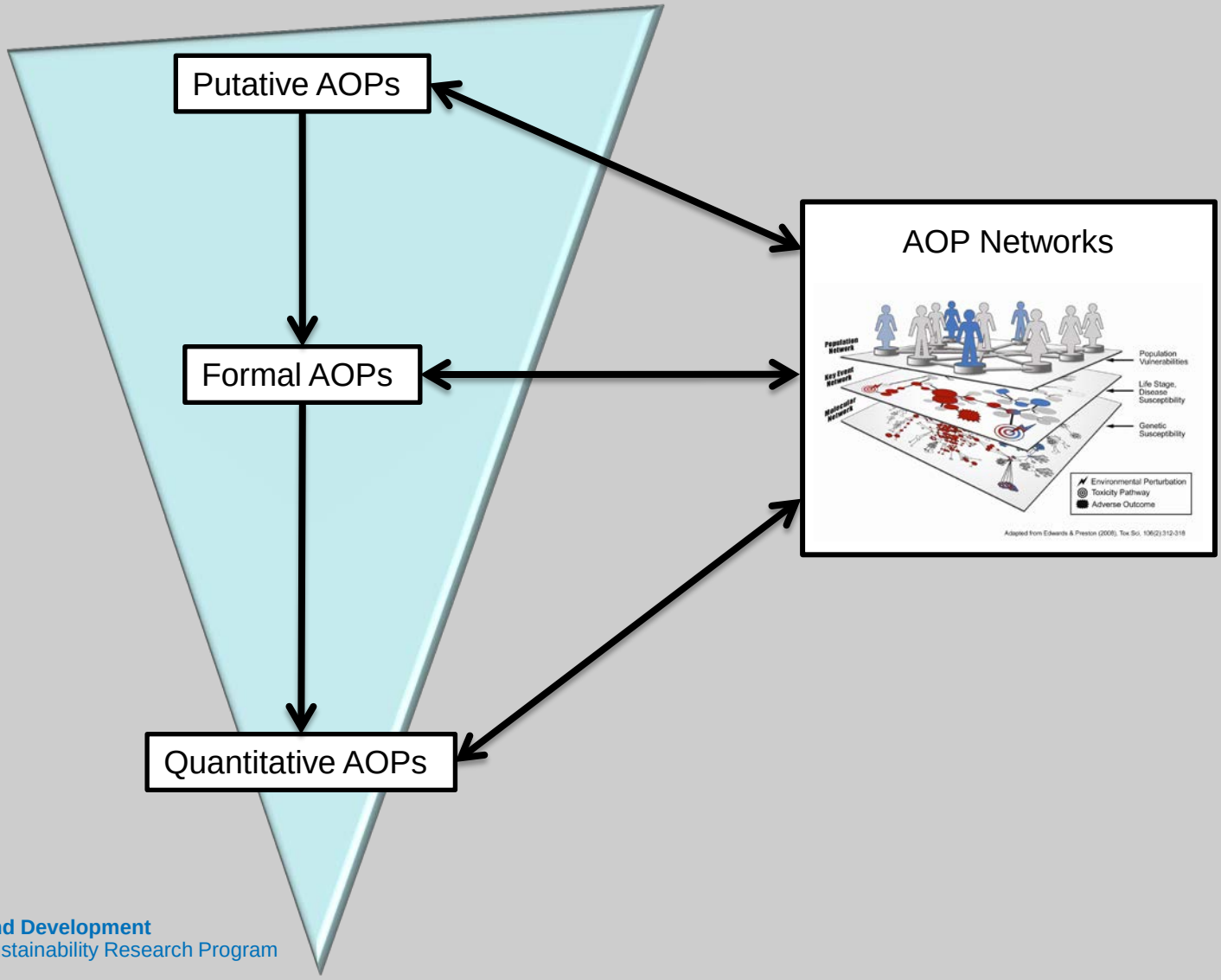
