

# Cooke's "Paper 2" – Probabilistic Inversion and Isotonic Regression:

## Tox / Epi View

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# Frambozadrine, Nectorine, and Persimonate

- Role of Tox / Epi in understanding Uncertainty of D-R?
  - Further data on these chemicals =  $\emptyset$
- So – either:
  - 1) Consider *hypothetical* Tox/Epi data, or
  - 2) Examine what a dataset *per se* does (and does not) contribute to Uncertainty in D-R

# e.g., suppose that Nectorine *hypothetically*:

- did not cause these tumors in mice (but caused lung tumors)
- gives rats (but not mice) marked target-tissue cytotoxicity at the higher bioassay doses
- is locally metabolized to a reactive compound by a CYP very active in these nasal tissues, but less so in other rat strains or in mice or in humans
- is not genotoxic in standard studies, but a reactive metabolite is formed
- produces oxidative stress, depletes GSH

What do such results say about:

- Shape of D-R for *this* dataset?
- Bearing of the D-R analysis (and its uncertainty characterization) on the overall uncertainty of low-dose potency of Nectorine?

# . . . about D-R for *this* dataset

- Non-linear PK? (is shape all PD?)
- Non-linear PD? (threshold? secondary to cytotoxicity?)
- Monotonic? (hormesis? U-shaped?)
- Extra-binomial variation?
- How different are endpoints? (do they inform one another? poolable? over-lumped?)
- How is time dimension collapsed? (survival effects? regressing lesions? stages?)

## These affect:

- Whether data are to be taken at face value
- Whether they represent a “pure” process or the net of several
- What models are plausible *beyond the issue of fitting these particular data*

# ANY specified model imposes additional constraints that arise external to the dataset

- Even “empirical” models
- Embody some kind of hypothesis about reasons for D-R and nature of data-generating process -- and even about reasons for lack of fit of particular datapoints
- Poor fit refutes, but adequate/good fit does not confirm
- Variance among outcomes is asserted by model (and fitting) to be partitioned among “explained” and “sampling error” -- and in so doing, constrains error-generating process
- Points borrow information from one another (via model structure) in a way that is absent from  $i$  unconnected samples
- So why shouldn't uncertainties around a model's prediction of response for a dose be different than the unmodelled empirical uncertainty deriving from the isolated observation alone?

# SO...

- Imposition of model adds constraints
- Characterization of D-R Uncertainty is contingent on the model choice
- Where does the “extra information” come from?
  - Fit? -- a bit, but chiefly in rejection
  - Plausibility of implied process based on external (to dataset) knowledge
    - General (smoothness, monotonicity)
    - Specific (shape, especially in low-dose extrapolation)
- Thus, qualitative, non-dataset factors (via data interpretation and model choice) affect Uncertainty

# Main Components of Uncertainty

- Is each potential endpoint a human-relevant hazard?
  - Choice of dataset to represent human risk
- 
- D-R model fit
    - Uncertainty in response measure
    - Uncertainty in dose measure
  - Low-dose extrapolation of high-dose effects
  - Toxicologic equivalency of exposures across species

