

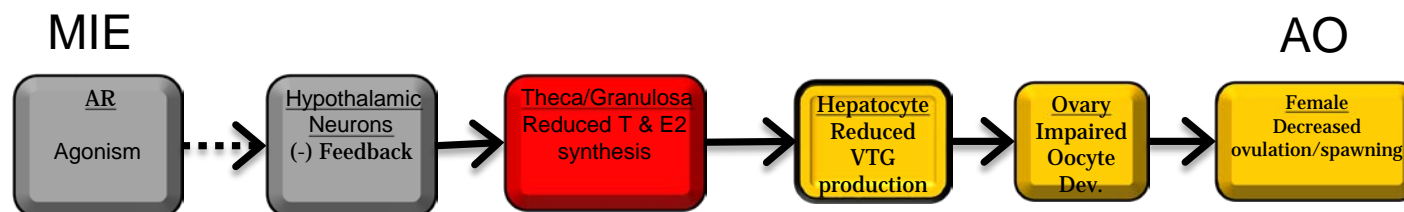
Adverse Outcome Pathways: Challenges in Use and Development

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Baltimore
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Outline

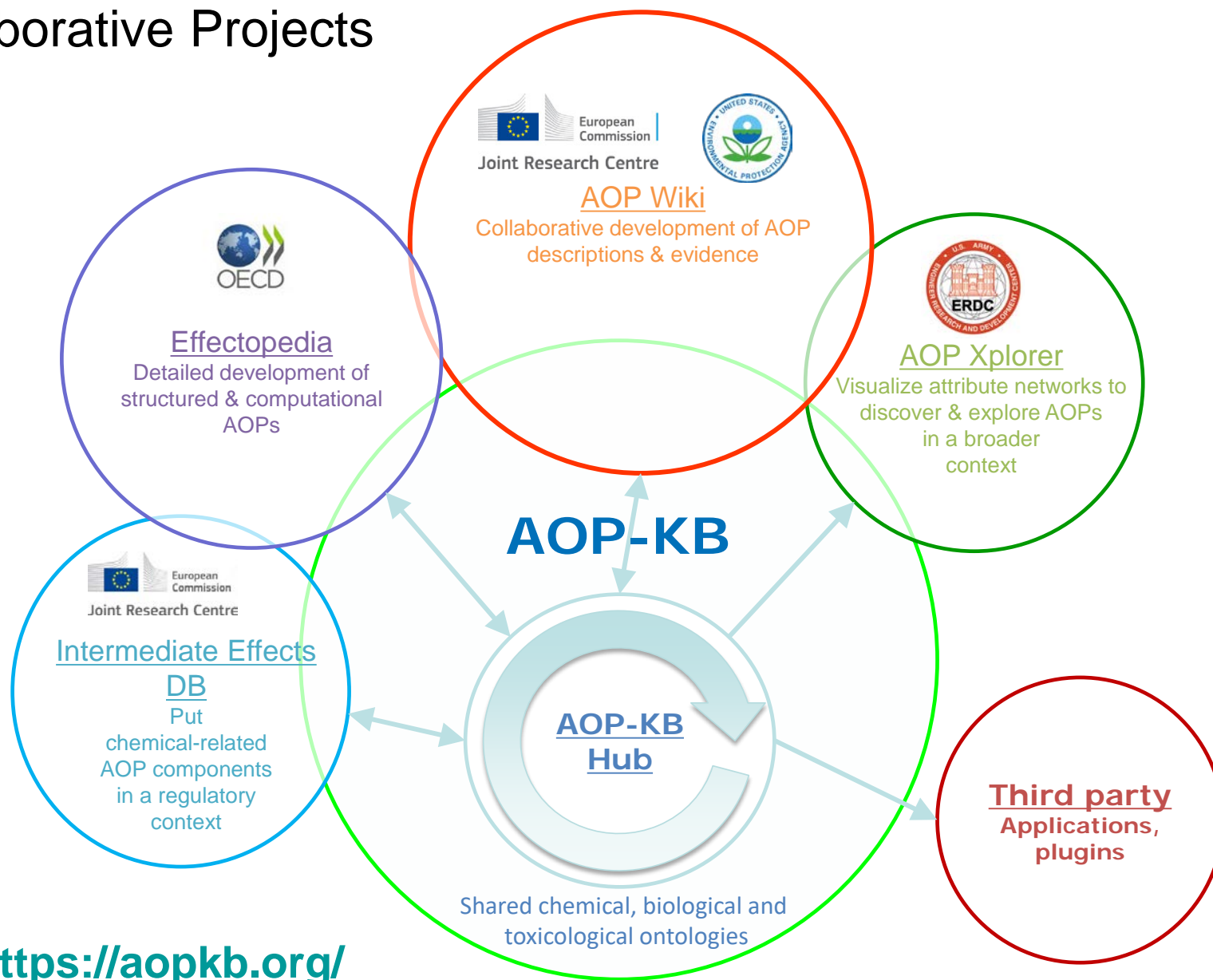


- AOPs – What are they good for?
- Challenges
 - Collaborative Efforts - AOP Wiki
 - How to efficiently build more AOPs
 - AOP integration – Biology is not linear

AOPs – What are they good for?

