Default Low-Dose Linearity for All Endpoints?

Implications for Risk Assessment and Risk Management

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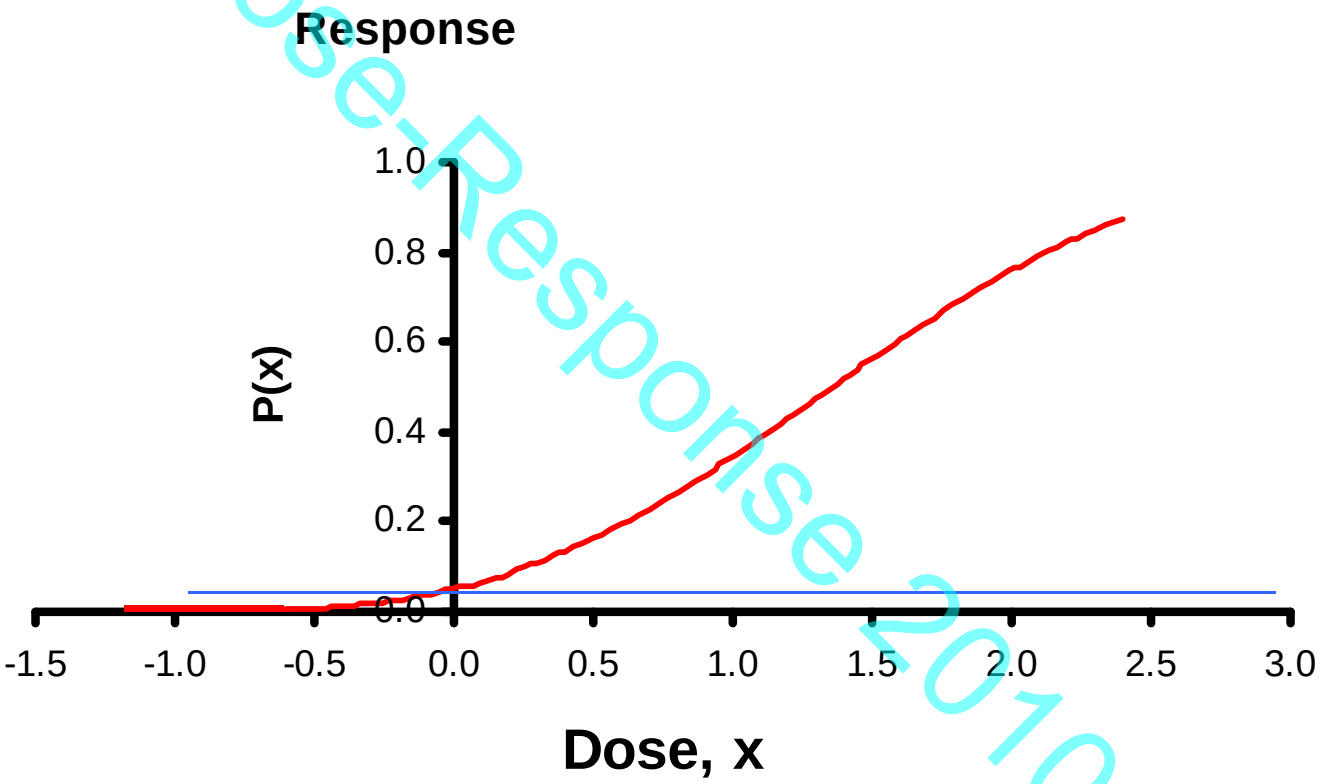
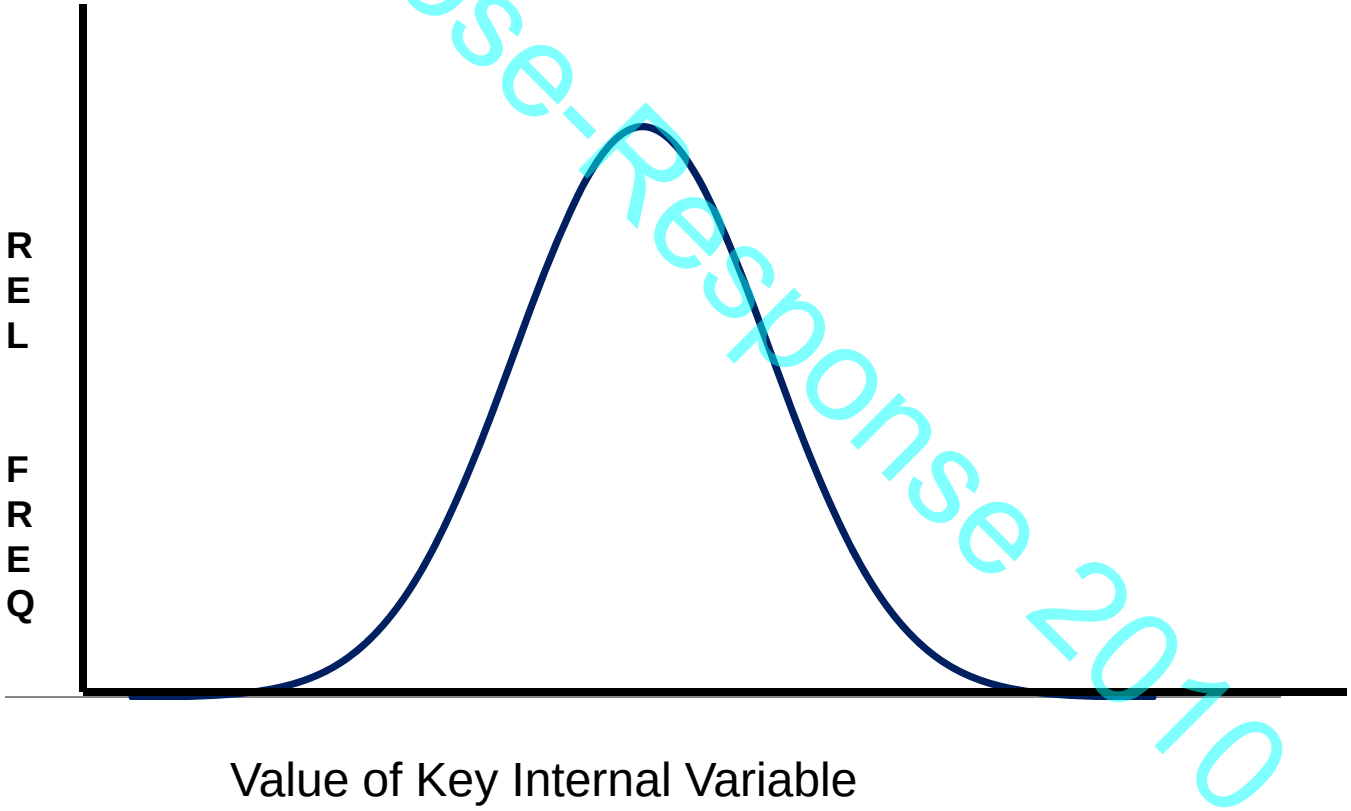
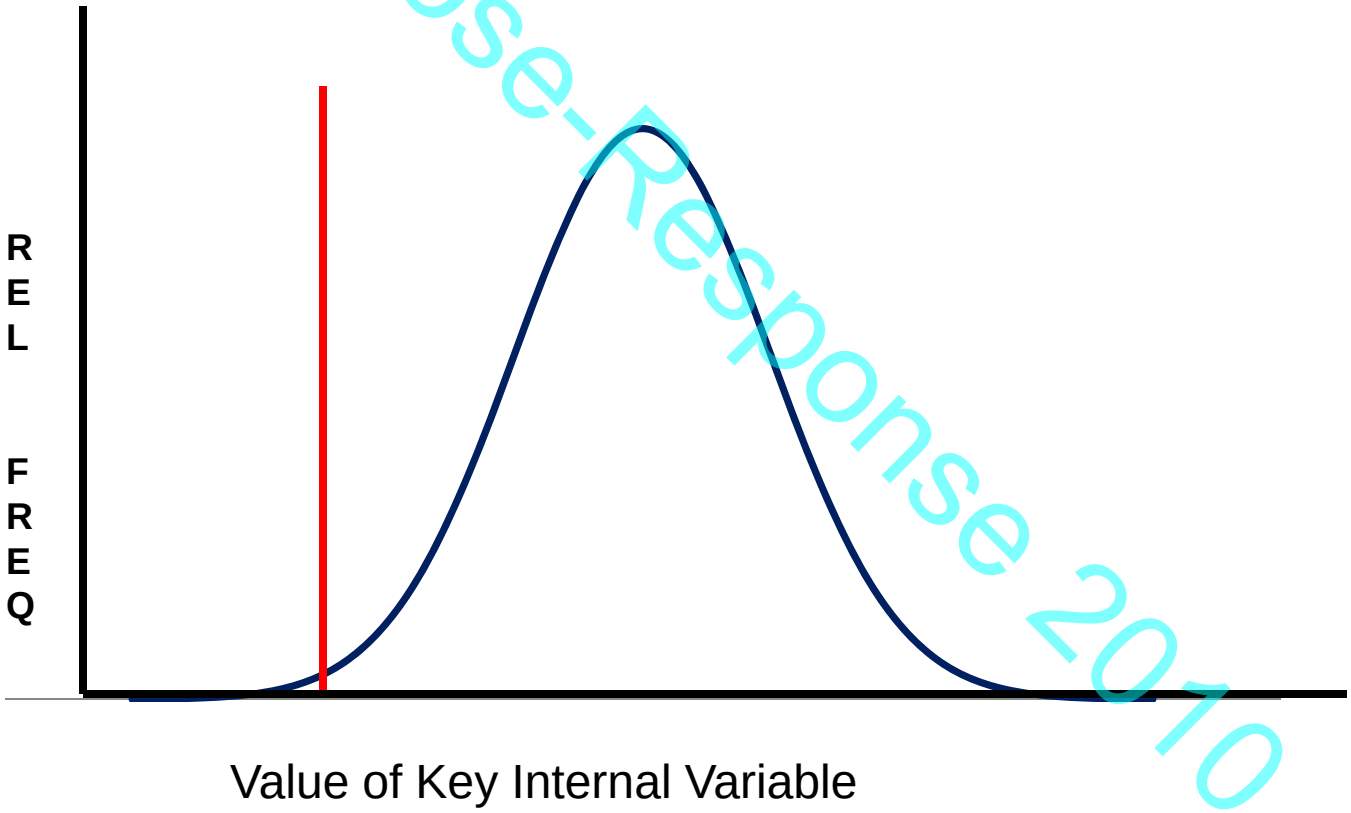
Additivity to Background