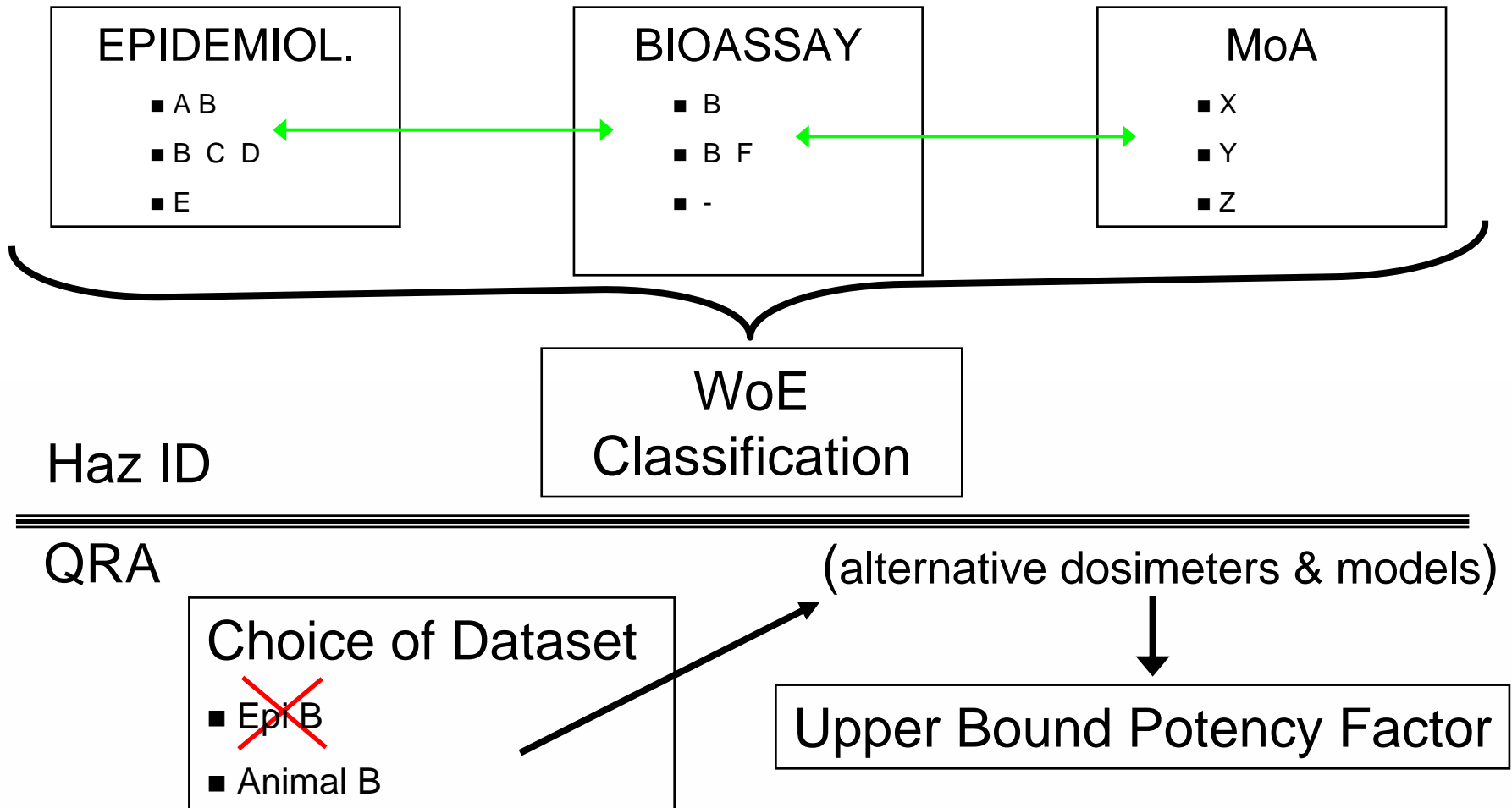
# Where QRA Uncertainty Gets Stuck

Significant Qualitative Uncertainties that do not fit easily into “statistical distribution” characterization (questions of bearing, relevance, extrapolability)

Qualitative questions complicate even straightforward uncertainty approaches (through questions about model misspecification)

And they are the most consequential elements of the overall uncertainty!