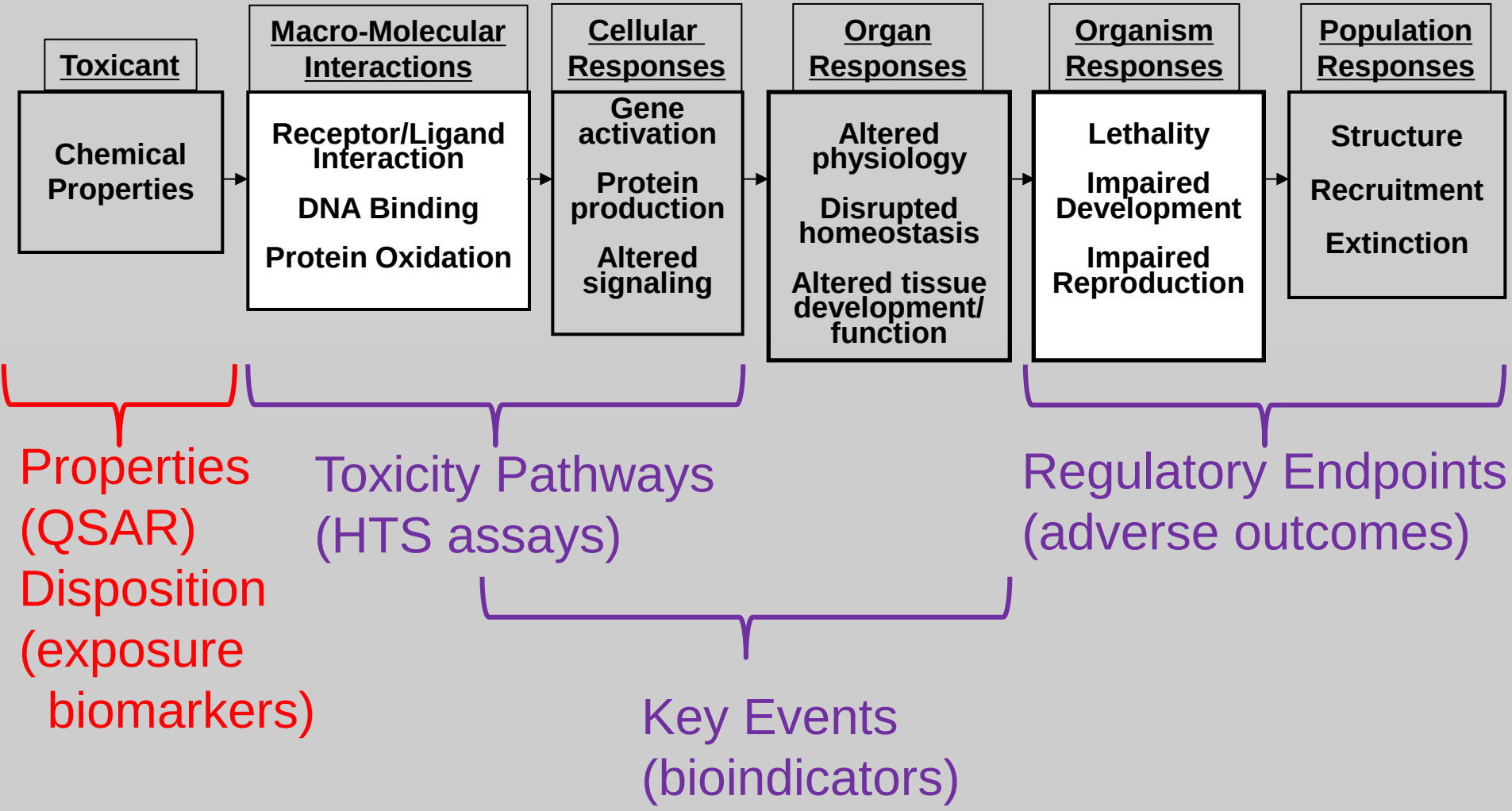
# AOP Discovery & Development



