NTP
National Toxicology Program

Approaches for considering mechanistic information in systematic reviews

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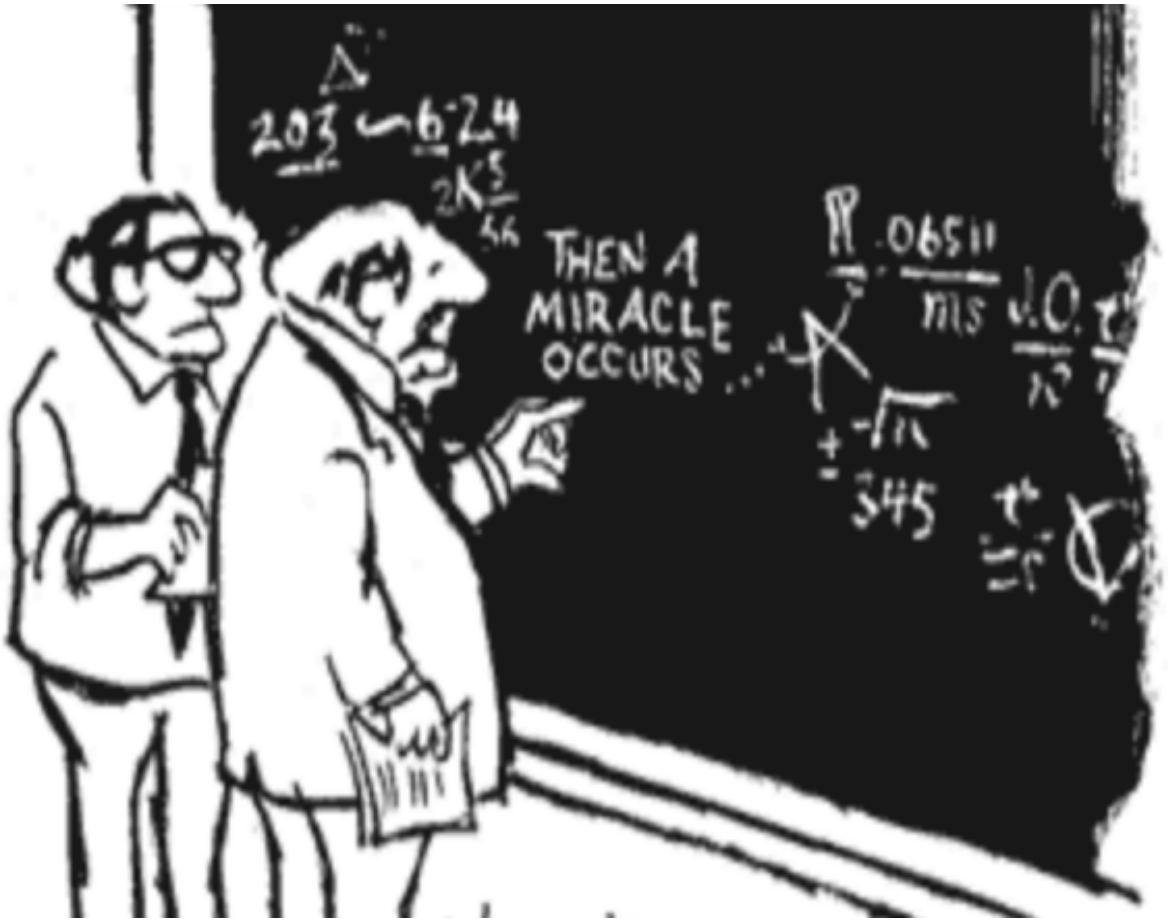
The problem



The mechanism miracle

In Search of Bradford Hill?