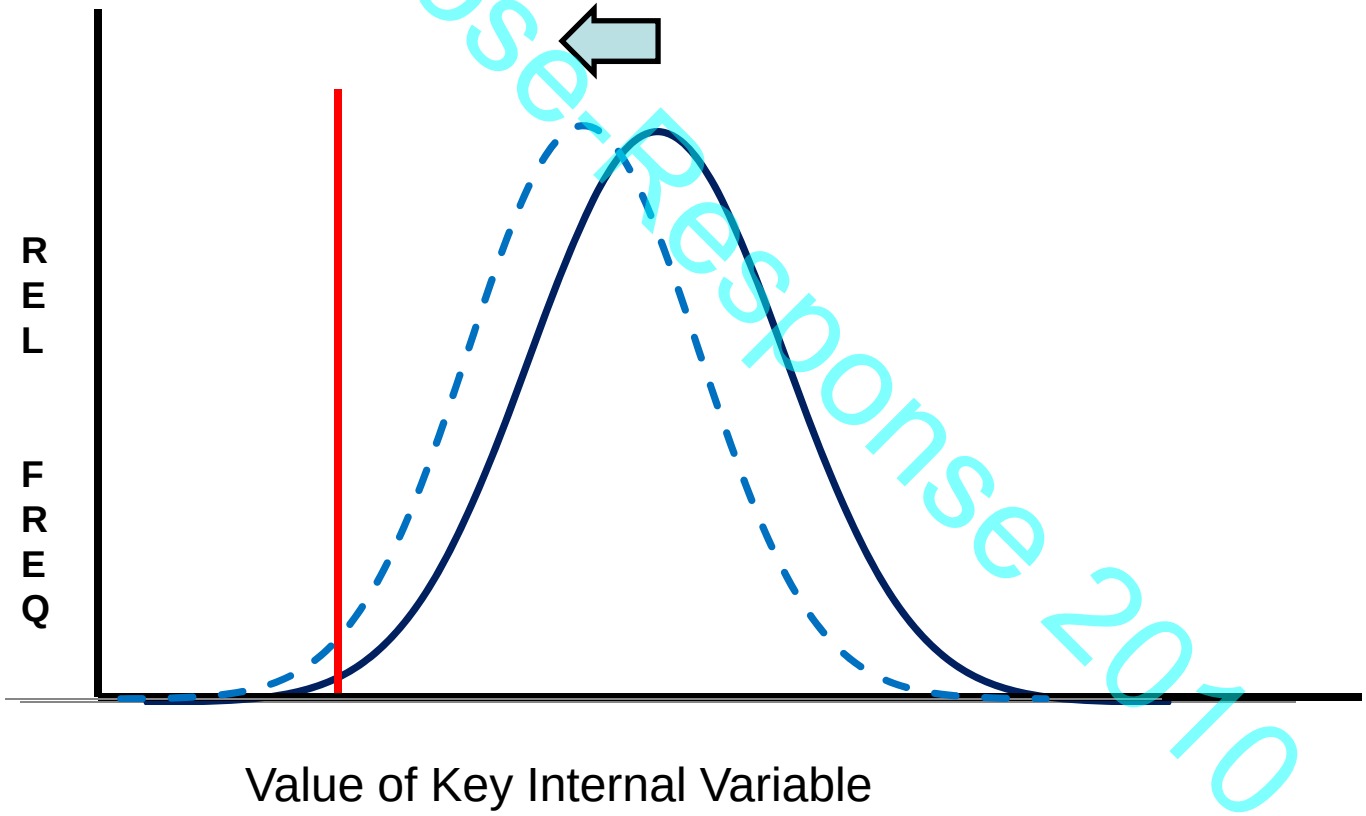
Population Distribution of Internal State