# Using AOPs for Informed Decisions



# AOP Confidence + Testing Data -> Regulatory Decision Making

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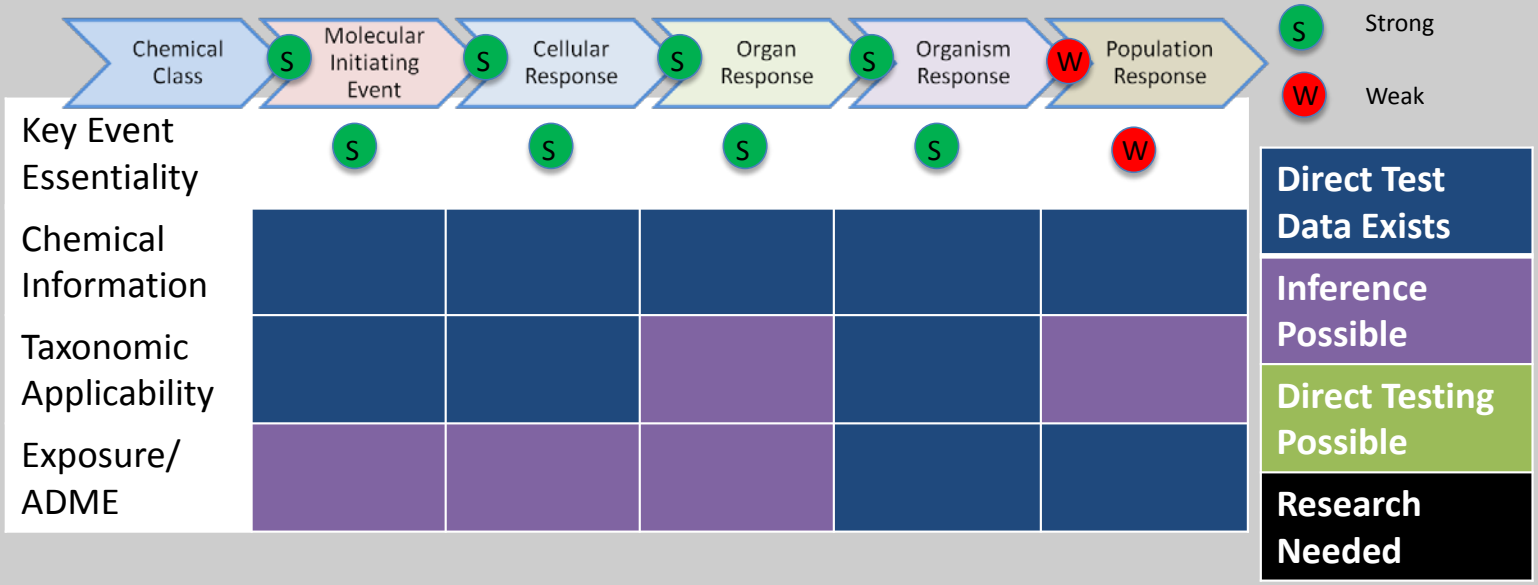


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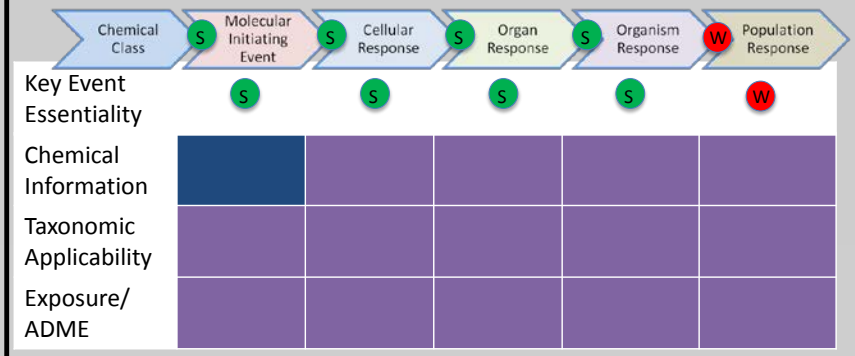


