

# Comments on Draft Report on the Use of CompTox To Advance Risk Assessment

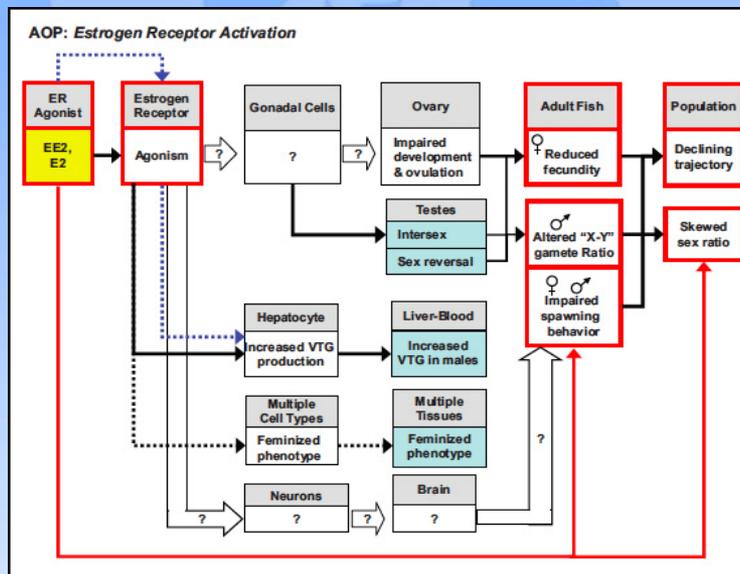


**Catherine Willett, PhD**

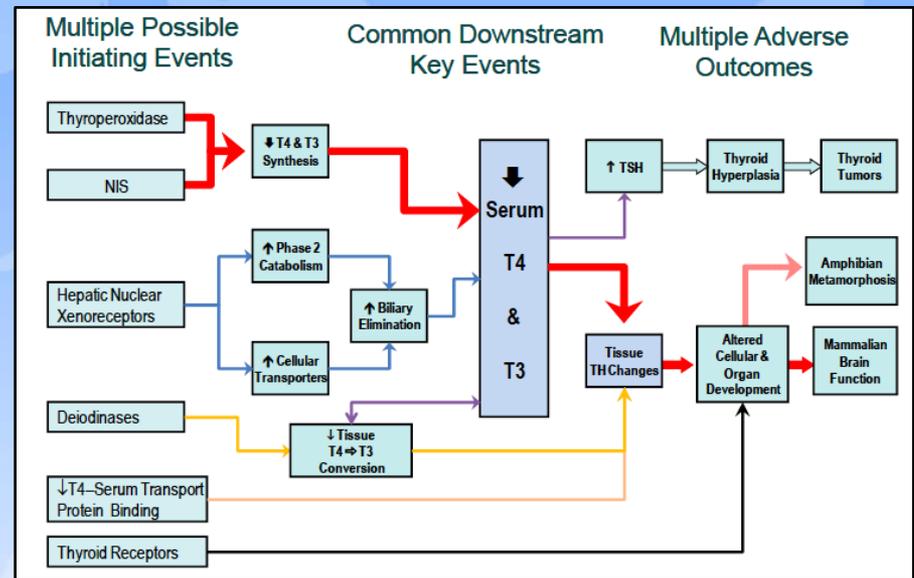
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# Study Question 1: Are the outputs of CompTox currently being used by EPA? How well do the outputs align with EPA's programmatic needs?

Page 10: it's true that AOP development is in its infancy; however...

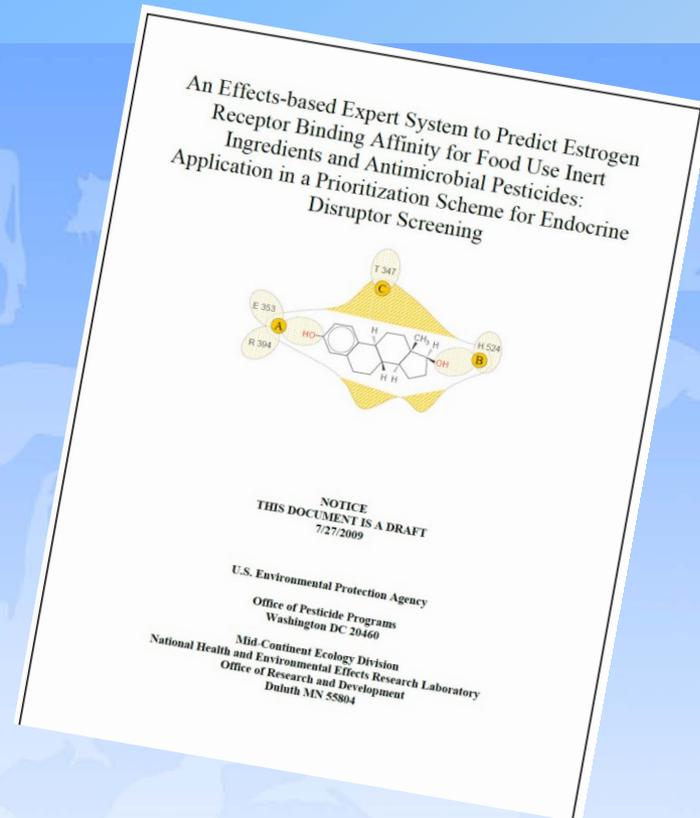
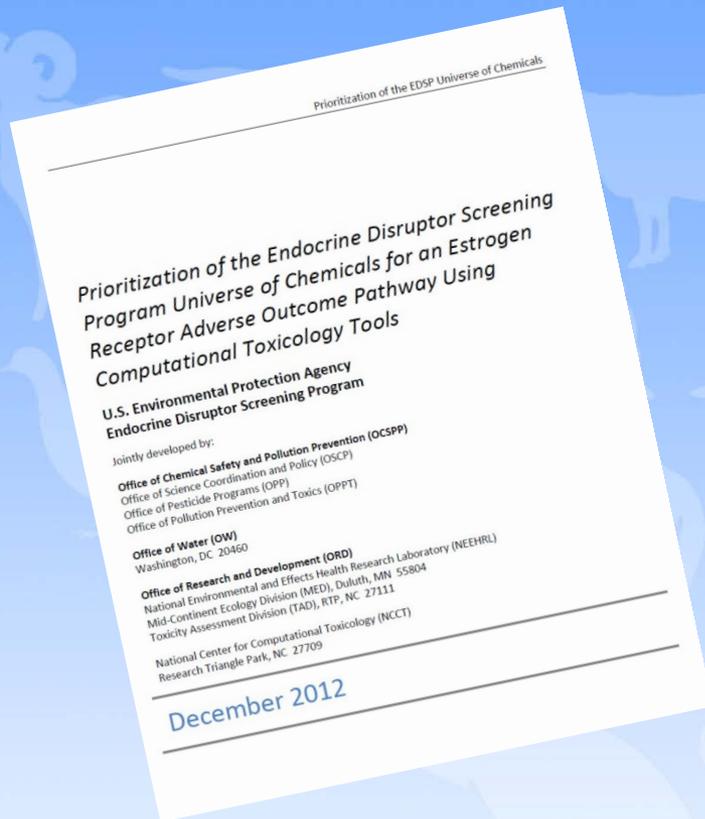


