



Gradient

## Linear Low-Dose Extrapolation for Noncancer Health Effects is the Exception, Not the Rule

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& Julie Goodman*  
Gradient

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### *Science and Decisions (2009)*

- Problem-Focused Risk Assessment
- Science-Based Defaults
- Cumulative Risk
- Uncertainty and Variability Characterization
- **“Unified” Dose-Response** (Ca and Non-Ca)
  - Address Both Risk and Sensitivity Variation
  - *Risk-Specific Doses* (Instead of RfDs)
  - Population Risk Leads to No-Threshold

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## Low-Dose Linearity for Noncancer Toxicity?

- White et al. 2009 *EHP* 117(2):283
- *Science and Decisions* – Chapter 5

### **THREE LINES OF ARGUMENT:**

- Additivity to Background Processes that Produce Background Disease;
- Heterogeneity in Sensitivity Among Humans;
- Observed Linearity of Noncancer Effects in Epi Studies (of Criteria Pollutants)

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## References

Rhomberg, LR; Goodman, JE; Haber, LT; Dourson, M; Andersen, ME; Klaunig, JE; Meek, B; Price, PS; McClellan, RO; Cohen, SM. 2011. "Linear low-dose extrapolation for noncancer health effects is the exception, not the rule." *Critical Reviews in Toxicology*. 41(1):1-19.

Rhomberg, LR. 2011 [in press]. "Practical risk assessment and management issues arising were we to adopt low-dose linearity for all endpoints." *Dose Response*.

Rhomberg, LR; Chandalia, JK; Long, CM; Goodman, JE. 2011 [in press]. "Measurement error in environmental epidemiology and the shape of exposure-response curves." *Critical Reviews in Toxicology*. doi:10.3109/10408444.2011.563420.

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## Framing the Problem / Defining Terms :

- Binary Response (w/wo discrete apical disease state)
  - “Response” = % of *population* with apical endpoint
  - “Response” = probability that a random *individual* becomes a case
- Yet, continuous variation underlies causation of these apical binary responses
  - Physiological perturbations and varying susceptibility factors
  - These vary in populations
- CRUX: How do small dose-induced quantitative changes in underlying continuous variables translate into Dose-Response for risk of becoming a “case”?

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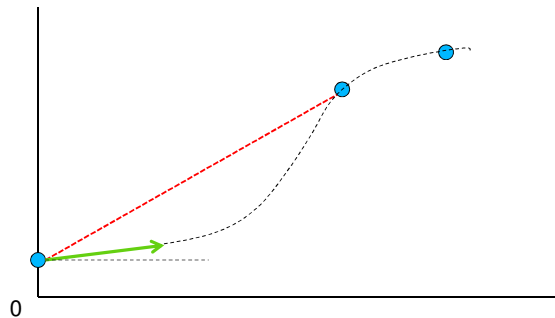
## Framing the Problem / Defining Terms :

- Issue is potential for low-dose linearity of the POPULATION Dose-Response Curve
  - Individual D-R may have (sometimes MUST have) a threshold
  - Question: Does any dose, no matter how small, increase the rate of cases appearing in an exposed population
- In HUMANS (though Animal data may be used to address)
- Low-Dose LINEARITY
  - positive 1st derivative, not just no-threshold
- Linearity FROM ZERO UPWARD
  - Not the same as linear from POD downward!!!

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*“Note that low dose linear means that at low doses ‘added risk’ (above background) increases linearly with increasing dose; it does not mean that the dose-response relationship is linear throughout the dose range between zero dose and the high dose.”*

-- NRC (2009) p. 131

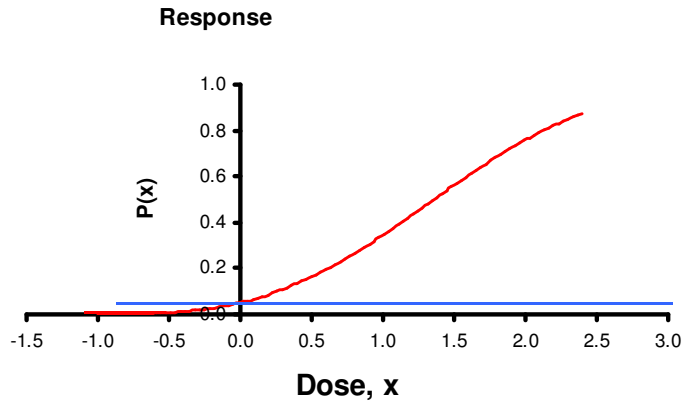


NRC. 2009. *Science and Decisions: Advancing Risk Assessment*. National Academies Press.

