

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

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Adverse Outcome Pathways - From Research to Regulation

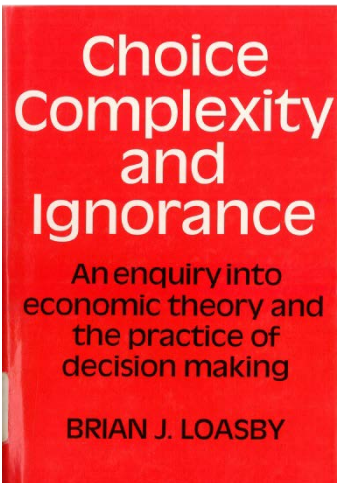
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When is my AOP good enough?

“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?

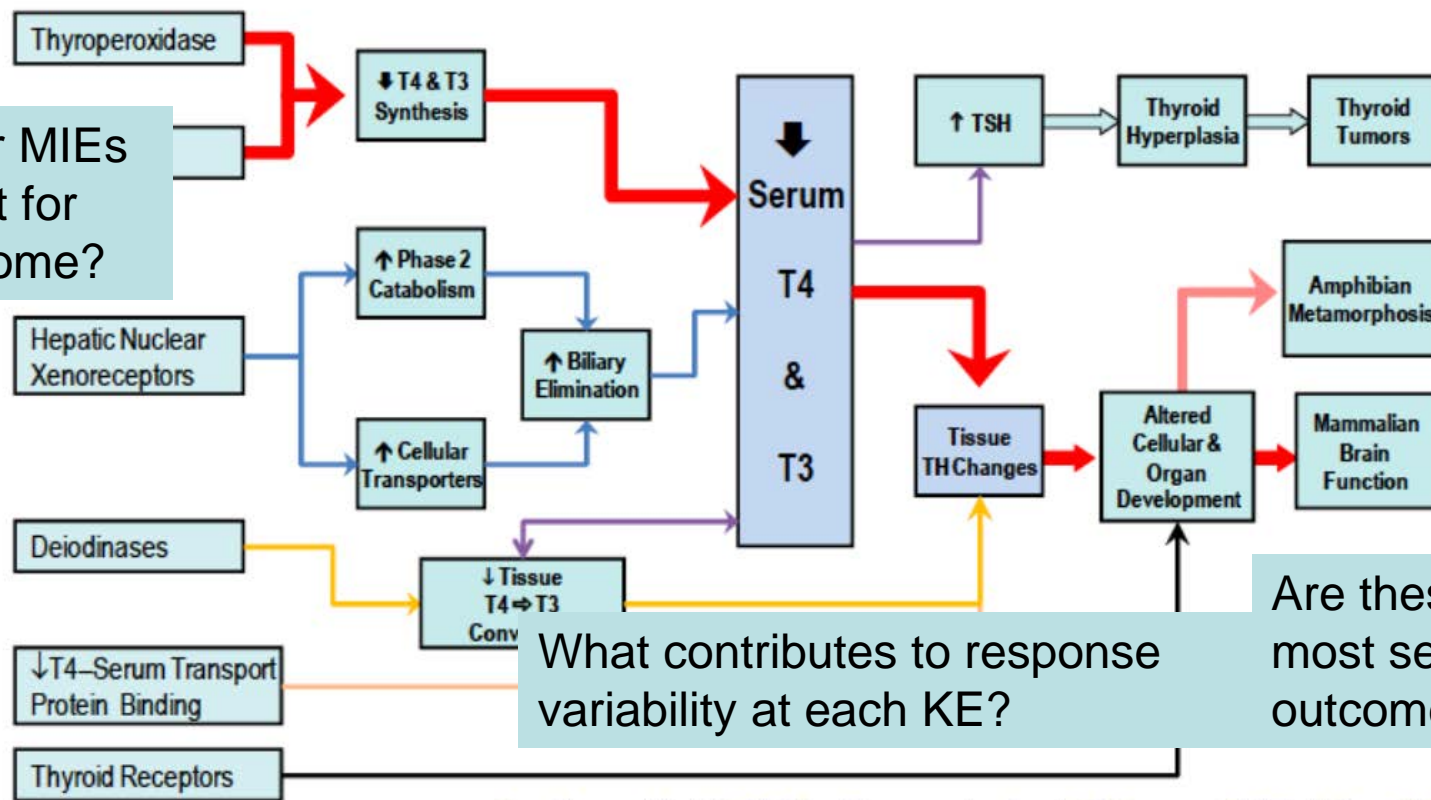
Grouping chemicals by common pathways

Thyroid hormone pathway

Multiple Possible Initiating Events

Common Downstream Key Events

Multiple Adverse Outcomes



Are other MIEs important for this outcome?

What contributes to response variability at each KE?

