United States Environmental Protection Agency

Adverse Outcome Pathways: Challenges in Use and Development

Kevin M. Crofton
Deputy Director
National Center for Computational Toxicology

Global Chem
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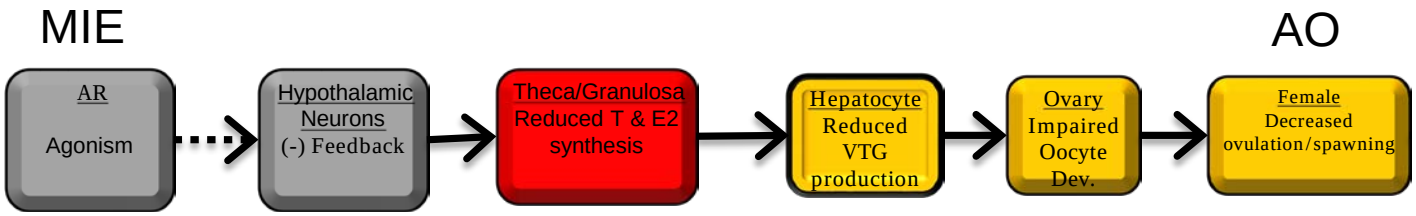
Office of Research and Development
National Center for Computational Toxicology

The views expressed in this presentation are those of the presenter and do not necessarily reflect the views or policies of the U.S. EPA

Outline

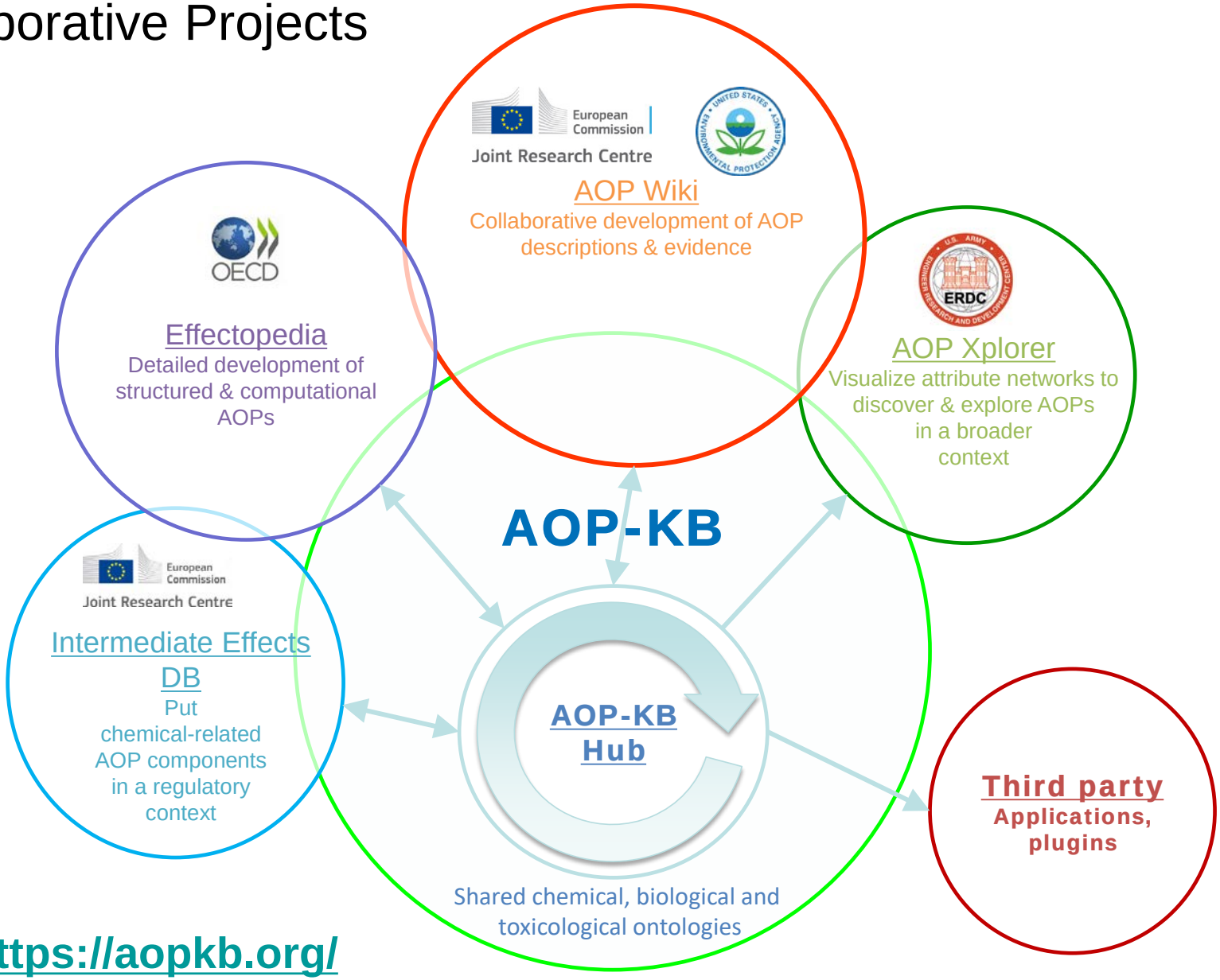


- AOPs – What are they good for?
- Challenges
  - Collaborative Efforts - AOP Wiki
  - How to efficiently build more AOPs
  - AOP integration – Biology is not linear