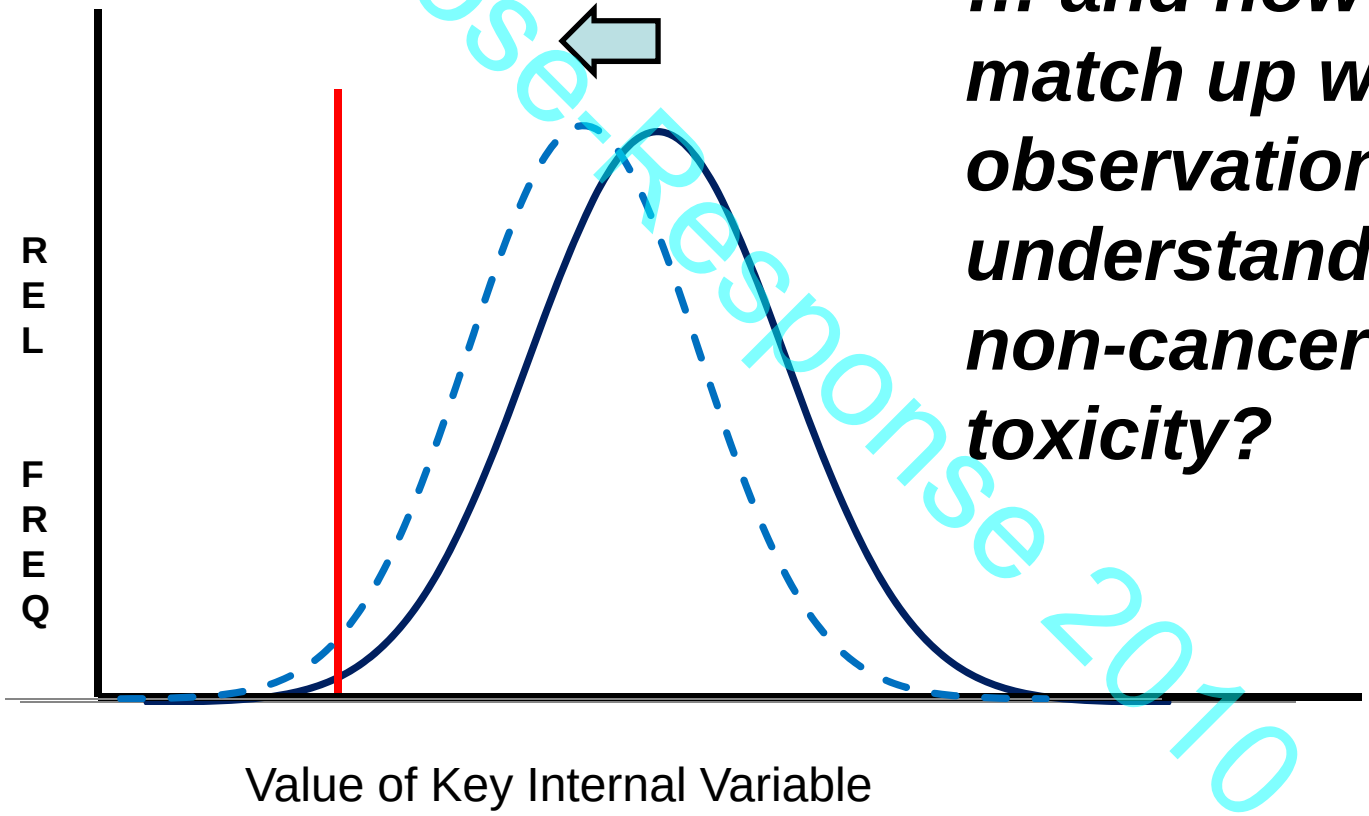
Some % Beyond Threshold – Leading to a Background Rate of Disease



Even a Small Shift in Distribution of Internal State Leads to Greater % Beyond Threshold