- 1. Improved predictions of toxicity via decreased uncertainty and increased transparency**
 - Increases level of confidence in the relationship between measured data and adverse outcomes that is critical for risk assessments
 - Allows use of ‘up-stream’ key events
- 2. Informs/enhances species to species extrapolation**
- 3. Can be Life-Stage specific**
- 4. Identification of Data Gaps**
 - Construction of an AOP should identify data gaps i.e., critical needs to build a useful model
- 5. Provide molecular targets for development of in vitro screening assays (e.g., ToxCast, Tox21) and QSARs (e.g., OECD Toolbox)**
- 6. Holy Grail = predictive computational models**
 - If the MIE predicts the Adverse Outcome – then you don’t need to measure the outcome
 - Must include compensatory mechanics

Collaborative Projects

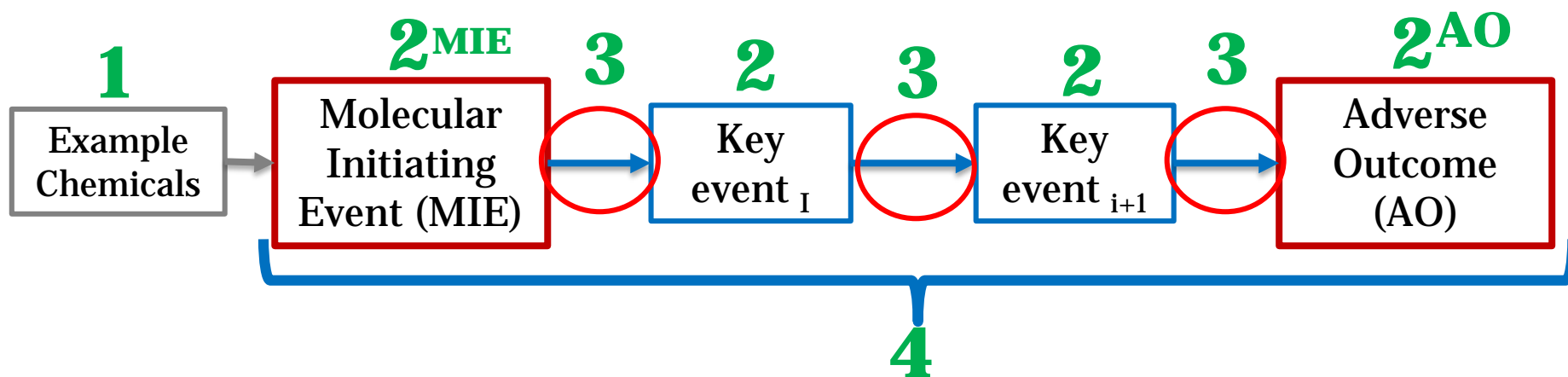
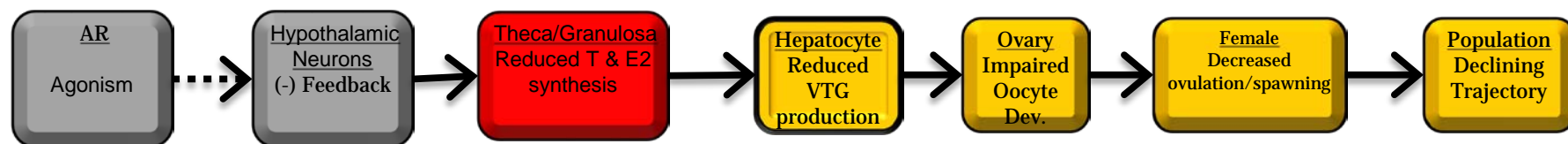


AOP Wiki

Collaborative development of AOPs

- Provides 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
- Interfaces with the **AOP Xplorer** to ***visualize*** AOP information in a network context
- Future interface with Effectopedia and Intermediate Effects dB
- ***Crowd-sourcing hypothesis*** - Online public access to encourage AOP development

Structuring and Storing AOP Information



AOP Components are mapped to specific entities in the Wiki

- | | |
|---|------------------------------------|
| 1. Chemical initiators | 3. KE Relationship (linkage; edge) |
| 2. Key event (nodes)
MIE & AO are special cases of KEs | 4. AOP |

Page [Discussion](#)

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Aop:23

[Main Page](#) > [Special:UserLogin](#) > [AOP List](#) > [Aop:42](#) > [Aop:23](#)

AOP Title [\[edit\]](#)

Androgen receptor agonism leading to reproductive dysfunction

Short name: Androgen receptor agonism leading to reproductive dysfunction

Authors [\[edit\]](#)

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

Status [\[edit\]](#)

Open for comment

OECD Project 1.12: The Adverse outcome pathways linking aromatase inhibition, androgen receptor agonism, estrogen receptor antagonism, or steroidogenesis inhibition, to impaired reproduction in small repeat-spawning fish species [↗](#)

This AOP page was last modified on 3/1/2015.