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



https://aopkb.org/

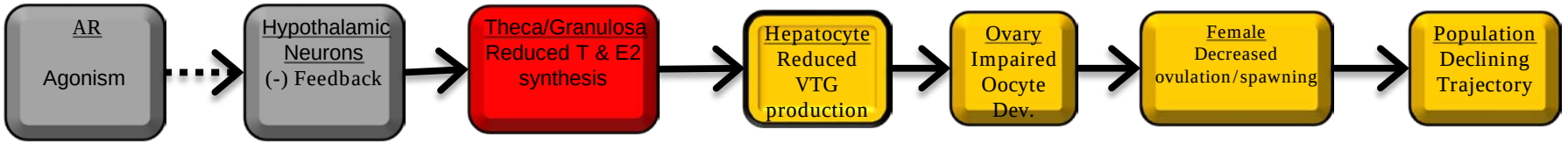
Slide from Clemens Wittwehr

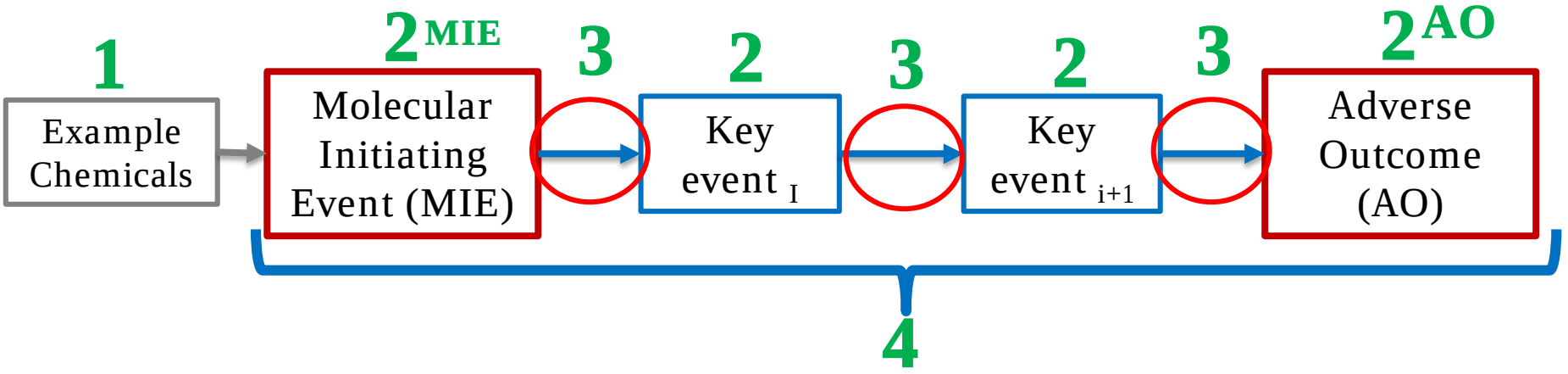
AOP Wiki

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



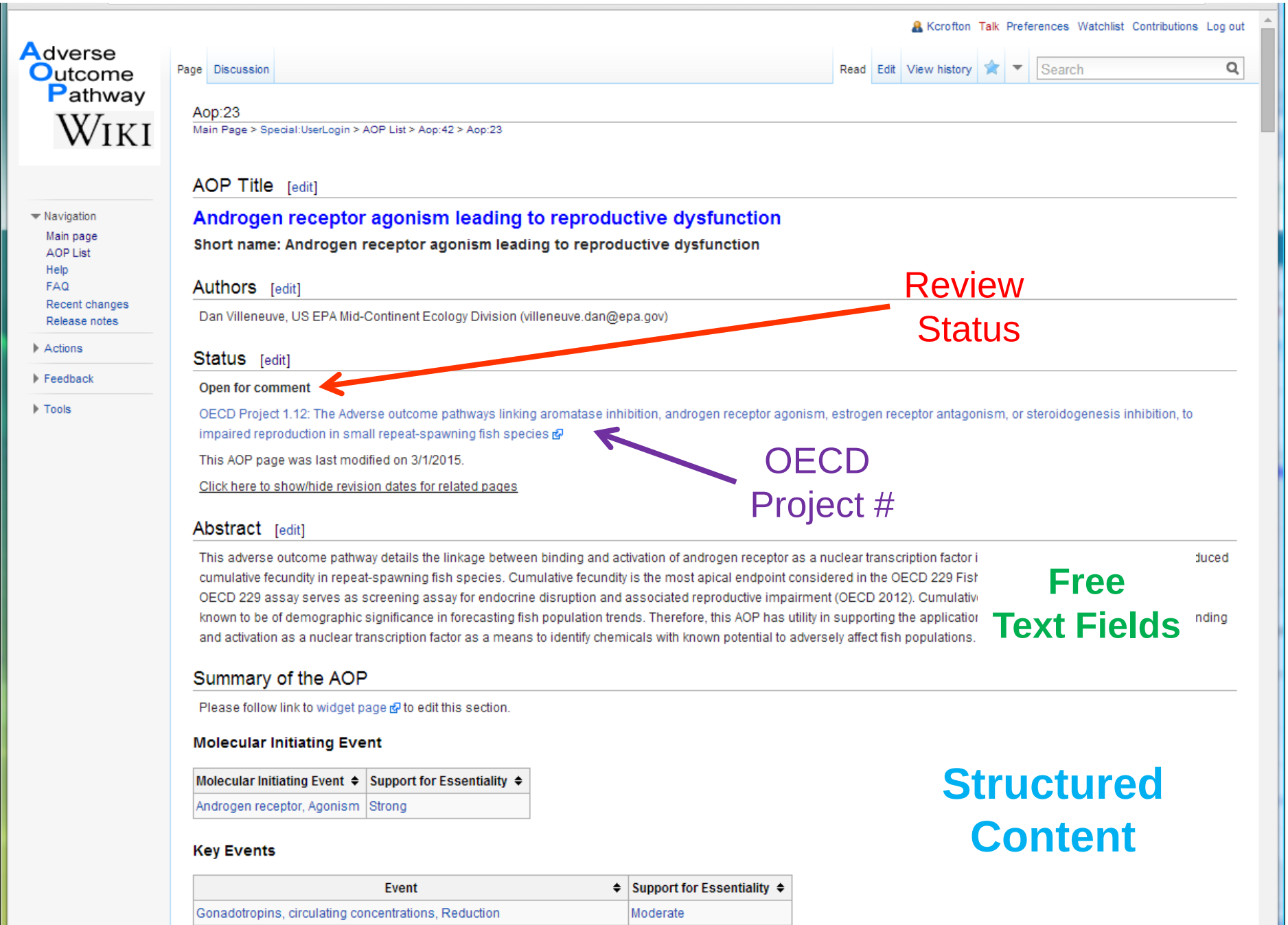


AOP Components are mapped to specific entities in the Wiki