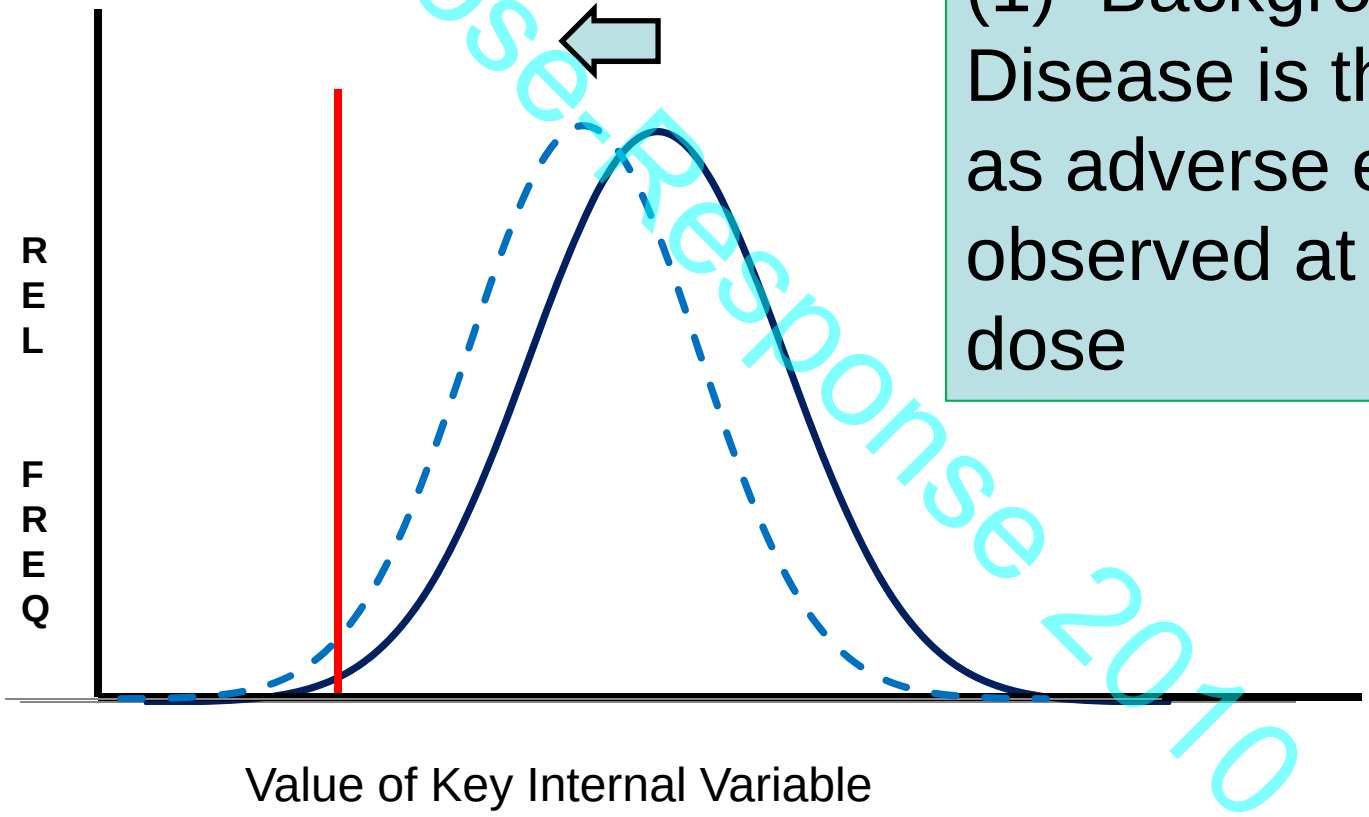


What *Biological* Assumptions Does Such Additivity-to-BG Implicitly Make?



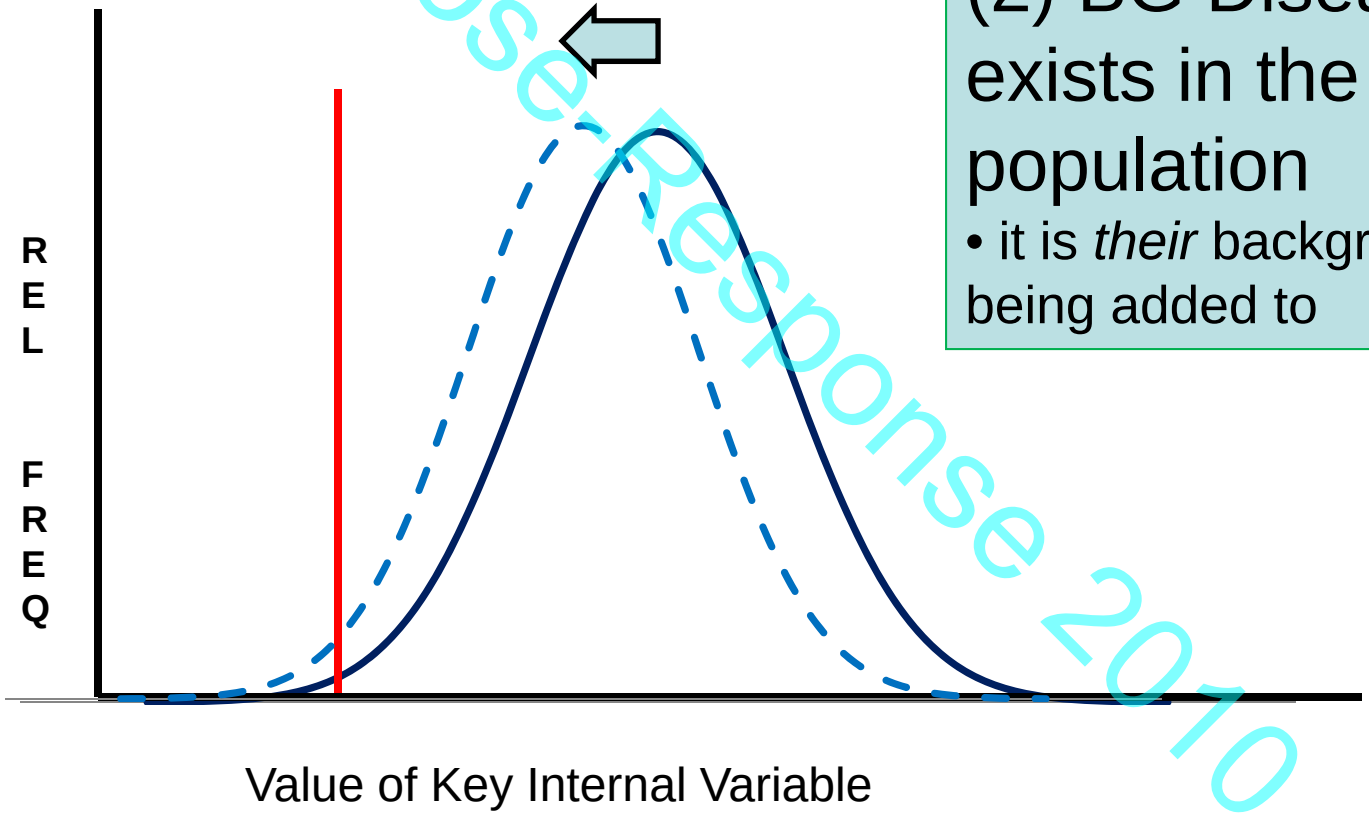
… and how do they match up with our observations and understanding of non-cancer toxicity?