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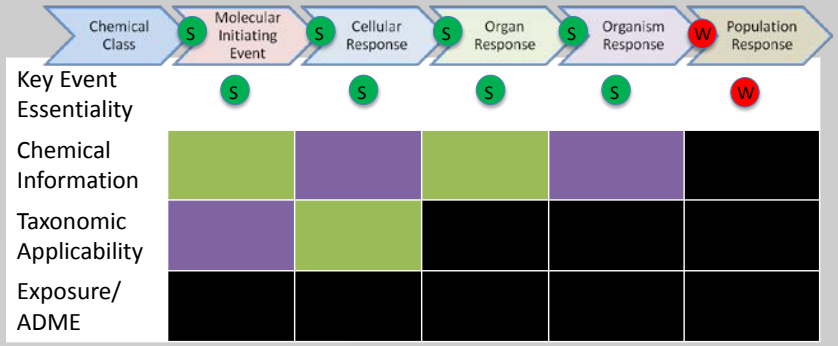

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- Gary Ankley
- Lyle Burgoon
- Robert Kavlock

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

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# Change is Good

# Questions?

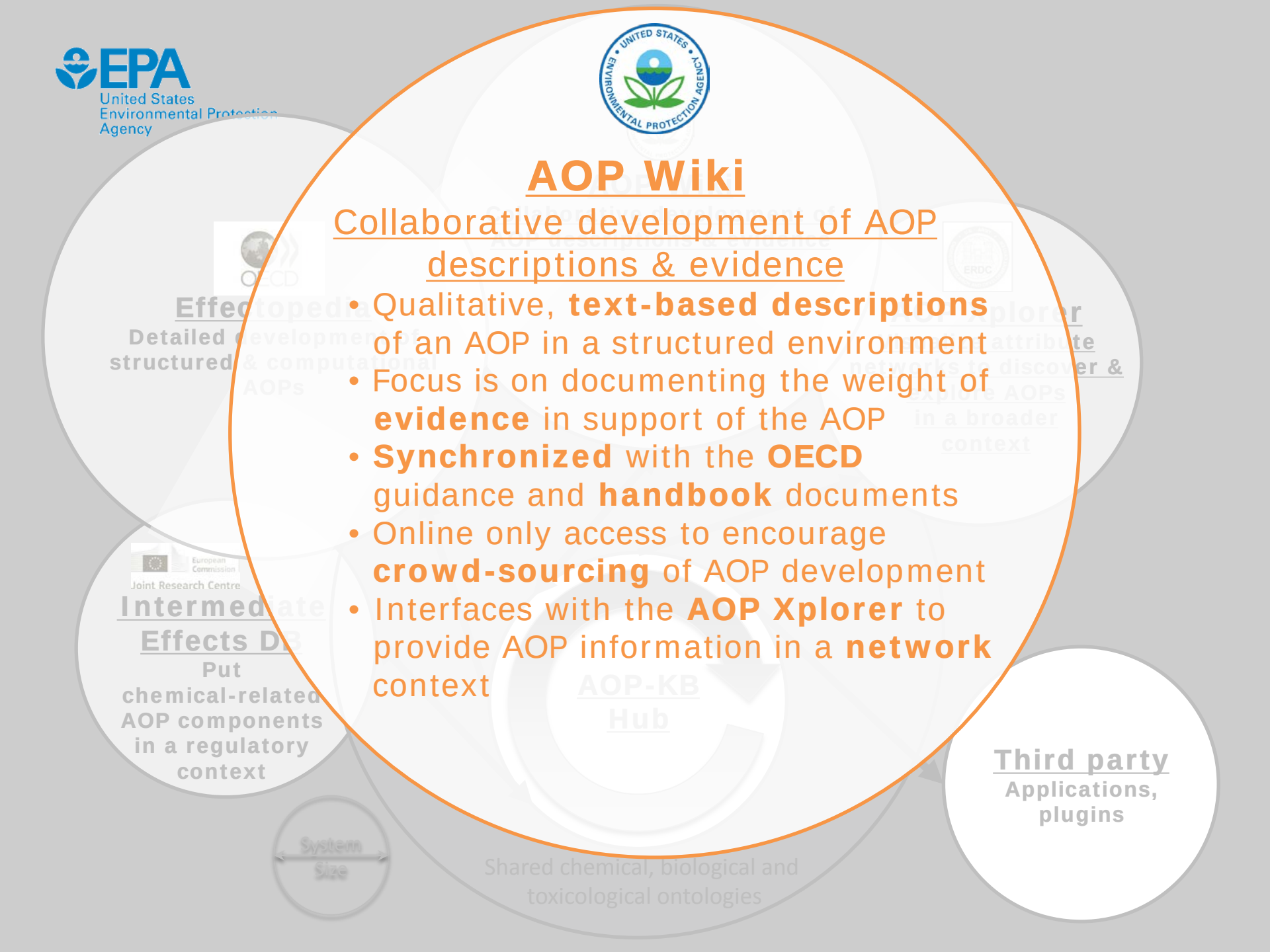
- Any interest in hiring a very talented scientist currently completing postdoctoral work in my group, please contact
  - Shannon Bell, Bell.Shannon@epa.gov

