Tox/EPI View---NPB

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- The major uncertainty in risk assessment is the shape of the dose-response curve at low doses, not at doses where bioassays are conducted: both biological and Statistical uncertainties.

- The challenge is how the usually incomplete biological information can be incorporated into a D-R model, and how the uncertainty is characterized.

An example of biological uncertainty---A possible reason for a U-shape curve. Scenario:

Background tumor: 5%

Assume that exposure to an agent inhibits 40% of I-cells.

This implies that background contribute only 60% of its tumor incidence when exposed: Thus, at low doses, the observed tumor incidence is 5%*0.6+P(d) which can be < 5% of background incidence when d is small enough; thus a U-shape D-R is observed such as in TCDD(?). *P(d)>0 for all dose d, with no threshold. Background is important in this case.*

- It may not always be easy to interpret a risk number using frequentist interpretation. What do you mean a lifetime risk of 1x10E-7?

- Is it a sample frequency, or degree of belief?

- A risk estimate of p=1x10E-7 derived from a model with low-dose linearity may not have a frequentist interpretation because of the assumption that low-dose linearity is the most conservative model; a subjective judgment.

Is the following observations correct?

- It would be more useful if the precision parameter, α, is dose-dependent; e.g., $\alpha 1$, $\alpha 2$ respectively for low and high doses.

- Otherwise, it seems “model averaging” has more practical utility; e.g., by considering a class of D-R functions with low-dose linearity.

Research needs:

- Uncertainty in low doses: how incomplete biological information can be incorporated in risk estimate, and uncertainty of risk estimate characterized.
- Comparison of NPB with other methods such as isotonic regression method (Cooke), Bayesian procedure (Leonid et al, 2007), model averaging (Ryan and Whitney) etc.
- Beyond 2-stage BBDR model.