What *Biological* Assumptions Does Such Additivity-to-BG Implicitly Make?



(1) Background Disease is the *same* as adverse effects observed at high dose

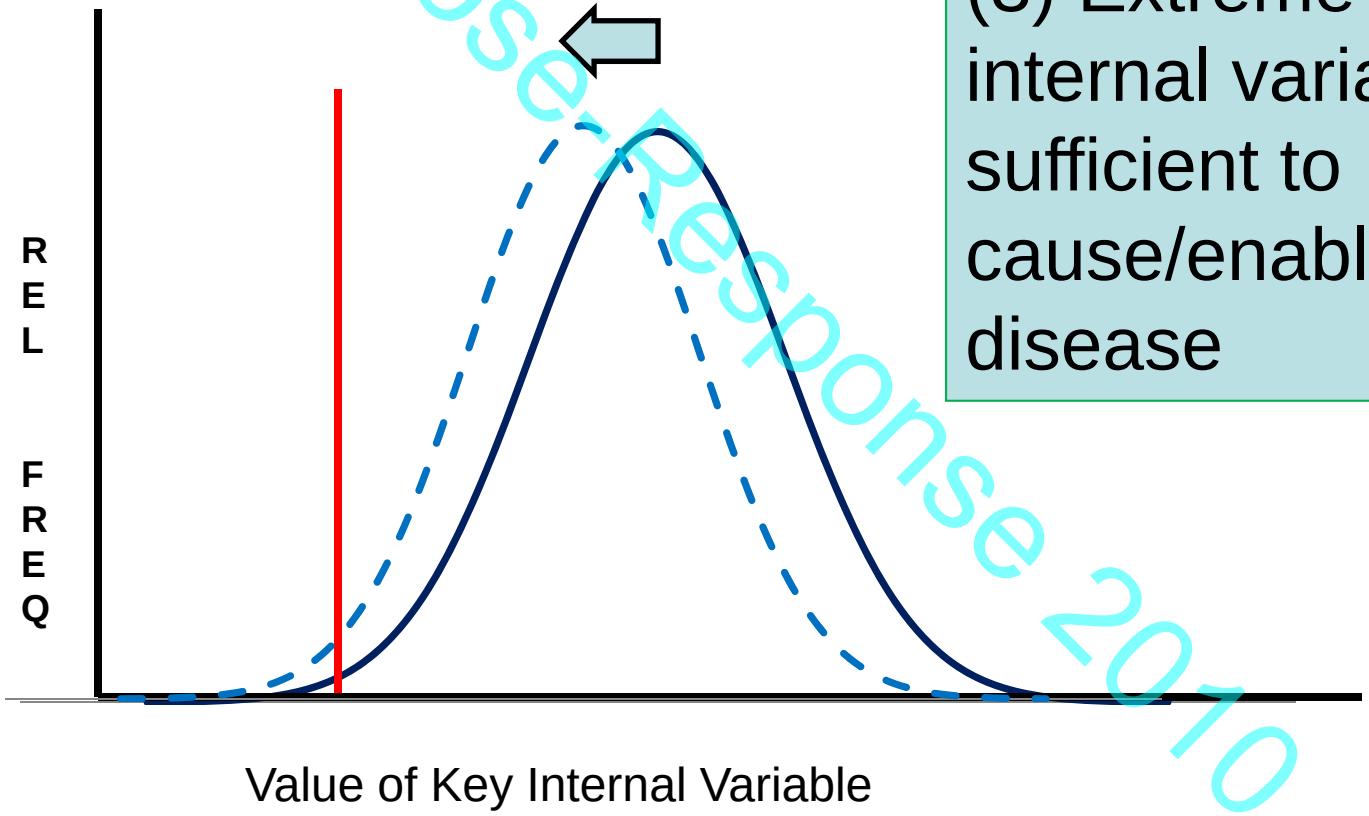
What *Biological* Assumptions Does Such Additivity-to-BG Implicitly Make?