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

AOP Page in Wiki

http://aopwiki.org



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

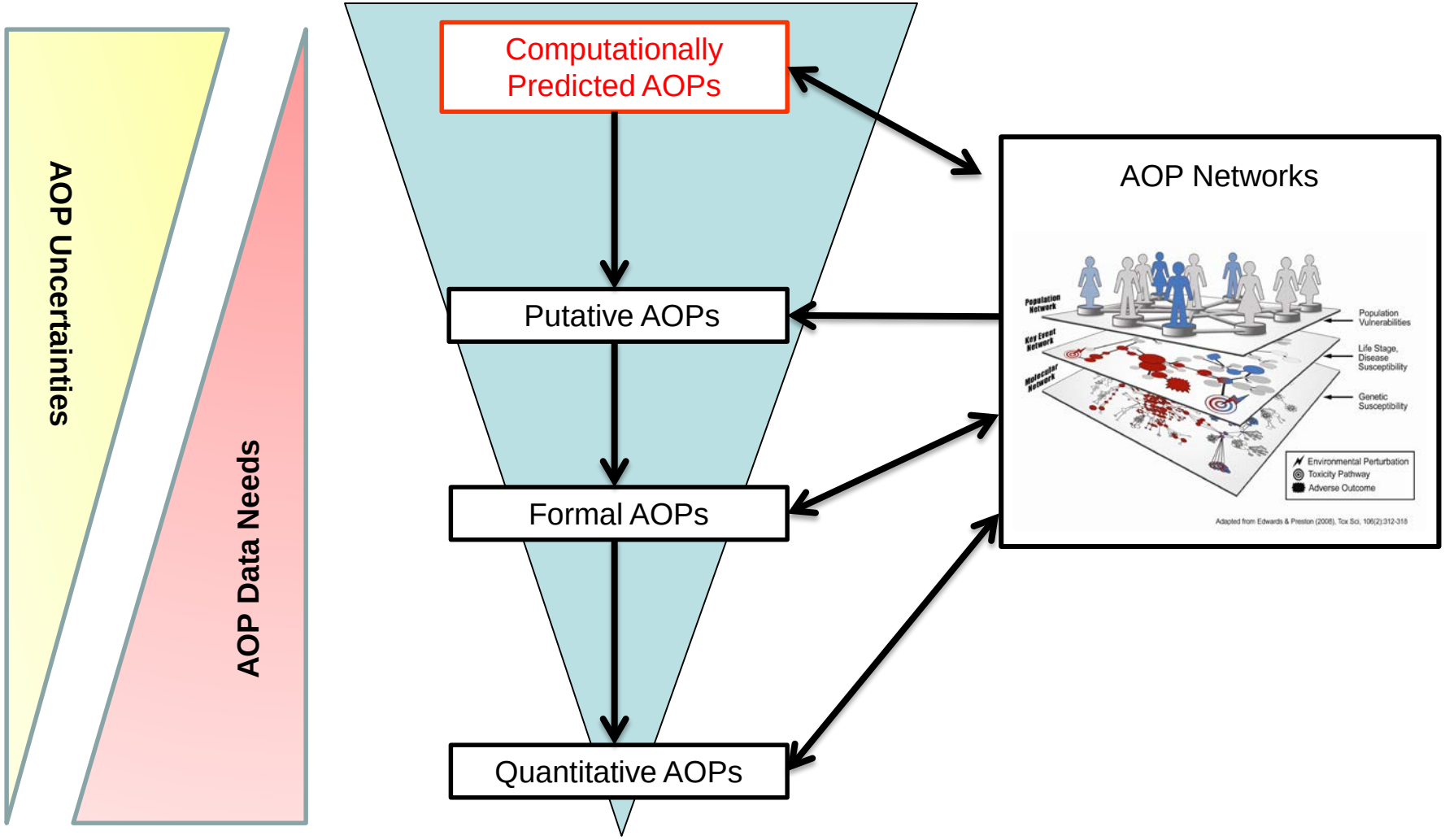
- **7 "AOPs Ready for Commenting"**
  - The AOPs are open for public comments
- **36 "AOPs Under Development"**
  - Available for viewing, but not comments
  - *Note: A number are not active*