[Click here to show/hide revision dates for related pages](#)

Abstract [\[edit\]](#)

This adverse outcome pathway details the linkage between binding and activation of androgen receptor as a nuclear transcription factor i
cumulative fecundity in repeat-spawning fish species. Cumulative fecundity is the most apical endpoint considered in the OECD 229 Fish
OECD 229 assay serves as screening assay for endocrine disruption and associated reproductive impairment (OECD 2012). Cumulative
known to be of demographic significance in forecasting fish population trends. Therefore, this AOP has utility in supporting the application
and activation as a nuclear transcription factor as a means to identify chemicals with known potential to adversely affect fish populations.

Summary of the AOP

Please follow link to [widget page](#) [↗](#) to edit this section.

Molecular Initiating Event

Molecular Initiating Event ↕	Support for Essentiality ↕
Androgen receptor, Agonism	Strong

Key Events

Event ↕	Support for Essentiality ↕
Gonadotropins, circulating concentrations, Reduction	Moderate

**Review
Status**

**OECD
Project #**

**Free
Text Fields**

**Structured
Content**

How many AOPs do we have and how many do we need?

OECD reviewed and approved AOPs

- Only one so far – Skin Sensitization

AOP Wiki AOPs

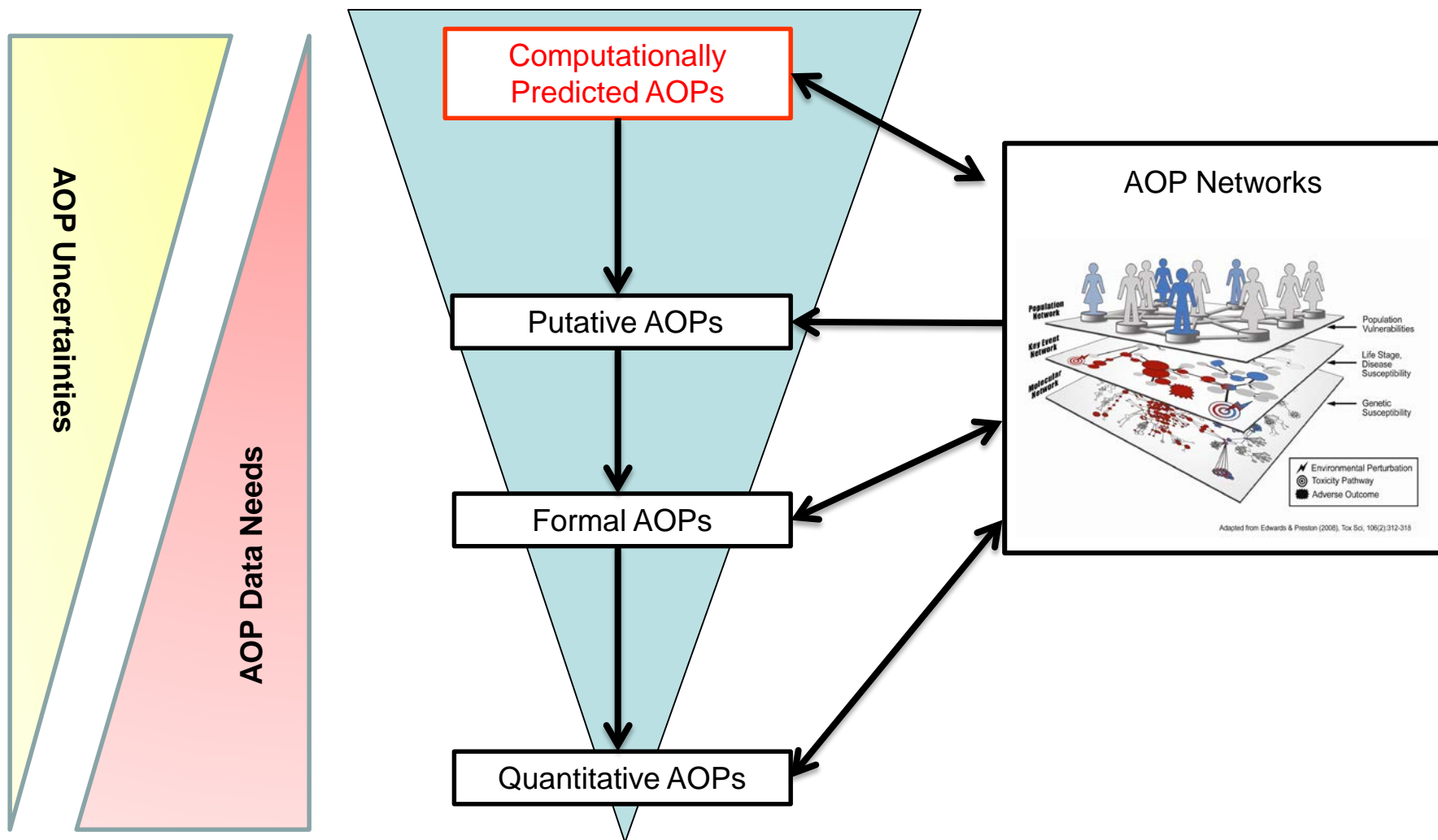
- 7 “AOPs Ready for Commenting”
 - The AOPs are open for public comments
- 36 “AOPs Under Development”
 - Available for viewing, but not comments
 - *Note: A number are not active*

