Regulatory Acceptance: How to strengthen protection of susceptible populations in AOP approaches

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Adverse Outcome Pathways - From Research to Regulation
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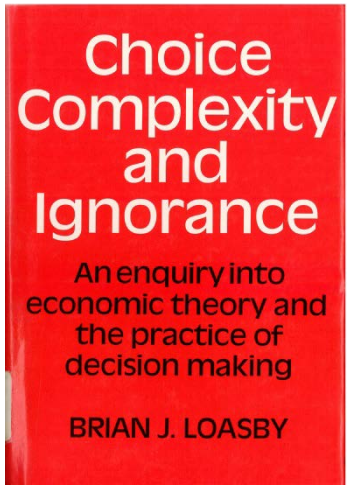
When is my AOP good enough?

"Perfect is the enemy of good"

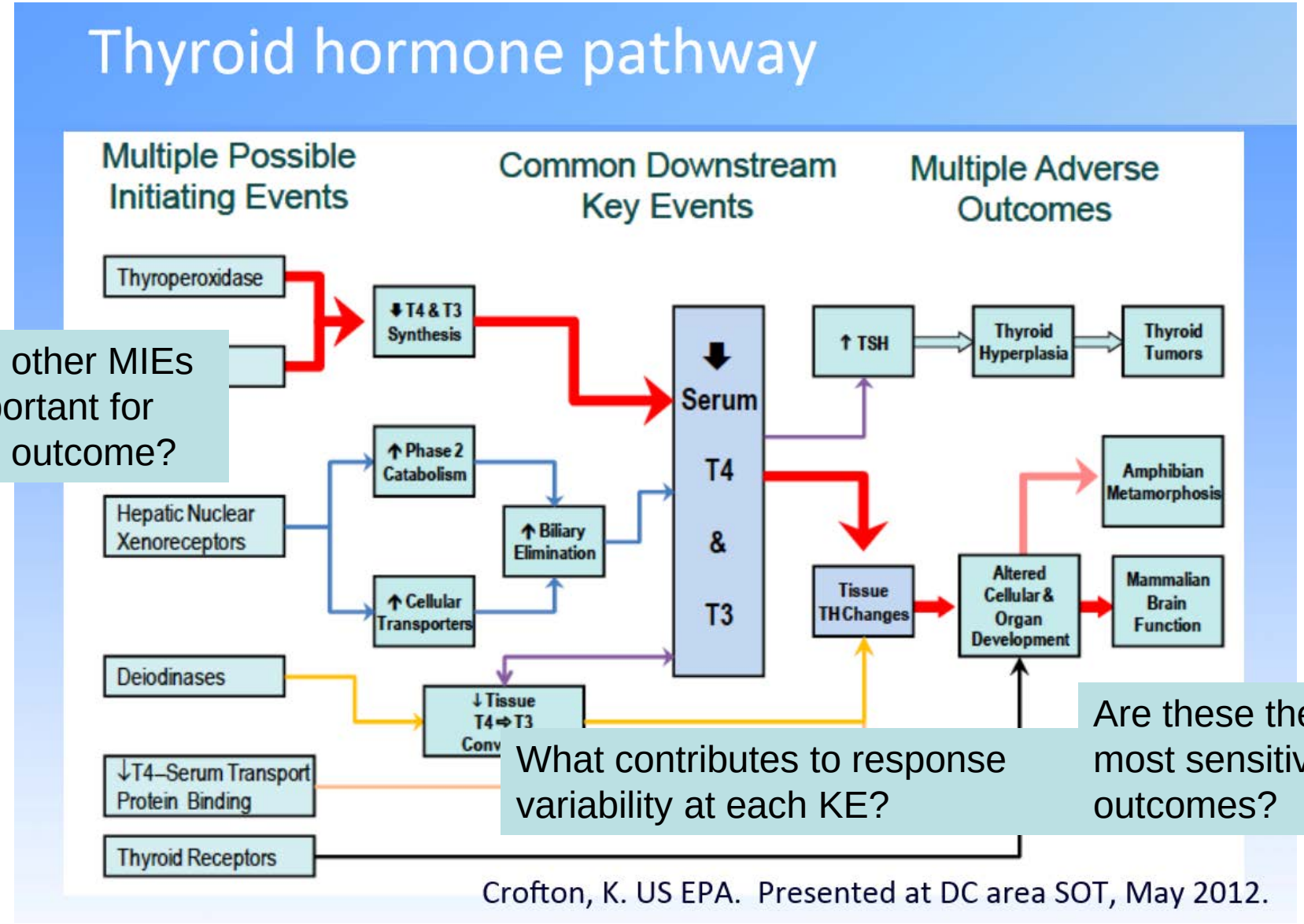