- History- connections to cancer
  - Mutagenicity
  - Cell proliferation
- Drivers- divergent intents
  - Replace cancer bioassay
  - “Explain” cancer bioassay findings
- Language- divergent intents?
  - Clarify
  - Obfuscate

Language

“two nations separated by a common language”

- Quiz- order by increasing complexity
  - Key events
  - AOPs
  - Key characteristics
  - Mode of action
  - Toxicity pathway
  - Mechanism
  - Molecular initiating events
  - S--t happens

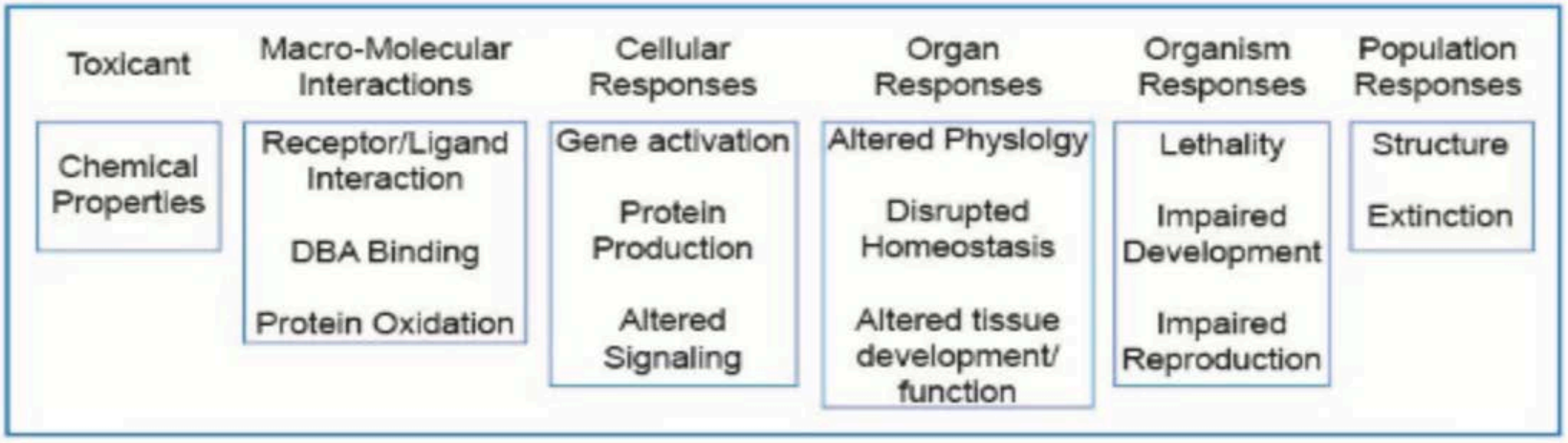
But seriously

“best of times, worst of times”…age of wisdom.. foolishness”

- Moving target
  - Rapidly increasing in complexity and heterogeneity
  - Weakening linkage to traditional apical endpoints
  - Increasing speculation more so than understanding
- Study quality?
  - How to measure?
  - Should one measure?
- Risk of Bias?
  - Can one realistically evaluate systematic error?

a case study

- **What is an Adverse Outcome Pathway (AOP)**
  - an analytical construct that describes a sequential chain of causally linked events at different levels of biological organisation that lead to an adverse health or ecotoxicological effect. AOPs are the central element of a toxicological knowledge framework being built to support chemical risk assessment based on mechanistic reasoning



Approaches for systematic review

finally

- Top down
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  - Heterogeneous study support
  - Acknowledge remaining “black boxes”

Approaches for systematic review

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- Top down
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- Bottom up
  - If you build it they will come

Top down

prevailing wisdom

- Advantages
  - Clear target to shoot at
  - Identified in protocol
  - Counterfactuals can be established in advance
- Disadvantages
  - Vary widely in scientific support
  - Many conceived to discredit human relevance of animal studies
  - Most likely partially or completely wrong
  - May deflect attention to multiple mechanisms

Bottom up

build it

- Advantages
  - Could conceivably discover unappreciated cohesion (MOA)
  - Could conceivably evaluate study quality (key events)
- Disadvantages
  - Lots and lots of work
  - Lack of directed studies of the credibility of the association
  - Skeptical peer reviewers
  - Dose response is a critical consideration
  - Strength of association would require knowledge of probabilities of each following step

Bottom up

build it

Conversely, if the probabilities were known, could lead to a quasi-quantitative estimate of confidence in the mechanistic data stream

Recommendations

good luck

- One size fits all doesn’t apply
- Clearly decide and publicize how mechanistic information will be considered in an evaluation
- Propose the approach in public “concept” and/or protocol comment stage
- Remain flexible during review to change approach with appropriate public notification
- Identify areas of uncertainty in final evaluation
- Reserve right to use mechanistic information in establishing PoDs for dose response modeling