Peer Reviewed Publications

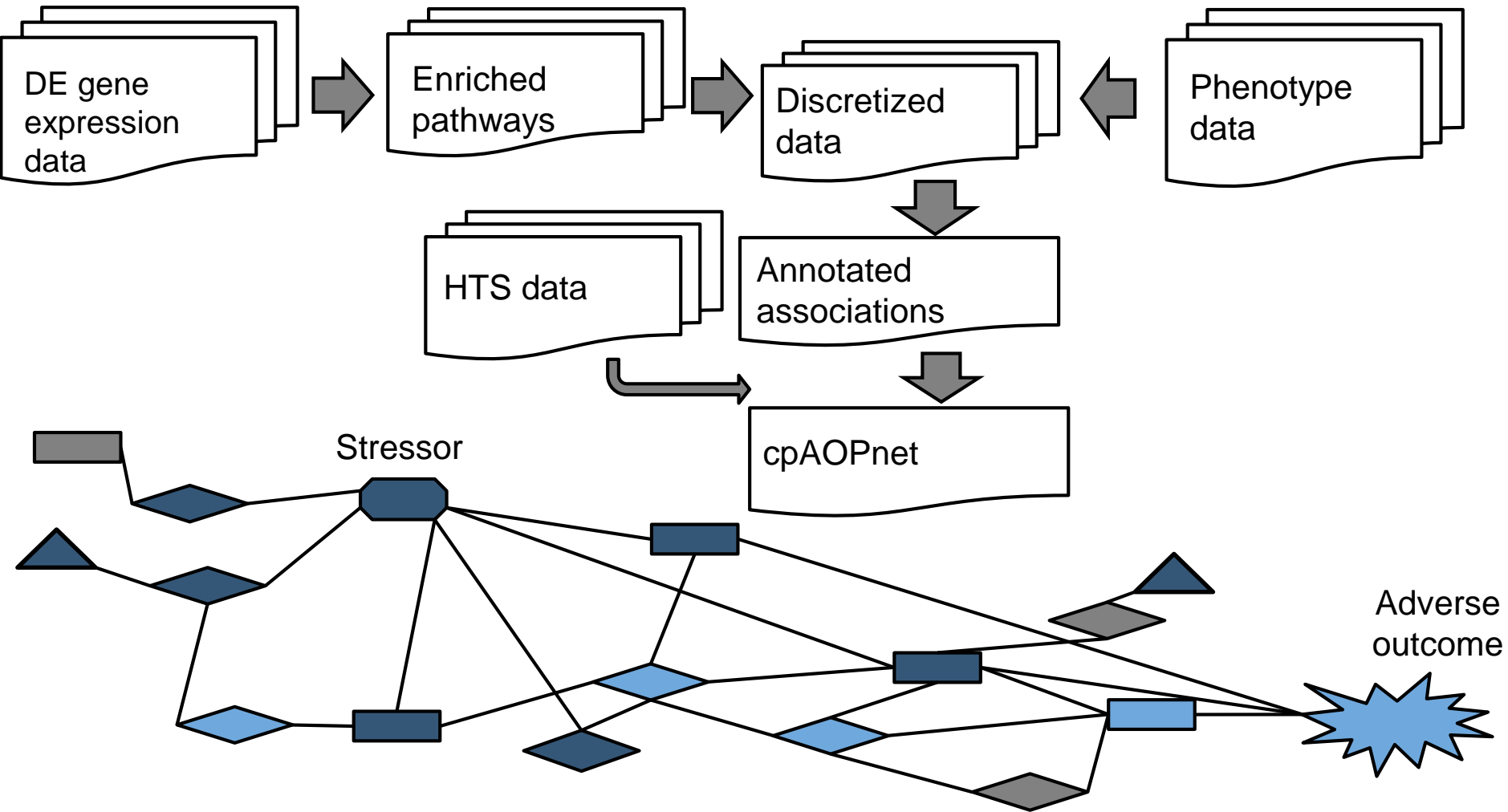
- ~ 5 (some overlap with AOP Wiki)