- Anyone interested in a postdoctoral position in my group, please contact me (Edwards.Stephen@epa.gov) or see the following ad
  - http://orise.orau.gov/epa/applicants/description.aspx?JobId=14771
  - Google search:  orise epa aop stephen edwards

Research Opportunity Description

Bioinformatics Approaches to Grouping Chemicals Using High-Throughput Screening Data
Research Participation Program
Office of Research and Development
National Health and Environmental Effects Research Laboratory
U.S. Environmental Protection Agency
Research Triangle Park, NC

EPA-ORD/NHEERL-ISTD-2014-01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AOP Wiki
Collaborative development of AOP descriptions & evidence
• Qualitative, text-based descriptions of an AOP in a structured environment
• Focus is on documenting the weight of evidence in support of the AOP
• Synchronized with the OECD guidance and handbook documents
• Online only access to encourage crowd-sourcing of AOP development
• Interfaces with the AOP Xplorer to provide AOP information in a network context
Effectopedia
Detailed development & computational structured AOPs
AOP Xplorer
networks to discover & explore AOPs in a broader context
Intermediate Effects DB
Put chemical-related AOP components in a regulatory context
AOP-KB Hub
Third party
Applications, plugins
System Size
Shared chemical, biological and toxicological ontologies

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# Effectopedia

## Detailed development of structured & computational AOPs

- Visual interface for design and collaborative editing of AOP and chemical case studies
- AOP structure guidance is embedded in the system
- Ability to store and process quantitative information, including formal description of test methods, algorithms and models along with their applicability domains and verification methods
- Provides offline editing capabilities and robust capabilities for managing data access
- Embeds the concept of AOP networks directly in the system
- Provides capabilities for sharing, discussing, and reviewing AOPs