(2) BG Disease exists in the *target* population

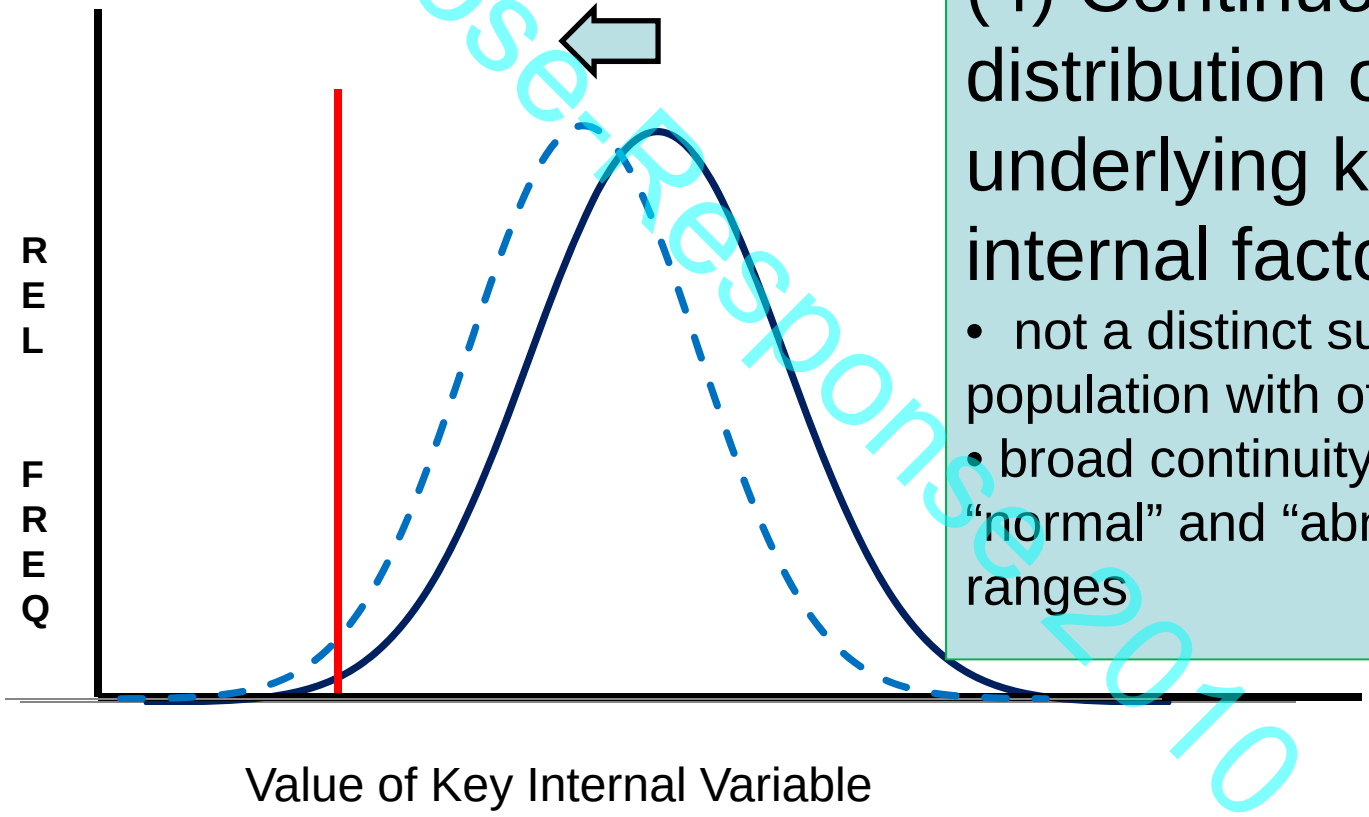
- it is *their* background that is being added to

What *Biological* Assumptions Does Such Additivity-to-BG Implicitly Make?



(3) Extreme value of internal variable is sufficient to cause/enable BG disease

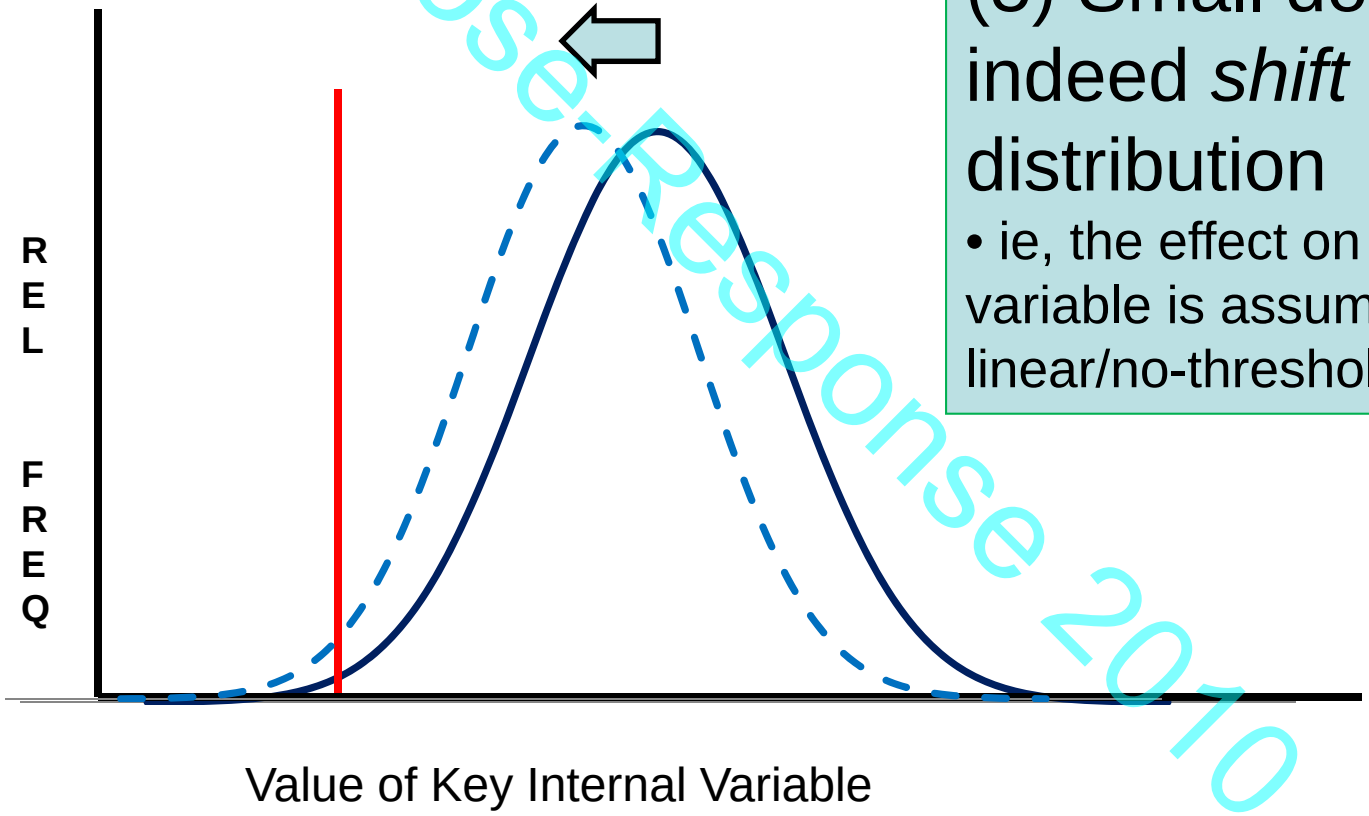
What *Biological* Assumptions Does Such Additivity-to-BG Implicitly Make?