**Biological Space Coverage for
AOPs is limited**

Speeding AOP Discovery & Development

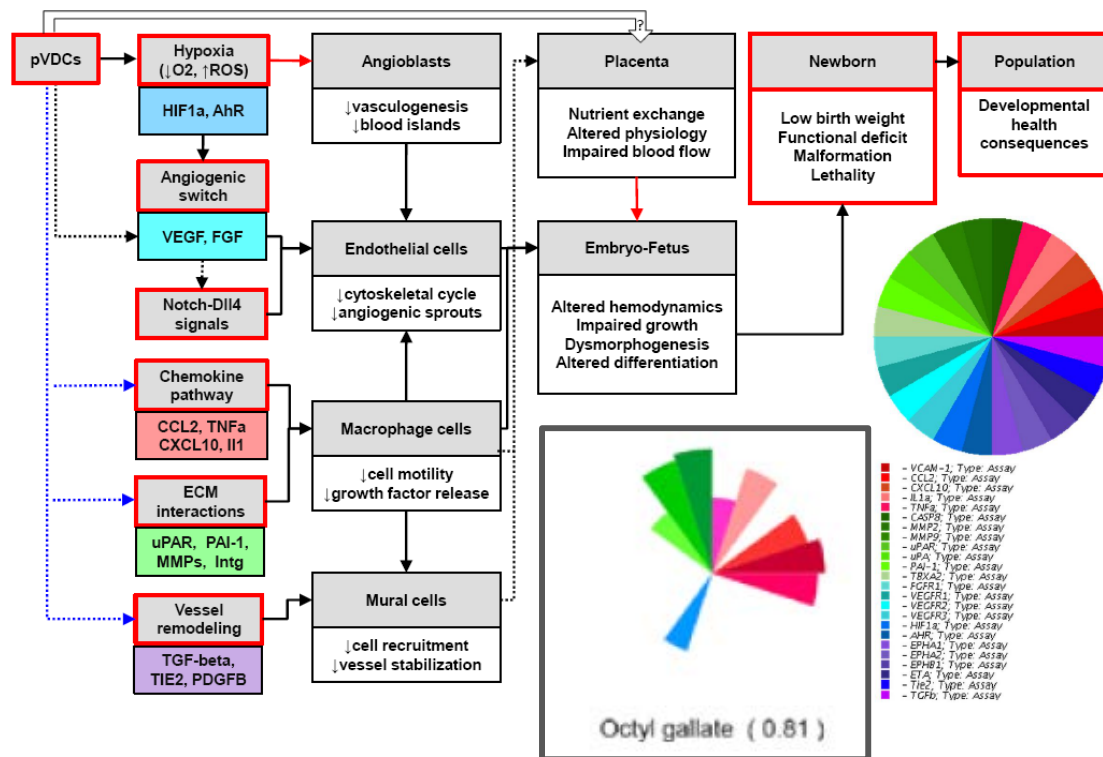


Computational approach for data integration and putative AOP identification



Computational Modeling – Using ToxCast and ToxRef AOP for Vascular Disruption

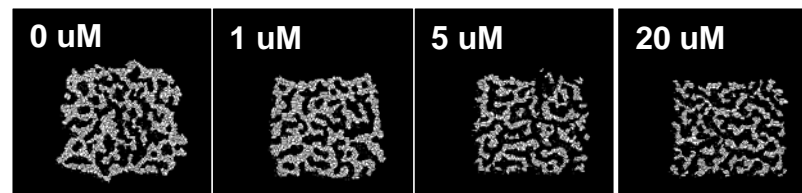
AOP for Developmental Vascular Disruption



- AOPs for embryonic vascular disruption developed from biology of vascular development and used ToxCast data to parameterize models
- Validated model results with orthogonal organotypic assays and reference teratogens