Peer Reviewed Publications

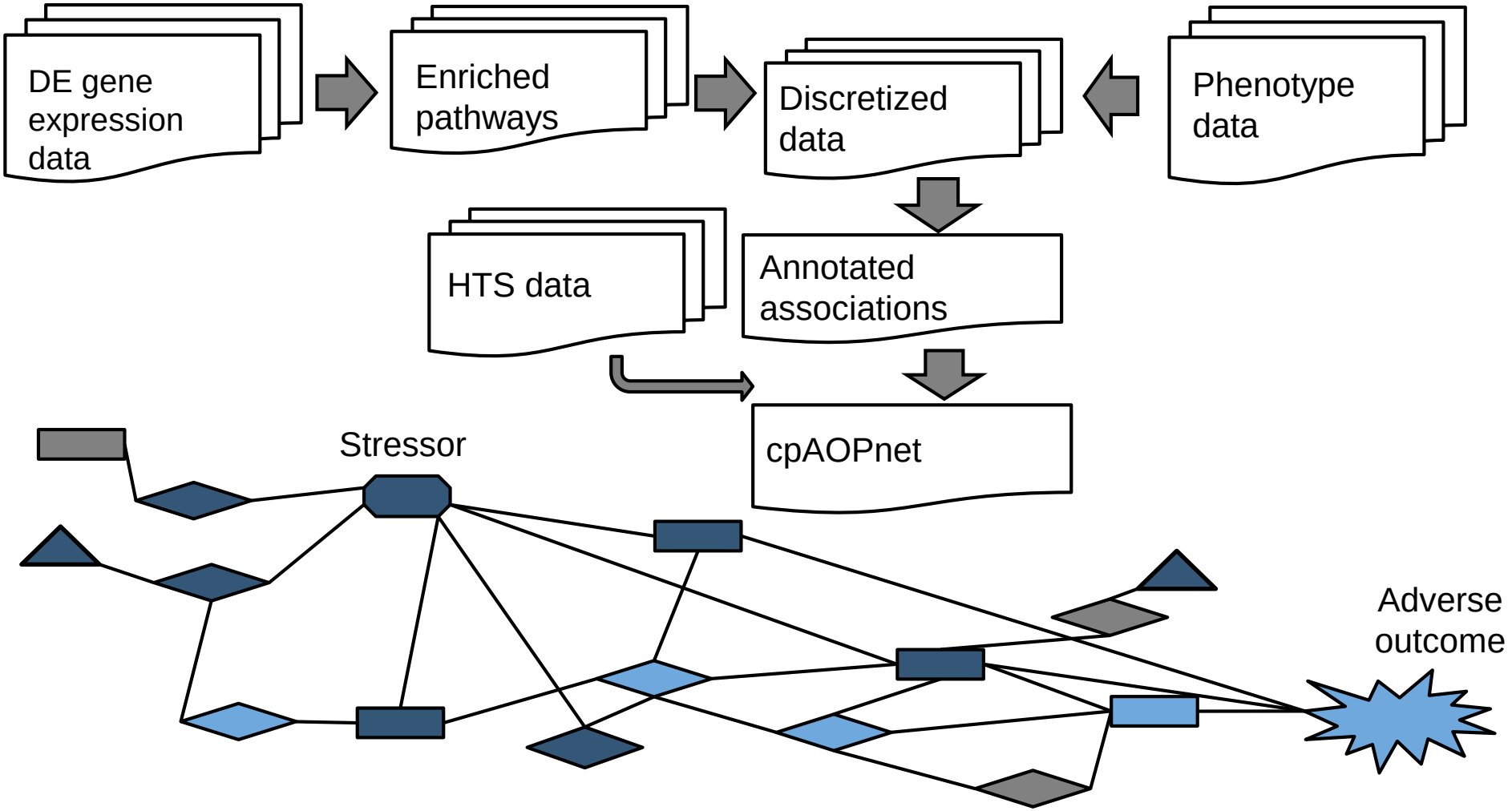
- **~ 5** (some overlap with AOP Wiki)