(4) Continuous distribution of underlying key internal factor

- not a distinct sub-population with other causes
- broad continuity between "normal" and "abnormal" ranges

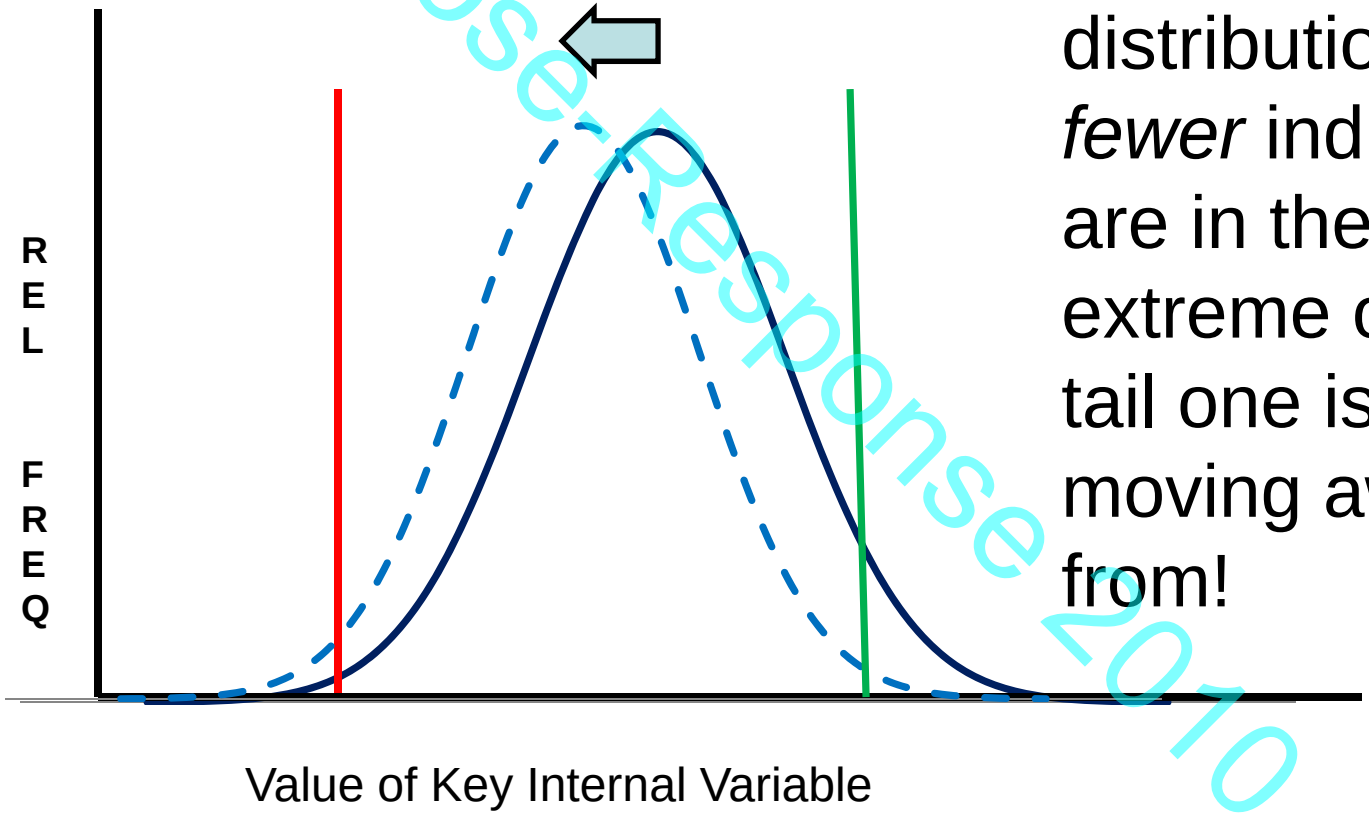
What *Biological* Assumptions Does Such Additivity-to-BG Implicitly Make?