Kleinstreuer *et al.*, PLoS Comp Bio, 2013

Model Simulations of Dev Vascular Disruption

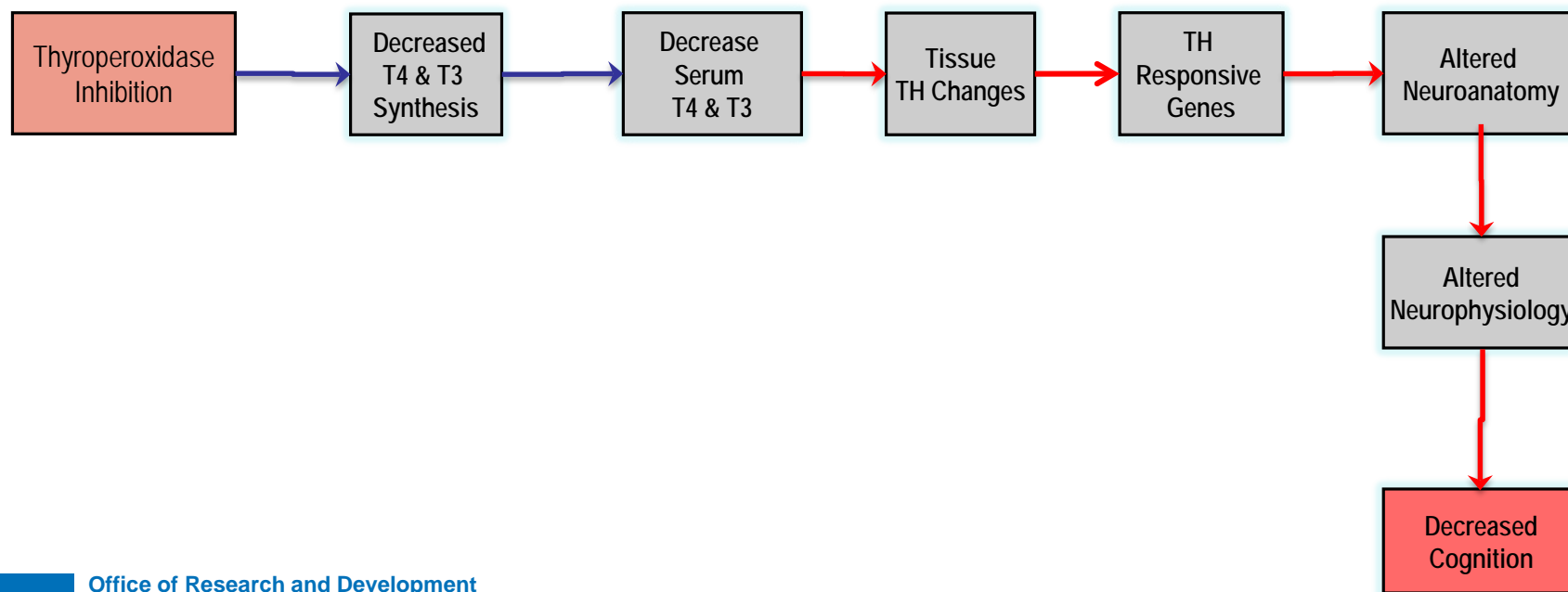


Knudsen *et al.*, unpublished

Biology is not Linear

Integrating AOPs - Thyroid Disruption as Example

OECD Project 1.10: Xenobiotic Induced Inhibition of Thyroperoxidase and Depressed Thyroid Hormone Synthesis and Subsequent Adverse Neurodevelopmental Outcomes in Mammals.