## Framing the Problem / Defining Terms :

- Low-Dose Linearity as a GENERAL DEFAULT expectation for the true low-dose shape
  - How/Whether to implement as an assessment default is a further question
- Arguments FOR Low-Dose Linearity have been cast in terms of EXISTENCE-IN-PRINCIPLE, not observation
  - i.e., SOME low-dose linearity to be expected as a consequence of generally and widely operating principles
- So our critiques have to be cast in similar terms; QUESTIONING WHETHER THE PRINCIPLES REALLY APPLY AND REALLY ARE GENERAL

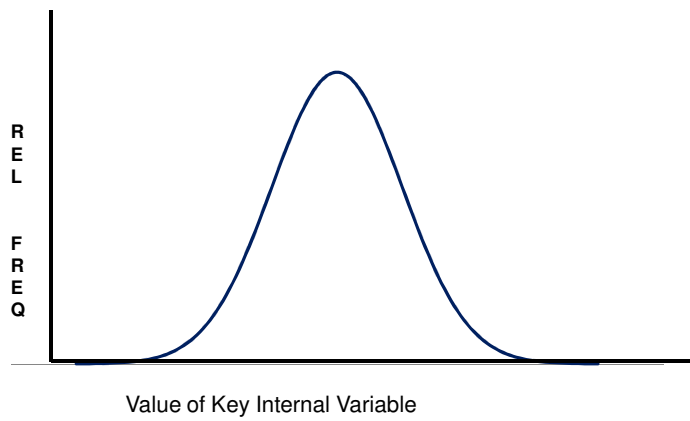
### Additivity to Background



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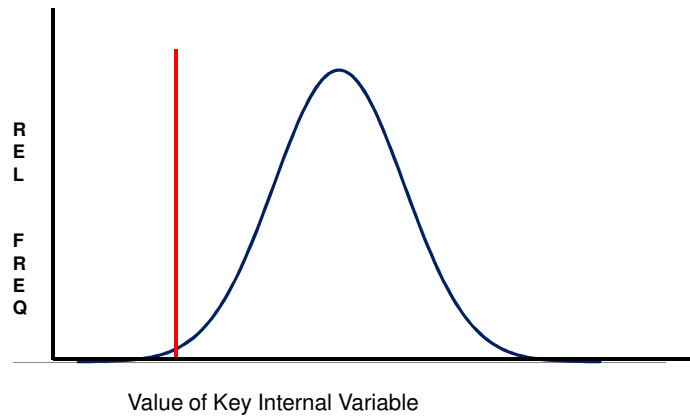
### Population Distribution of Internal State



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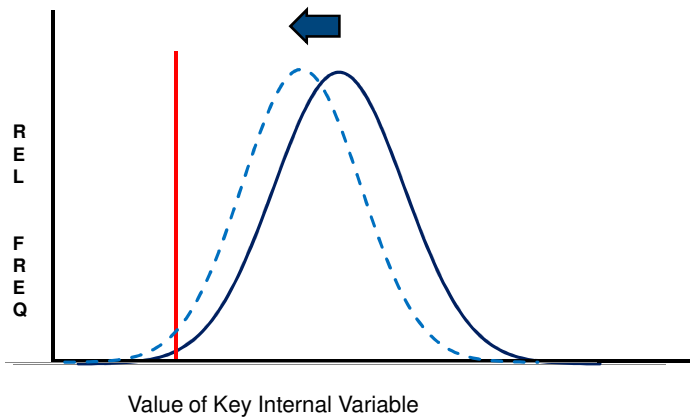
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### Some % Beyond Threshold – Leading to a Background Rate of Disease