OECD

Third party
Applications, plugins

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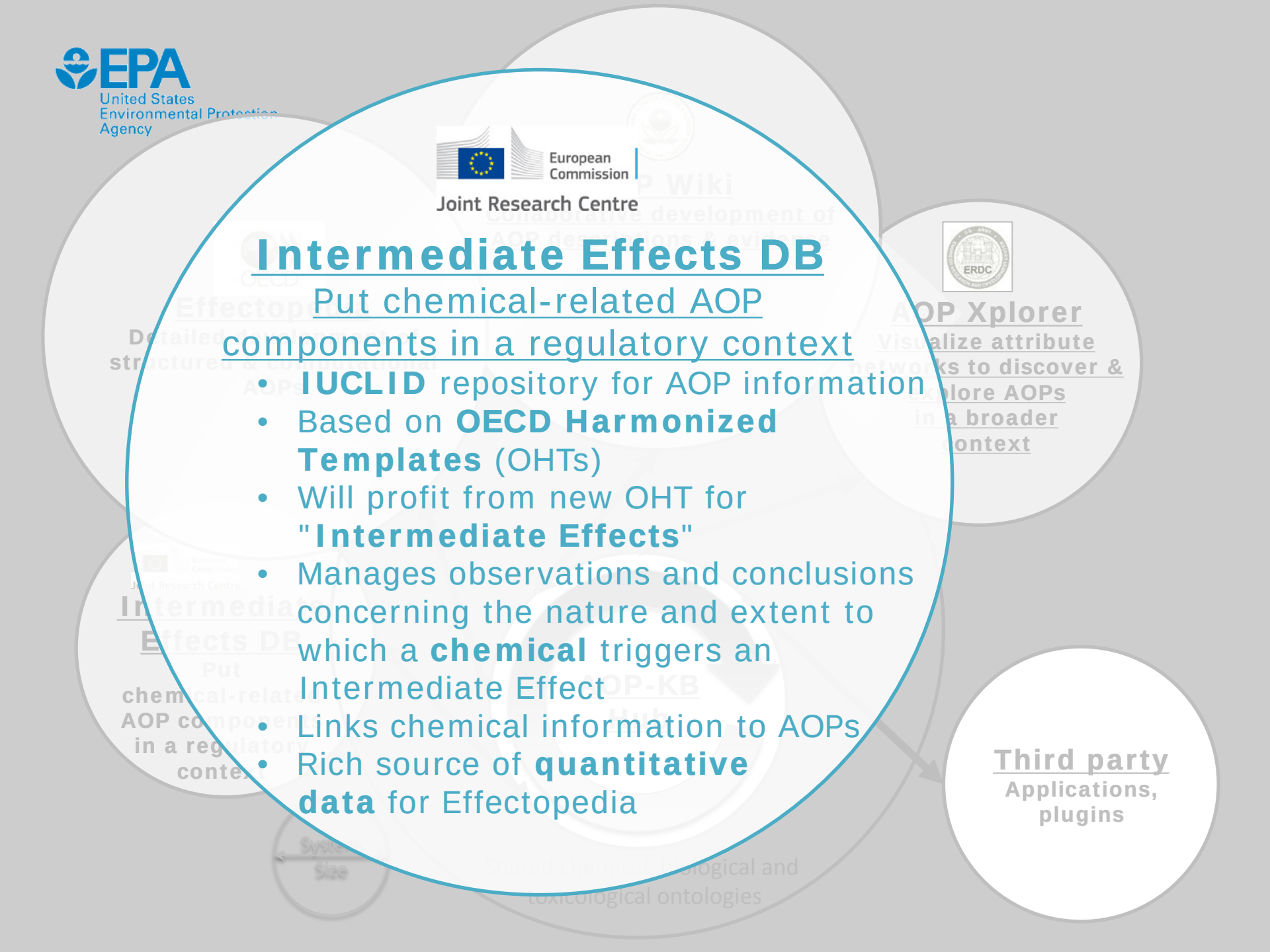
European Commission
Joint Research Centre

# Intermediate Effects DB

## Put chemical-related AOP components in a regulatory context

- **IUCLID** repository for AOP information
- Based on **OECD Harmonized Templates** (OHTs)
- Will profit from new OHT for "**Intermediate Effects**"
- Manages observations and conclusions concerning the nature and extent to which a **chemical** triggers an Intermediate Effect
- Links chemical information to AOPs
- Rich source of **quantitative data** for Effectopedia



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OECD

**Effectopedia**

Detailed development of structured & computational AOPs

European Commission Joint Research Centre

**Intermediate Effects DB**

Put chemical-related AOP components in a regulatory context

# AOP Xplorer

## Visualize attribute networks to discover & explore AOPs in a broader context

- Allows user to **explore AOPs** in a **network context** based on shared key events
- Provides additional **bioinformatics analysis tools** for annotating key events and traversing the network
- Incorporates **putative AOP** information and facilitates **AOP discovery**