Biological Space Coverage for AOPs is limited

Speeding AOP Discovery & Development



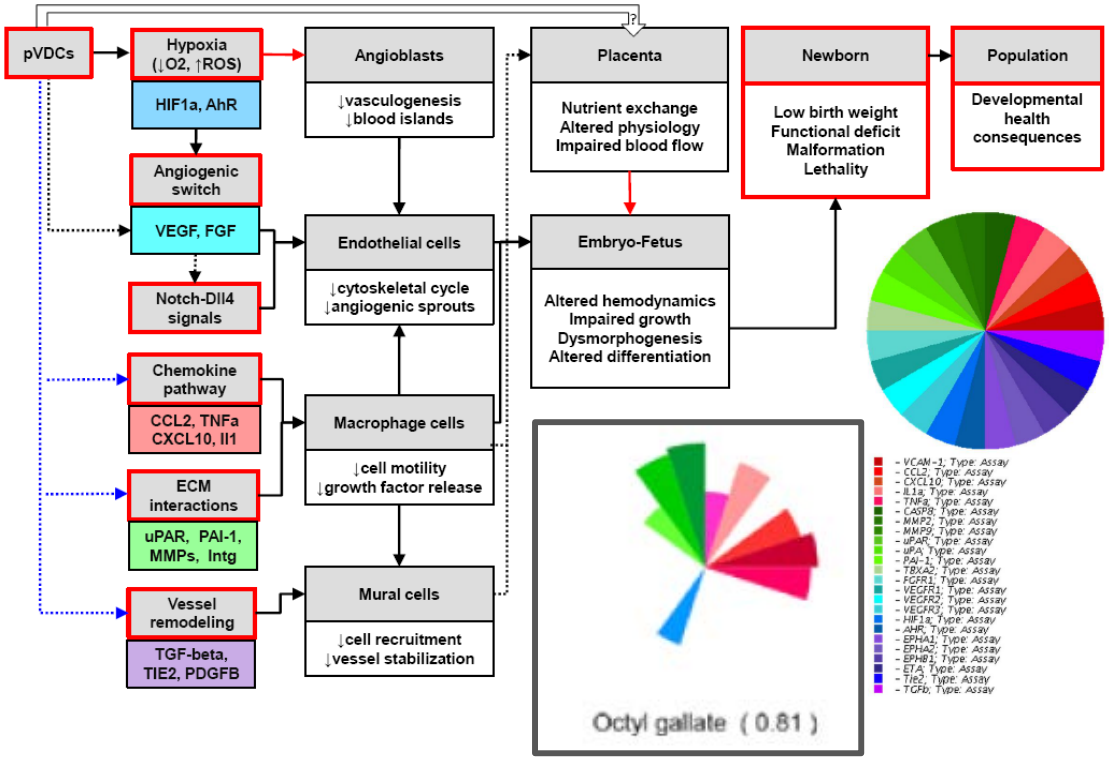
Computational approach for data integration and putative AOP identification



Slide courtesy of Steve Edwards & Shannon Bell

Computational Modeling – Using ToxCast and ToxRef AOP for Vascular Disruption

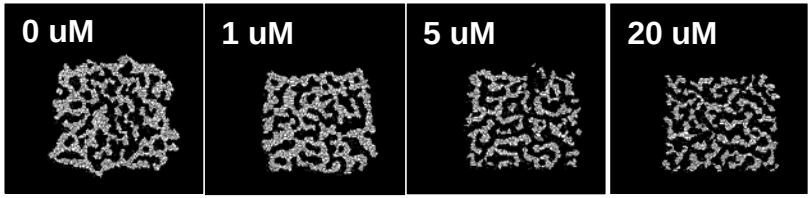
AOP for Developmental Vascular Disruption