# Carcinogen WoE & QRA -- Current



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# Endpoint-by-Endpoint Evaluation of Data

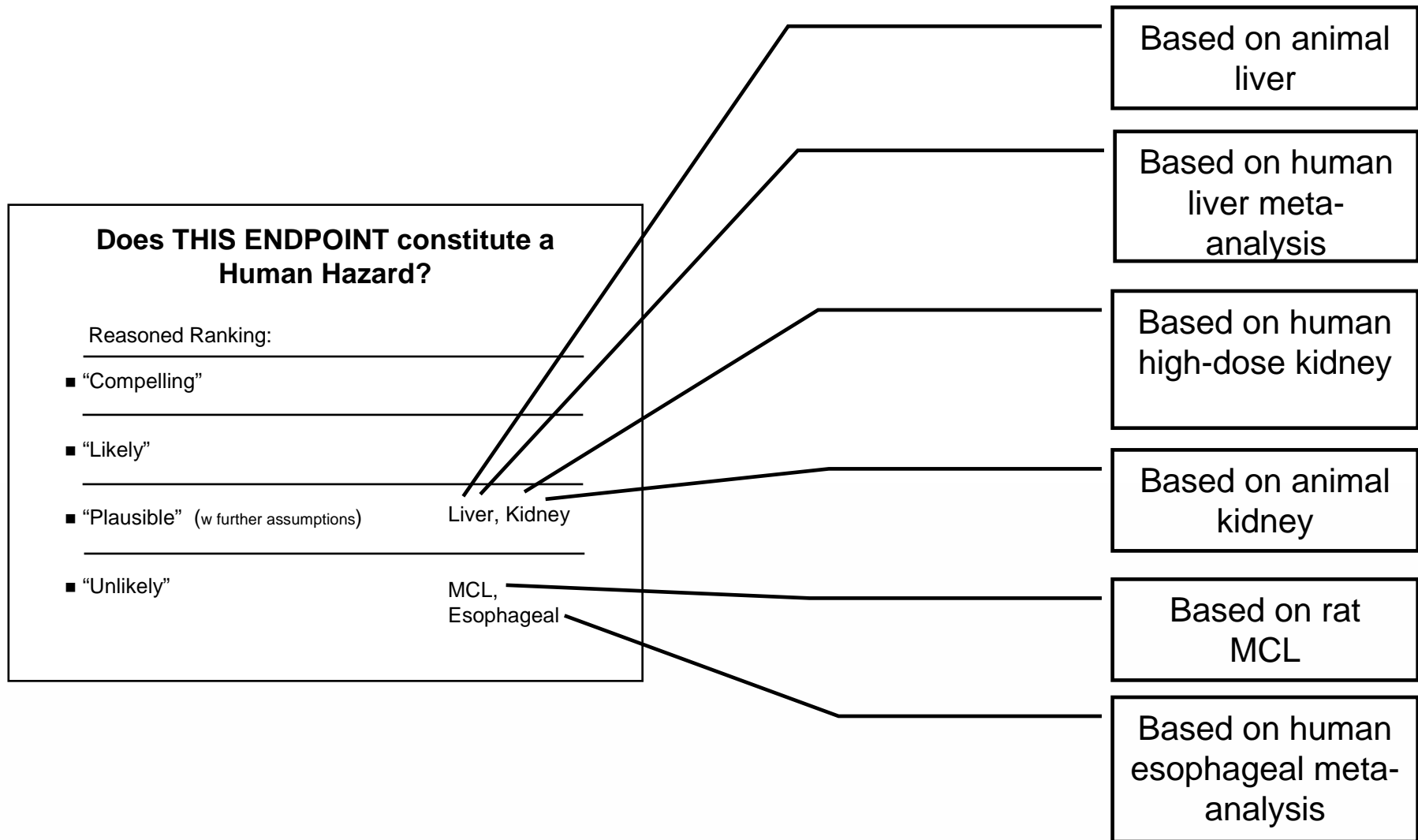
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BIOASSAY <ul style="list-style-type: none"> <li>■ B</li> <li>■ B F</li> <li>■ -</li> </ul>	
MoA <ul style="list-style-type: none"> <li>■ X -</li> <li>■ Y</li> <li>■ - Z</li> </ul>	

What is the *proposed basis* for inferring that a particular phenomenon seen in studies of a chemical's effects will also happen in environmentally exposed humans?

Test the GENERALIZATION (not the extrapolation) against all the pertinent results

**WoE for Endpoint "B"**

# QRA



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