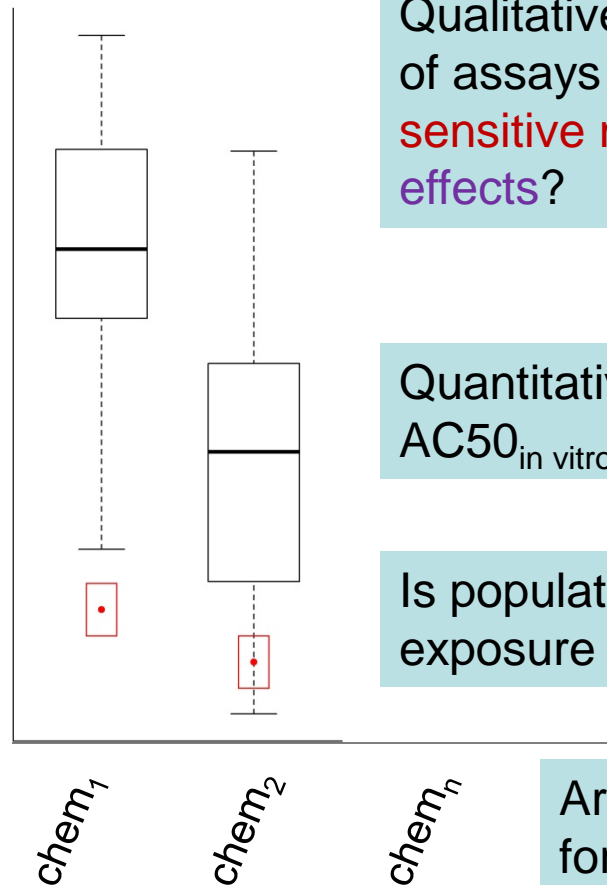
Are these the most sensitive outcomes?

Risk-based prioritization

Comparing population exposures with in vitro activity levels

AC50 as oral equivalent dose (box and whiskers)
or population exposures (red box)

Is ADME variability captured?



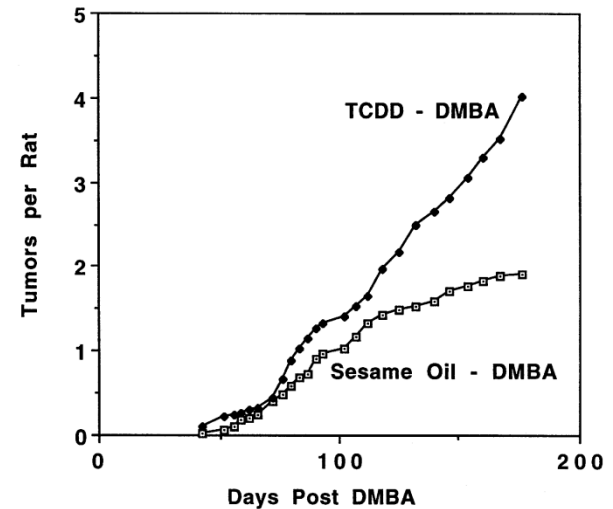
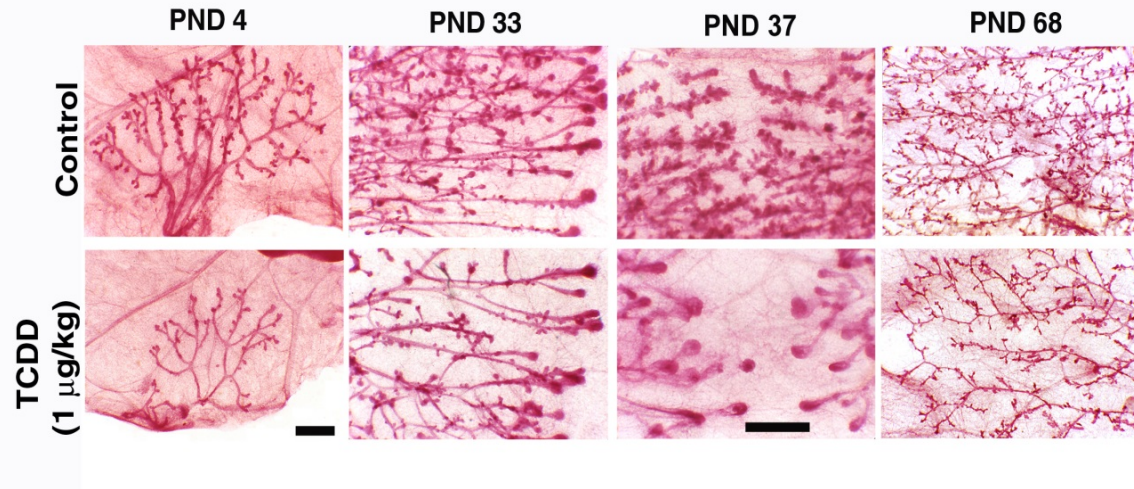
Qualitative validity: Does the suite of assays include MIEs/KEs in sensitive models for all critical effects?

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?”