(5) Small doses do indeed *shift* the distribution

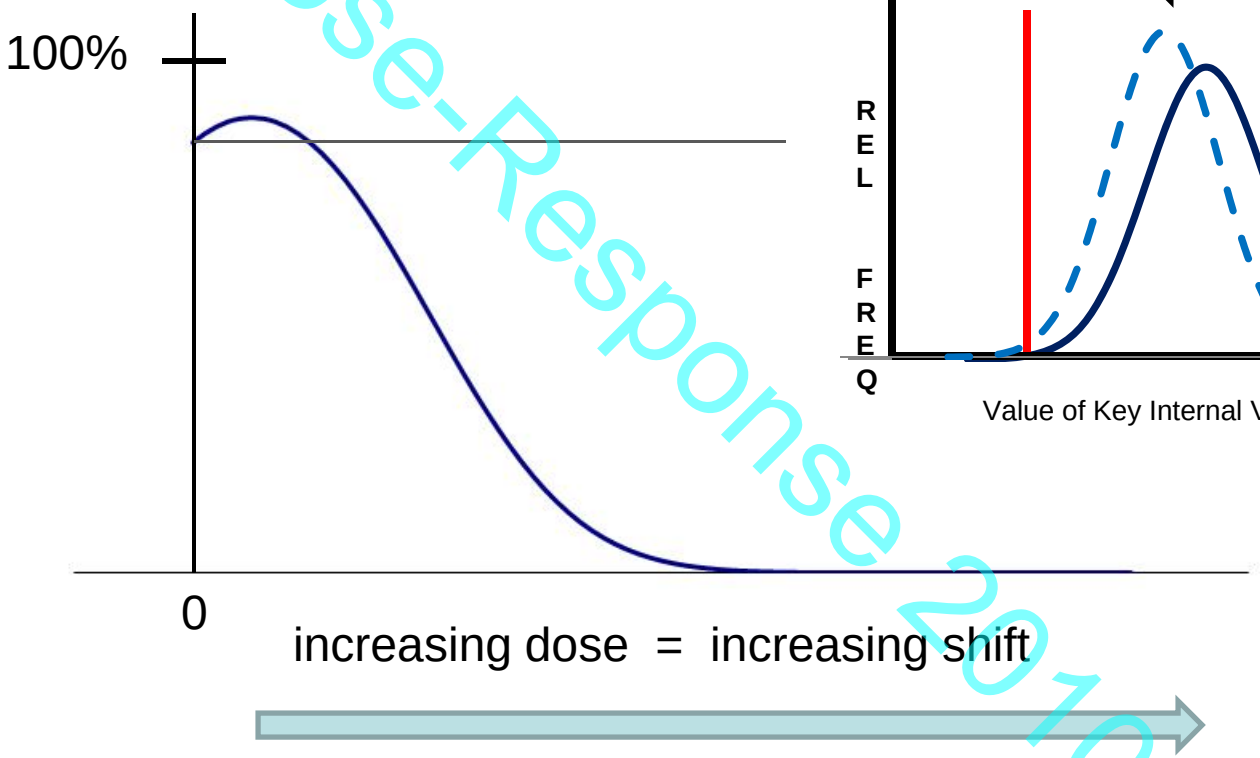
- ie, the effect on the internal variable is assumed to be linear/no-threshold!

The *OTHER* tail!



… with a shift in distribution, *fewer* individuals are in the extreme of the tail one is moving away from!

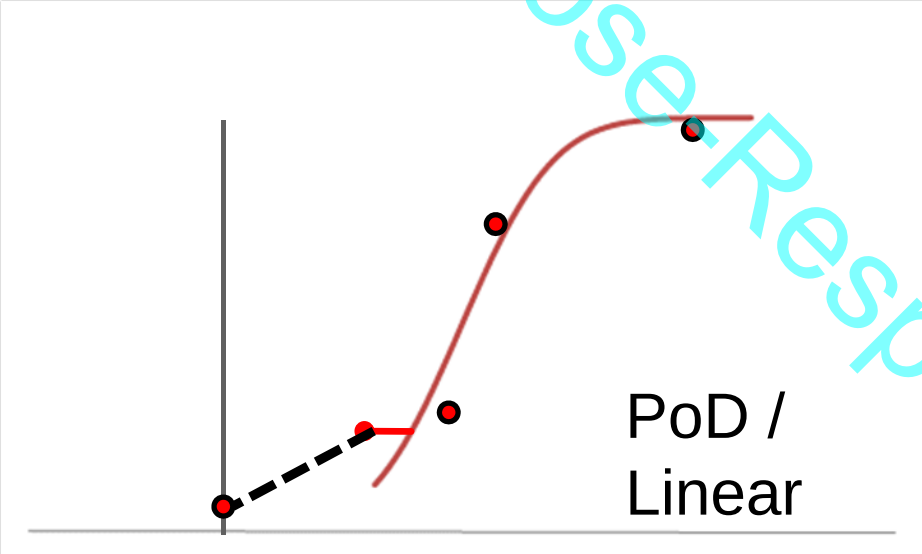
% “Unaffected”



What If We Used Linear Extrapolation for Everything?

- *If* Accept Additivity-to-Background as a Universal Principle (though I don't)
  - Use low-dose linear extrapolation for all endpoints
  - Everything is toxic at sufficient doses, therefore everything has some low-dose risk
- What Implications for Risk Assessment and Risk Management?

How to *Measure* Low-Dose Potency?



- Add-2-BG is an argument in principle, doesn't say how to measure
- High-dose animal data not a good guide
  - depends on *human* background's level and its place on *human* D-R curve
- Potency not the same for everybody
  - depends on other causes of variation in "internal variable"

PoD / Linear likely to be a major over-estimate of a largely unknowable and variable low-dose potency

No More “Critical” Endpoints?

- all toxicities will contribute low-dose risk components
- logic of “critical” effect – one appearing at lowest dose – is lost
- test at higher doses to discover high-dose toxicities?
- all animal endpoints contribute? (WoE for human relevance?)
- distinction between acute and chronic toxicity sustainable?

Control Decisions Become Risk-Risk Tradeoff Decisions

- Less exposure to X (and hence, less risk from X) → more exposure (and risk) from other substances
  - identified or unidentified?
- Shift in "internal variable" distribution has benefits on other tail
- Other benefits and costs may not be apparent or measureable
- Every regulatory decision is a cost-benefit decision, yet it is very difficult to know the components and whether overall benefit is being created

Equity / Env. Justice Issues Are Raised

- Different people are on the edge distributions for different endpoints
- So tradeoffs will be relieving risk on some by imposing risk of others
- Under the Universal Additivity-to-Background logic, any action entails a shift of some kind of health impact from someone to someone else. Does it matter what these are? From and to whom? Identifiable or not?

Need Best-Estimate Potencies (and Distributions)

- To adjudicate risk-risk trade-offs
- To be confident that regulation → public-health improvement
- Trade-offs in qualitatively different endpoints (QUALYs?)

Why don't we get these problems for linear-low-dose carcinogens? Because we can trade carcinogen exposures for exposures to threshold toxicants!

Two Views of the Living System

- Delicate balance
- Toxicity is falling off the edge of normal, and normal goes to the edge

- Robust, self-controlling in the face of environmental fluctuations
- Toxicity is a cascade of failures of control processes pushed too far

Be Careful What You Wish For!