Ankley et al. 2010. Adverse Outcome Pathways: A Conceptual Framework to Support Ecotoxicology Research and Risk Assessment. Environ.Toxicol.Chem. 29 (3): 730-741.



Crofton, K. US EPA. 2012. The Role of Thyroid Hormones in Neurodevelopment: Using the Adverse Action Pathway Concept to Focused Research Strategies. Presented at DC area SOT, May 2012.

# Study Question 1: Are the outputs of CompTox currently being used by EPA? How well do the outputs align with EPA's programmatic needs?



FIFRA SAP Meeting: Prioritizing the Universe of Endocrine Disruptor Screening Program (EDSP) Chemicals Using Computational Toxicology Tools. January 29 – Feb 1, 2013. Docket ID EPA-HQ-OPP-2012-0818.

## *Study Question 2: What issues are there in using CompTox in decision making for risk assessment and risk characterization as opposed to chemical screening, prioritization and green chemistry?*

Page 6

The suitability of CompTox data depends on:

- Level of decisions yes, and
- Quality of the data
- Completeness of the adverse outcome pathway(s)
- How well the assays query those pathways

1. Characterization of assays in terms of specificity, sensitivity, reliability
2. Develop theoretical framework in form of pathways
3. Different uses of AOPs require different levels of completeness
  - a) relatively sparse → prioritization or initial screening
  - b) well established → hazard and risk assessment

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Data Use Guidance

Item 11: Rate of false positive and negative results if it is to be used for predictive purposes (e.g. to forecast *in vivo* activity)



Caution in instituting animal results as the gold standard

1. May not represent target species
  2. *In vitro* endpoints generally not equivalent to *in vivo*
    - a) *in vitro* endpoints measure AOP events, not adverse outcomes
    - b) e.g. estrogen receptor binding  $\neq$  uterotrophic weight
    - c) could be predictive depending on the completeness of AOP
    - d) linking AOP to human biology AOs is critical for predictivity (for human health)
- Defining positives and negatives requires broad weight-of-evidence

*Study Question 3. What are the barriers and limitations that prevent the EPA from using CompTox outputs and how might they be overcome?*

Page 14, lines 16 – 18

OECD is developing guidance for the development of AOPs

- would be good to support the implementation of such harmonized guidance here.
- it is also important to develop guidance for the use of AOPs – including the different levels of confidence and proof necessary for different uses

**PROPOSAL FOR A TEMPLATE, AND GUIDANCE ON DEVELOPING AND ASSESSING THE  
COMPLETENESS OF ADVERSE OUTCOME PATHWAYS**

**2012**

<http://www.oecd.org/chemicalsafety/testing/draftguidanceandreviewdocumentsmonographs.htm>

## *Study Question 4: How should the use of the CompTox program be effectively communicated to stakeholders? How can the communication be enhanced?*

### Page 17:

- Pesticide Program Dialogue Committee
  - <http://www.epa.gov/pesticides/science/testing-assessment.html>
  - several FACAs to cover various aspects of Tox21;
  - FACA meeting covering AOPs is planned for July.
- The ToxRefDB could be made significantly more user-friendly for non-experts.

### Page 18:

- Relating CompTox and the AOP approach to human health effects is a very important point: not only can biomonitoring inform AOPs, but AOPs can inform the identification of relevant biomarkers.
- EPA could also continue to engage with NGOs who are interested in implementation of CompTox and AOP approaches
  - The Human Toxicology Project Consortium
  - The Environmental Defense Fund

## Other Issues

Page 19, line 28 – Page 20 line 8:

- EPA Office of Pollution Prevention and Toxics has a long history of using incomplete information in risk assessment
  - extensive use of QSAR and read-across
- The potential use of CompTox information in furthering the accuracy and coverage of chemical class groupings should not be overlooked

*Add to list:*

- A plan for incorporation of human information in AOP development
  - collaborations with epidemiologists *and*
  - FDA and pharmaceutical companies (human data)

# Thank You

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