**Third party**

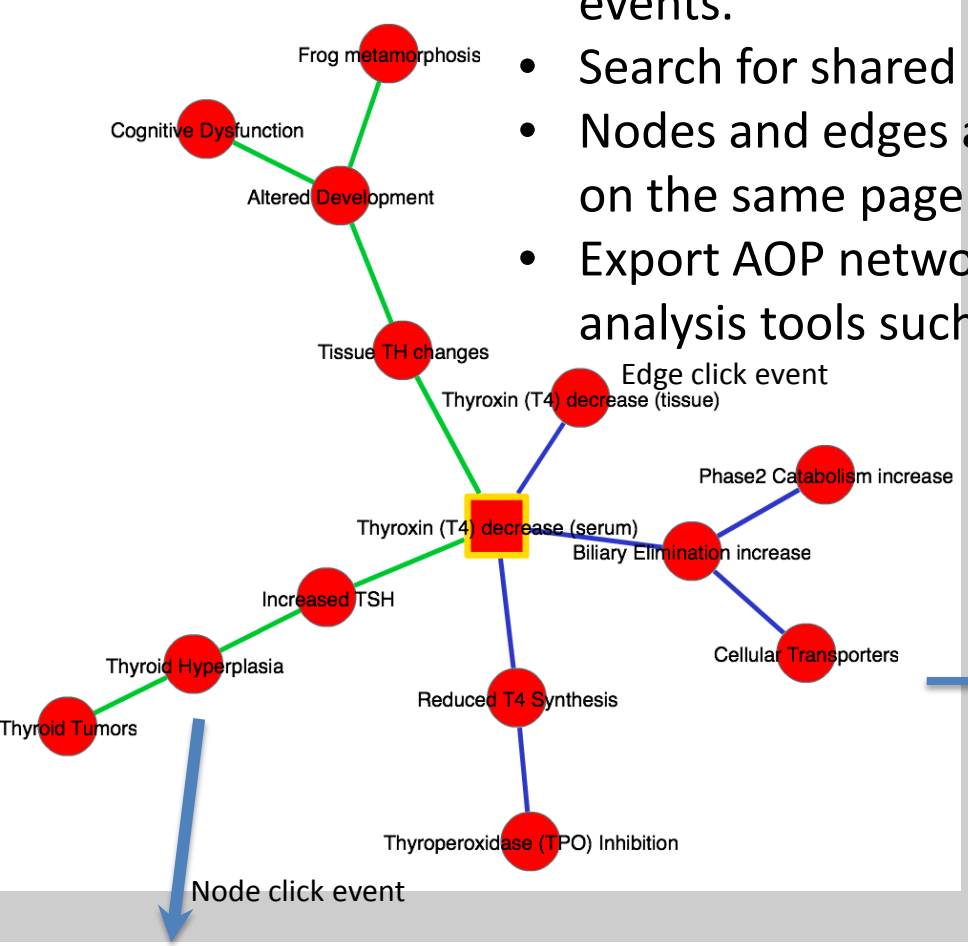
Applications, plugins

System Size

Shared chemical, biological and toxicological ontologies

# AOP Xplorer

- Explore AOPs in a network context based on the shared key events.
- Search for shared key events between AOPs or chemicals.
- Nodes and edges are clickable, that displays their attributes on the same page.
- Export AOP network into feature rich visualization and analysis tools such as Cytoscape.





| Title | Level of Organization | Description | Chemical | Upstream Cause | Downstream Effect | Species | Lifestages | Sex | Evidence | Genes | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Thyroxin (T4) decrease (serum) | Tissue | Large body of literature demonstrating that chemicals can reduce serum T4 in animals as well as some evidence in humans (for review, see Cooper et al., 1983). | | Reduced T4 Synthesis;Biliary Elimination increase;Thyroxin (T4) decrease (tissue) | Increased TSH; Tissue TH changes | rat;frog | Adult | Unknown | | | Cooper, D.S., Kieffer, Maloof, F., and Ridgw pharmacology in the r Endocrinology 113:92 |

EPA United States Environmental Protection Agency

# AOP-KB Hub

- Central hub for all **shared information** among the AOP-KB components
- Operates via web services for maximum **flexibility** in implementation of the other modules and to provide access for third party tools
- Based on **established** chemical, biological and toxicological **ontologies** unified by a specifically-designed AOP ontology

European Commission
Joint Research Centre

ERDC

Third party
Applications, plugins