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

- 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

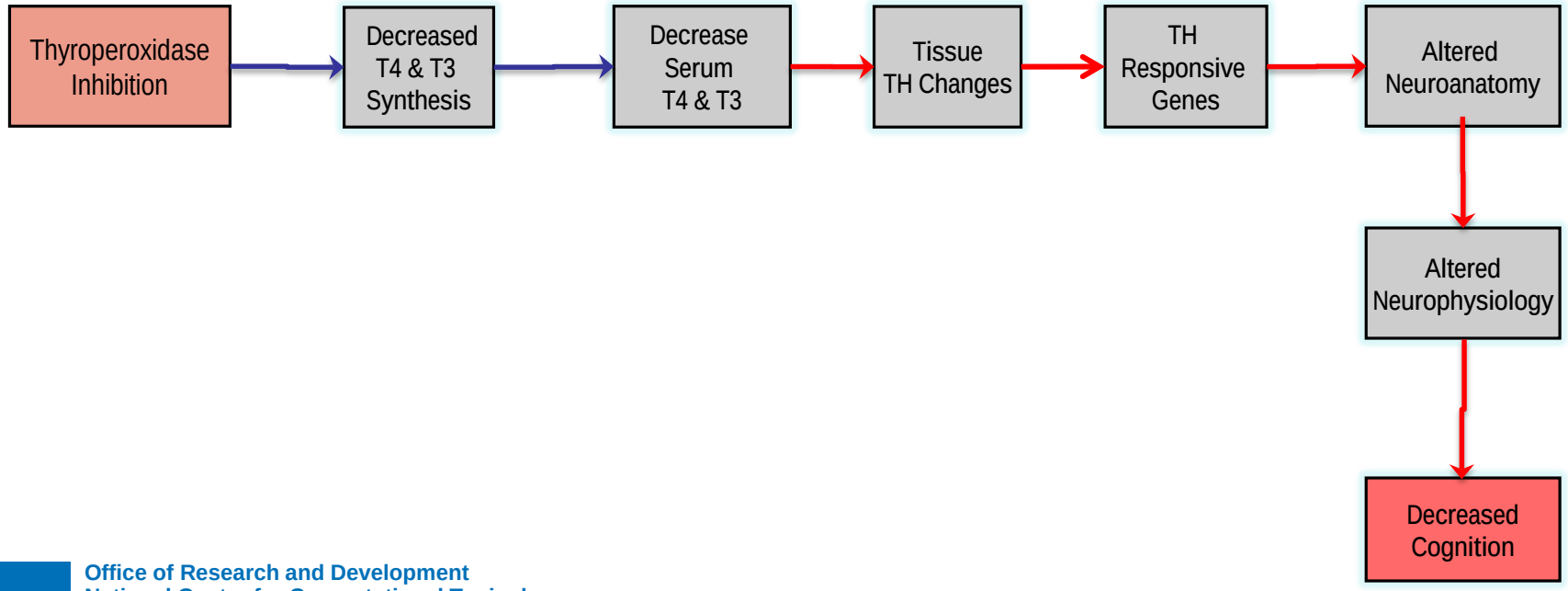
Model Simulations of Dev Vascular Disruption



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.



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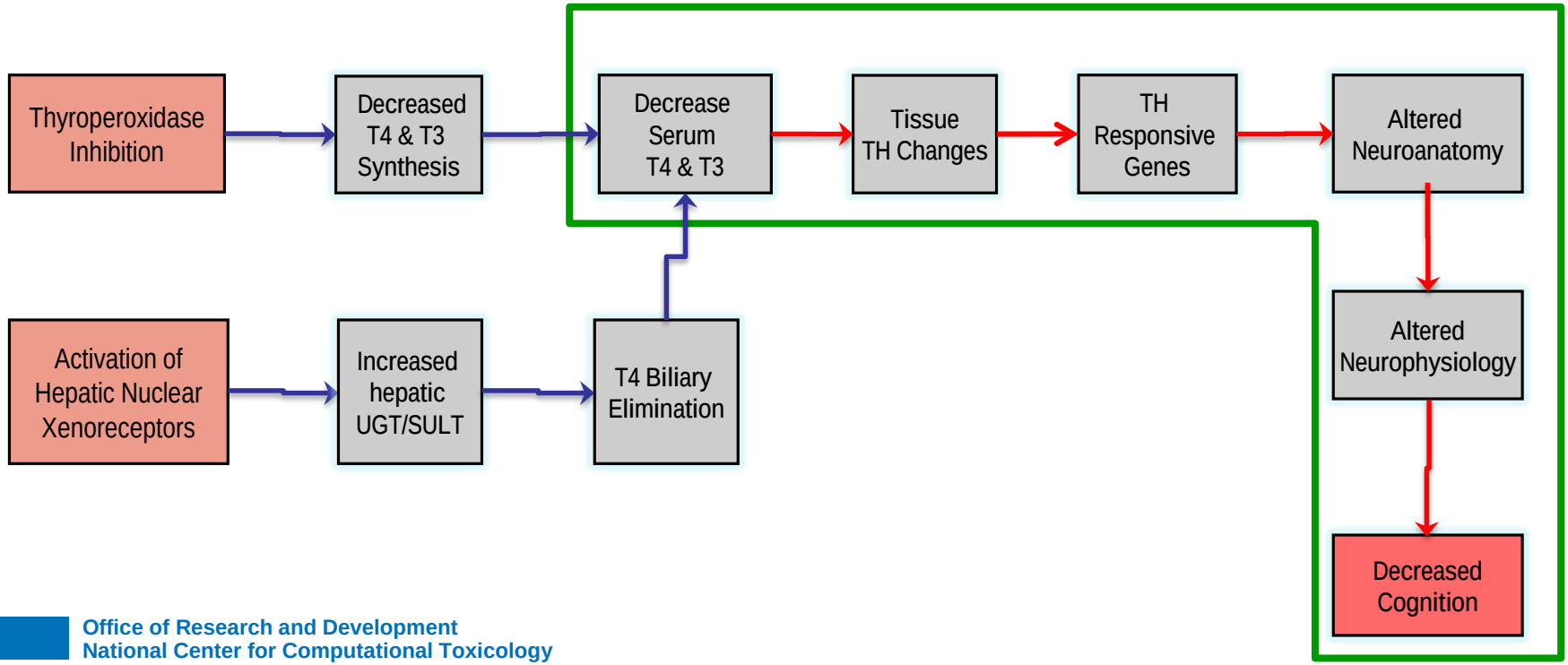
OECD Project 1.9: Upregulation of Thyroid Hormone Catabolism via Activation of Hepatic Nuclear Receptors, and Subsequent Adverse Neurodevelopmental Outcomes in Mammals.