OR



"We shall find a variety of devices which allow ignorance to masquerade as knowledge so that choices may be made . . ."

Is the AOP fit for its purpose?

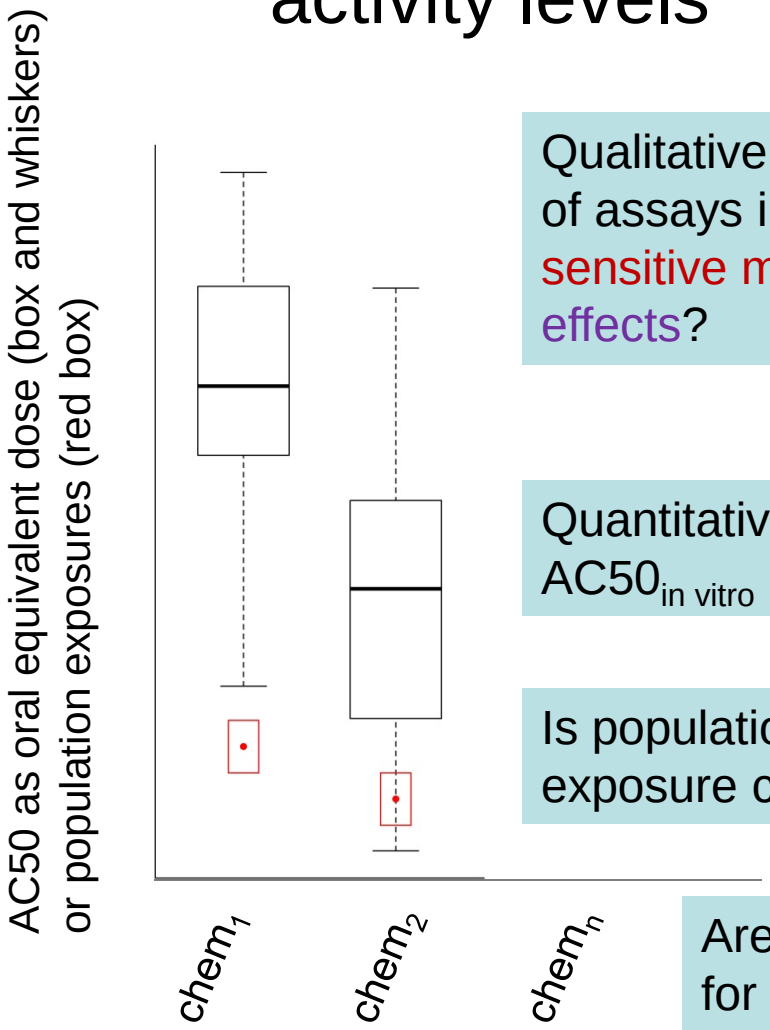
Grouping chemicals by common pathways



Risk-based prioritization

Comparing population exposures with in vitro activity levels

Is ADME variability captured?



