“I’m afraid what we have here is a failure to communicate”

--Prison warden in the movie

“Cool Hand Luke”

Why is important for a Bayesian analysis to "Communicate" by incorporating mechanistic theories of causal processes?

- Past experience and theories of the causal mechanisms of harm are important components of our "prior" information.
- Only by incorporating causal mechanism theories can a quantitative analysis shed even meager light on which mechanisms are made more vs less likely by the available data.
- Projections outside the range of observations critically depend on mechanistic theories and their quantitative implications.

Problems With The Prior for the Existing Analysis--”All Non-Decreasing Functions”

- Says too little in not incorporating any weights related to mechanistic possibilities
- Says too much--some respectable mechanistic theories do produce non-monotonic dose response:
  - Induction of repair processes can do more good than harm by inducing chemical over some dose range
  - Opposing effects are sometimes produced by binding to related receptors with different affinities

First Data Set (unrealistic in providing no information about endpoint or chemical)

- Approach to flat level well before 100% suggests Michaelis-Menten form for saturation of activating metabolism or receptor binding:

$$V = \frac{\text{Vmax Dose}}{\text{Km} + \text{Dose}}$$

- Generalization to allow a low dose upward-turning curve is achieved by morphing to a Hill function:

$$V = \frac{\text{Vmax Dose}^{N}}{\text{Km} + \text{Dose}^{N}}$$

Second Data Set

- Shows little or no response over a modest background until relatively high dose levels are reached.
- Have a little more information about the response, which is designated as “Hyperkeratosis”—usually a thickening of the skin, most famously associated with exposure to inorganic arsenic at very high levels.
- Mechanistic inference: most likely homeostatic system overwhelming with a lognormal distribution of individual thresholds for response--log probit mathematical form
- Generalization: mixed distribution of thresholds with two or more lognormals corresponding to various subgroups.
- “Straw Man” human risk modeling approach: use animal data only to estimate unc. dist for animal ED50; derive unc distribution for human ED50, and lognormal distributions of interindividual variability for PK and PD parameters from experience with other chemicals and related endpoints.

Third and Fourth Data Sets

- In both cases it is clear that we are dealing with tumor responses, but with apparent saturation at high doses.
- Most likely general form is therefore one-or multi-stage with a Michaelis-Menten transformation of dose.