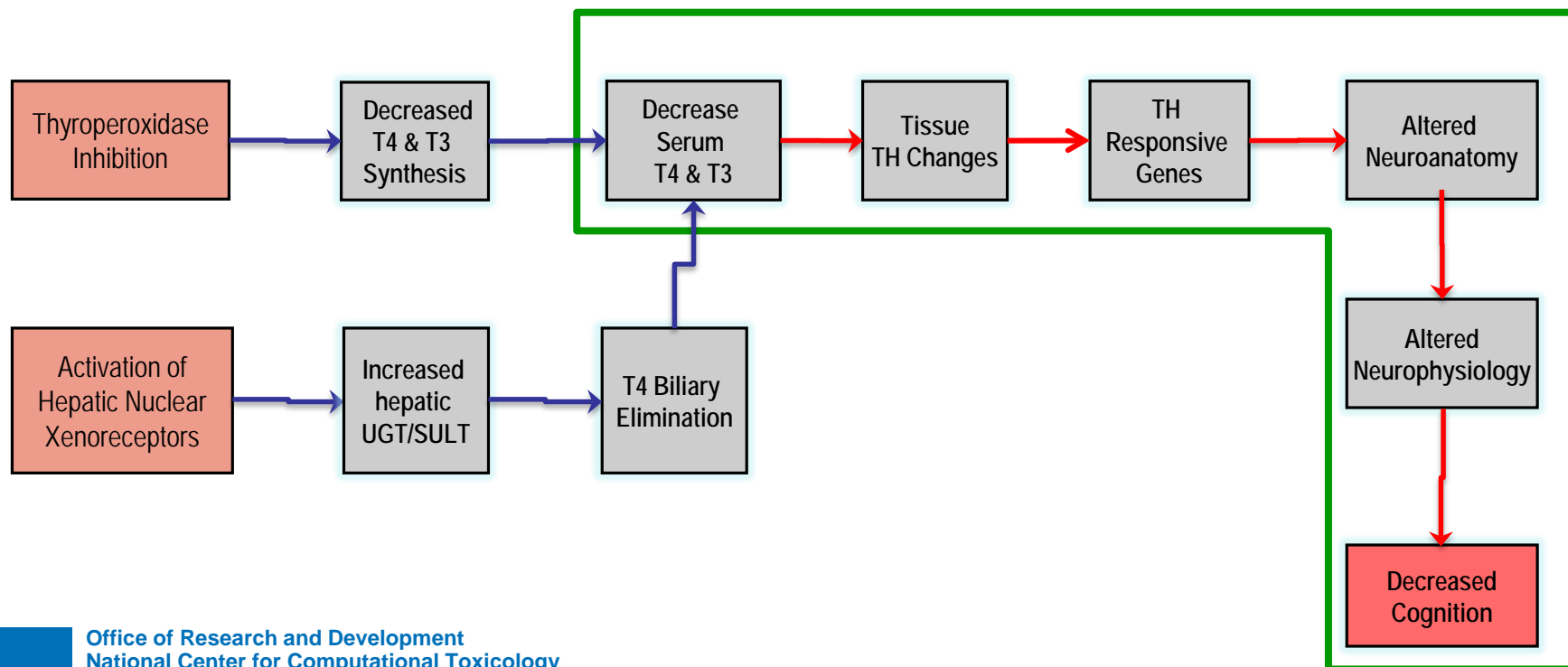


Integrating AOPs - Thyroid Disruption as Example

OECD Project 1.10: Xenobiotic Induced Inhibition of Thyroperoxidase and Depressed Thyroid Hormone Synthesis and Subsequent Adverse Neurodevelopmental Outcomes in Mammals.



OECD Project 1.9: Upregulation of Thyroid Hormone Catabolism via Activation of Hepatic Nuclear Receptors, and Subsequent Adverse Neurodevelopmental Outcomes in Mammals.