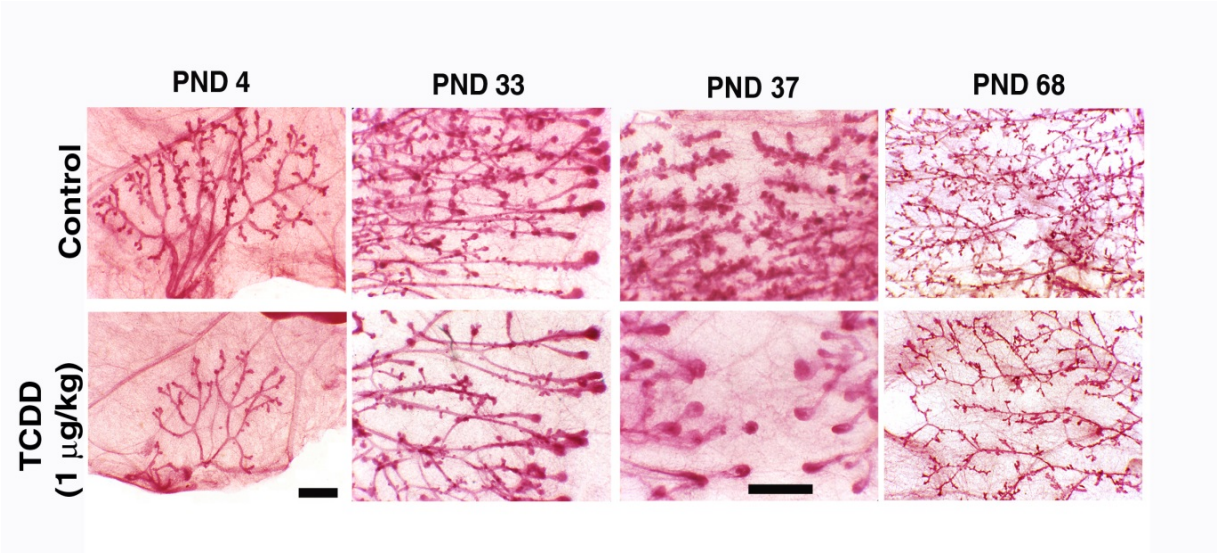
Qualitative validity: Does the suite of assays include MIEs/KEs in sensitive models for all critical effects?

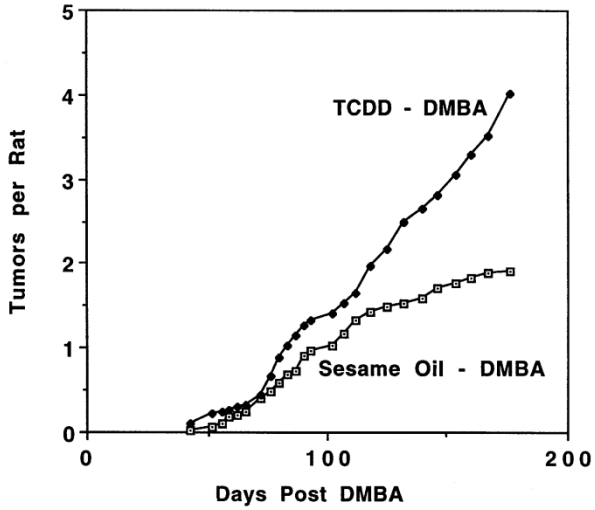
Quantitative validity: Does $AC50_{in\ vitro} = EC_{in\ vivo}$?

Is population variation in exposure captured?

Are equivalent data available for most chemicals?

Adverse vs adaptive?





- What is adaptive in one organism may be adverse in another because of genetic factors, co-exposures, etc.
- Effects on development are different adverse outcomes than effects on homeostatic processes

Quantifying variation in dose-response

- How much chemical does it take to get from KE_n to KE_{n+1}?
  - ADME variations e.g., due to genetic polymorphisms, co-exposures (alcohol, stress)
    - NTP – Benzene ADME variability in genetically diverse mice
  - Tissue responsiveness e.g., use intestinal cell model in normal and diseased (Crohn's) state
  - Rusyn group - human variation in response w/ primary human cell lines

Summary

- AOPs provide a framework for meaningful cumulative risk assessment
- In vitro models offer opportunities to quantify variation in dose response
- AOPs can foster discussion about adaptive vs. adverse response and suggest new endpoints
- Consider adding a section to AOPs that would describe (and quantify) anticipated sources of population variation and explain key limitations in the AOP
- Are the data “fit for purpose?”