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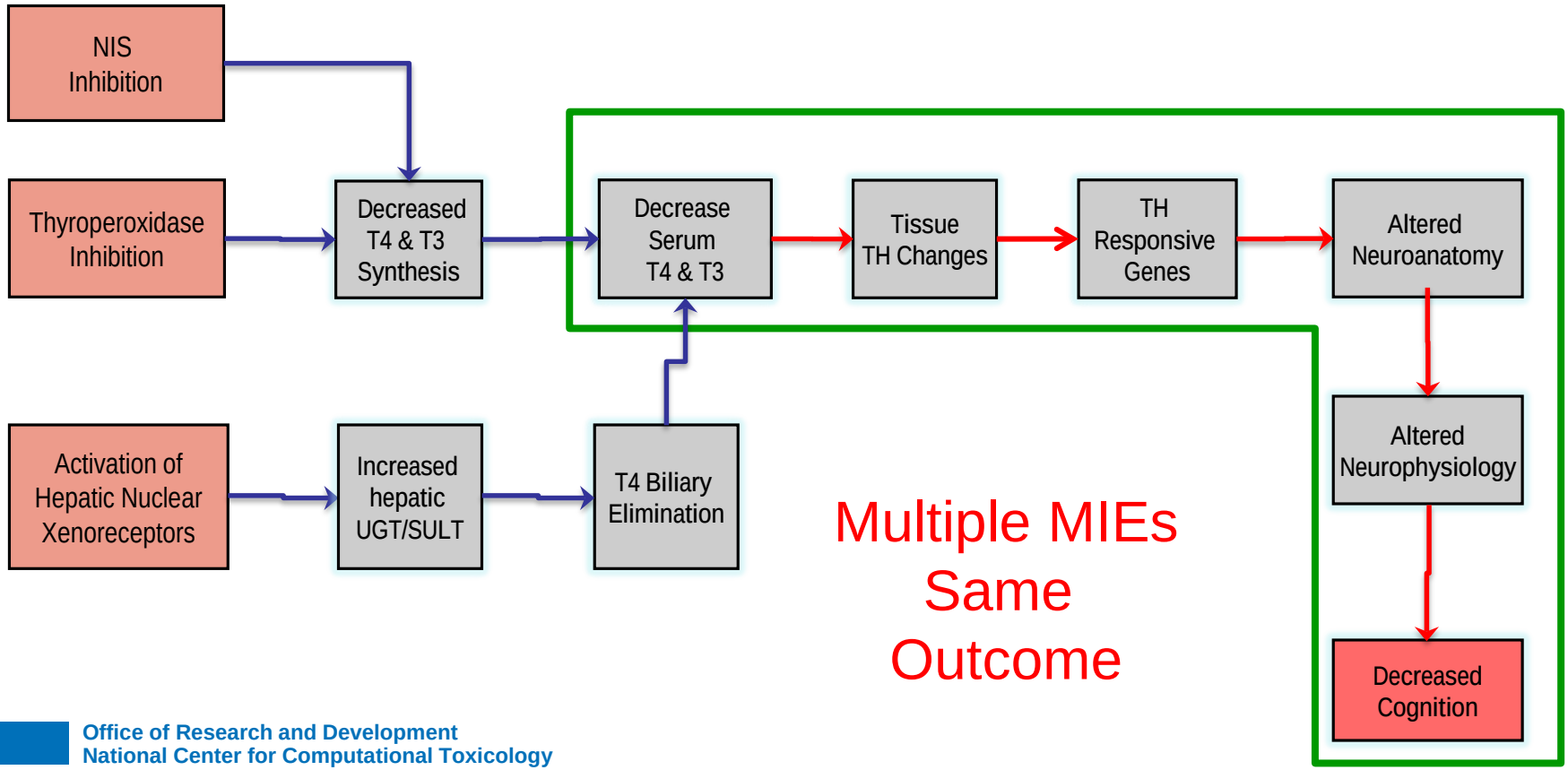
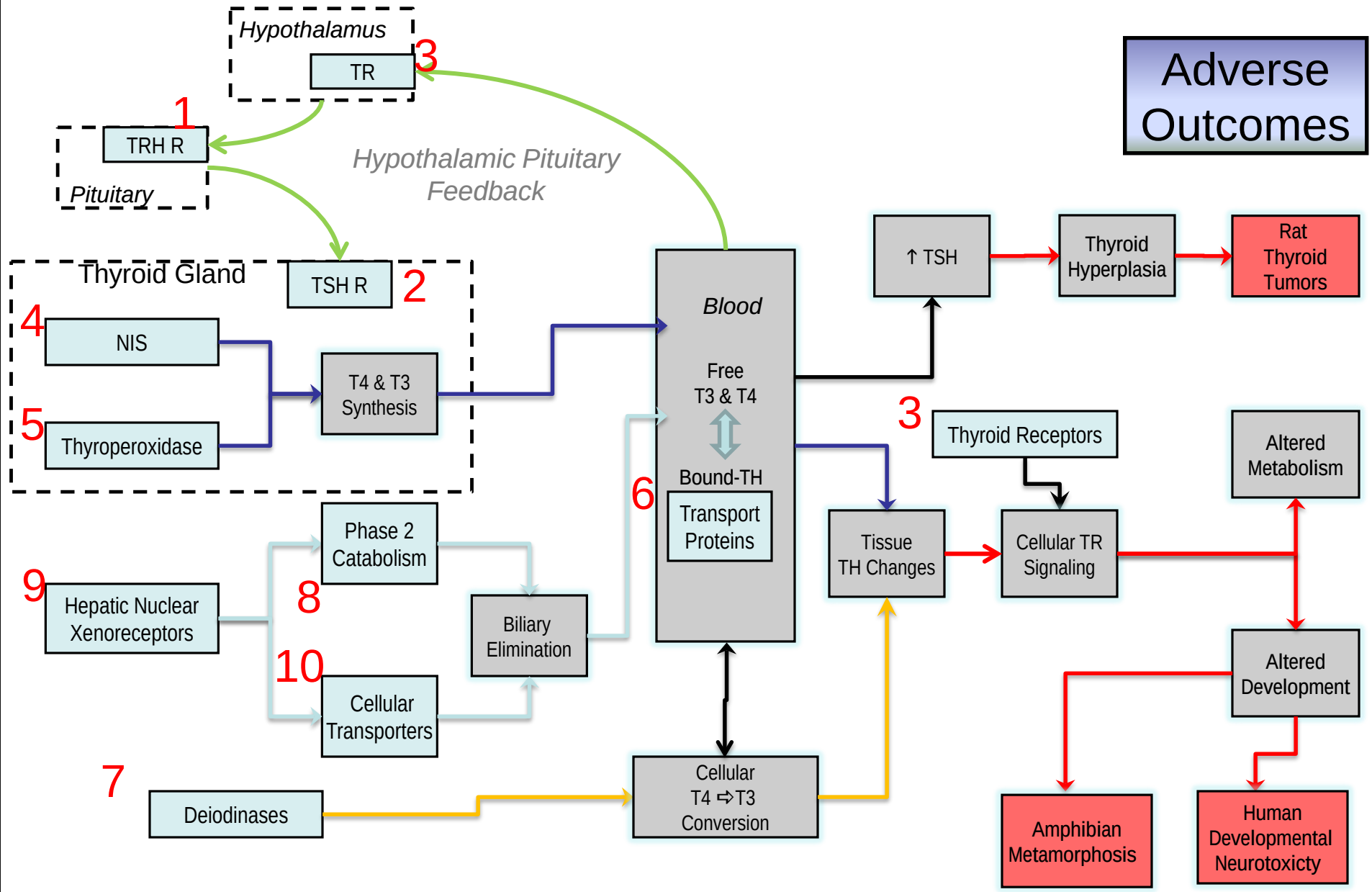
New OECD AOP Project: Inhibition of Na+/I- symporter (NIS) decreases TH synthesis leading to learning and memory deficit in children



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

Contacts: Edwards.Stephen@epa.gov
Clemens.Wittwehr@ec.europa.eu

Thanks for Listening