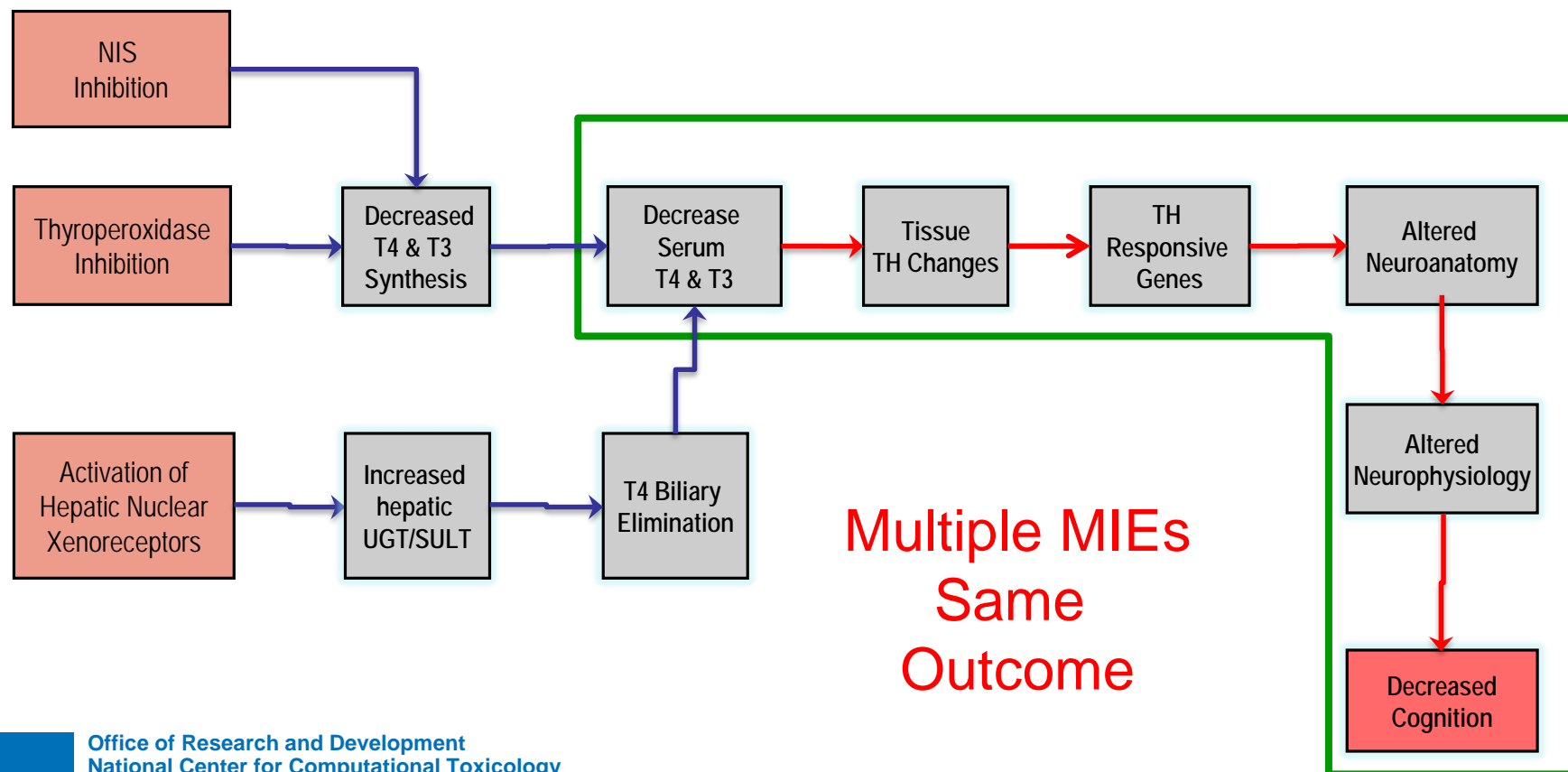
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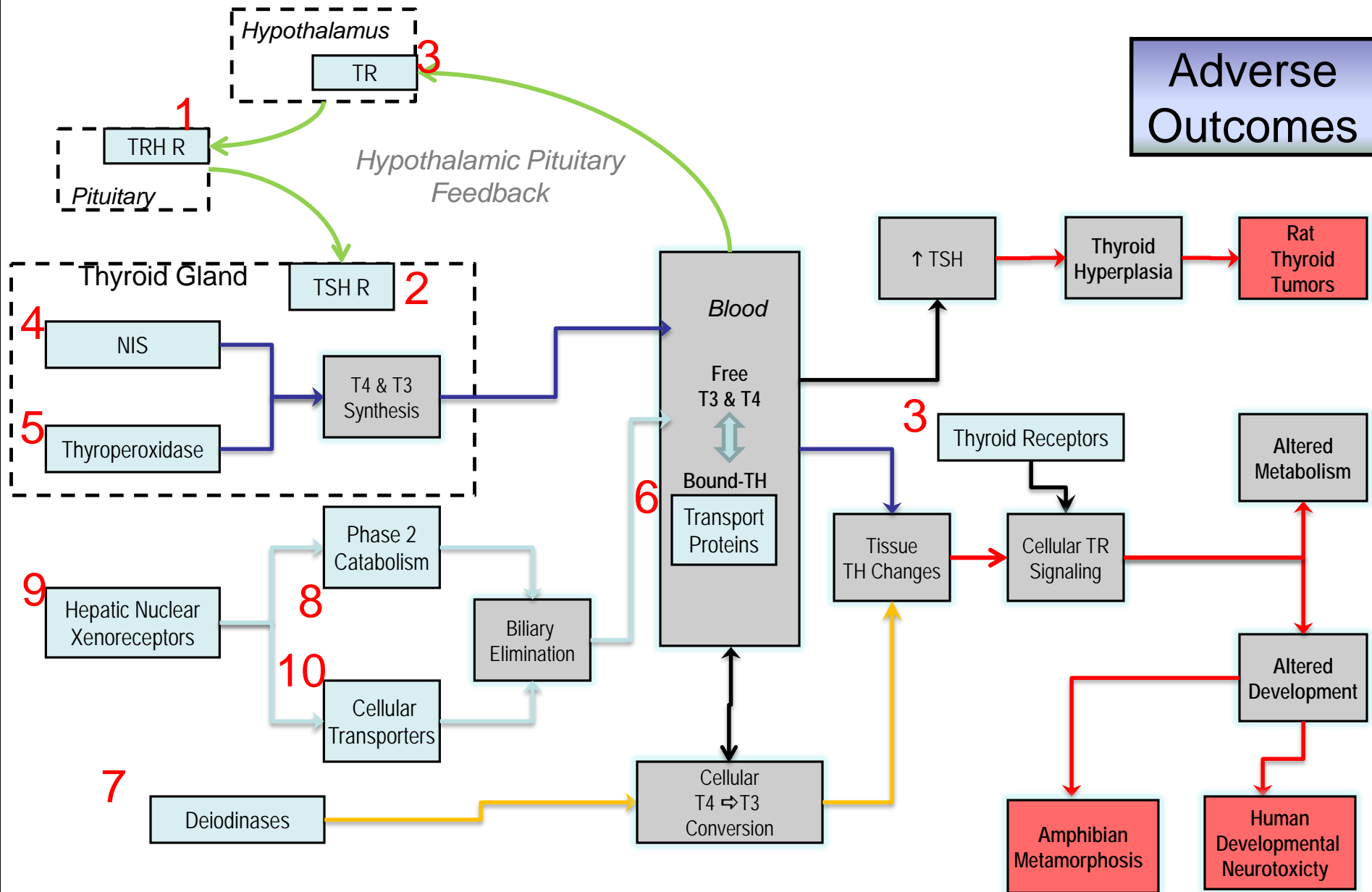
OECD Project 1.9: Upregulation of Thyroid Hormone Catabolism via Activation of Hepatic Nuclear Receptors, and Subsequent Adverse Neurodevelopmental Outcomes in Mammals.



New OECD AOP Project: Inhibition of Na⁺/I⁻ symporter (NIS) decreases TH synthesis leading to learning and memory deficit in children



Integrated Pathways – Multiple MIEs & Species Dependent and Independent AOs



AOPWiki

Beta version released September 2014.

- Developed as a joint project between:
 - OECD, EU Joint Research Center, Italy, US EPA, US Army Engineering Research and Development Center, Vicksburg MS
- Provides a ‘user-friendly’ interface for ‘crowd sourcing the development of AOPs

Link - www.aopwiki.org

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Thanks for Listening