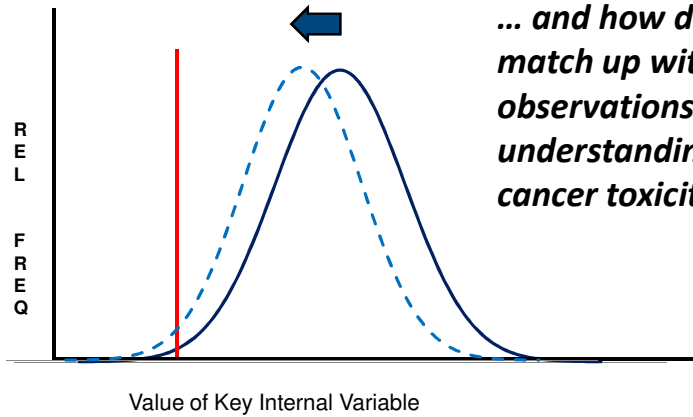
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### Even a Small Shift in Distribution of Internal State Leads to Greater % Beyond Threshold



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

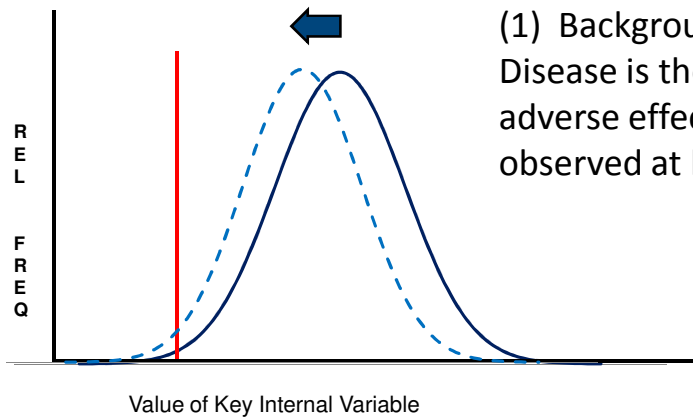


*... and how do they match up with our observations and understanding of non-cancer toxicity?*

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

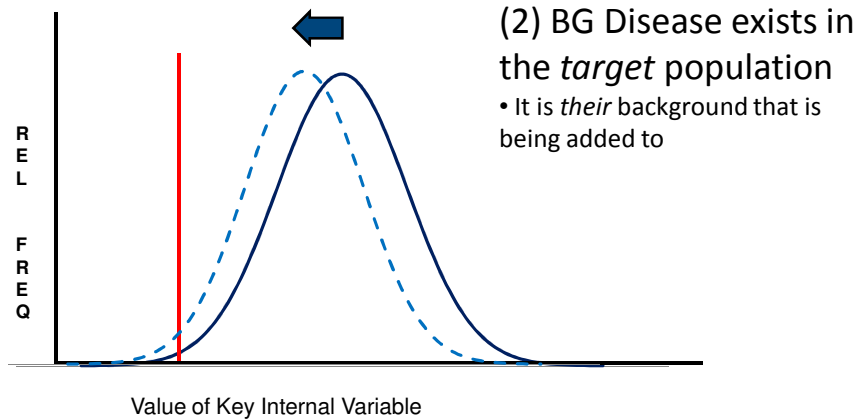


(1) Background Disease is the *same* as adverse effects observed at high dose

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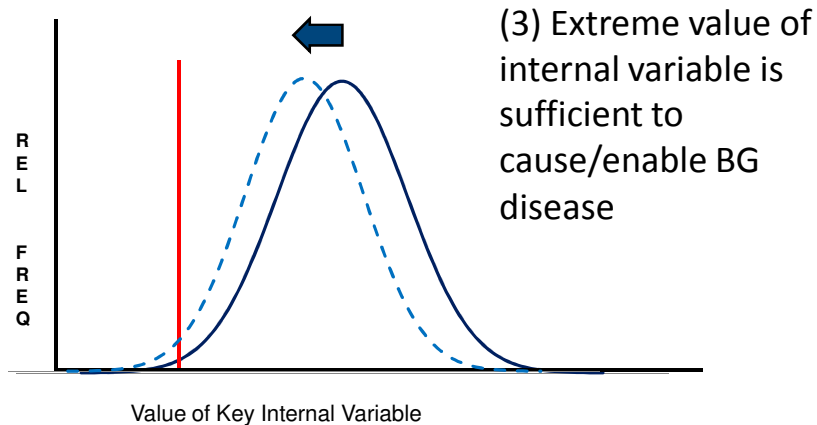
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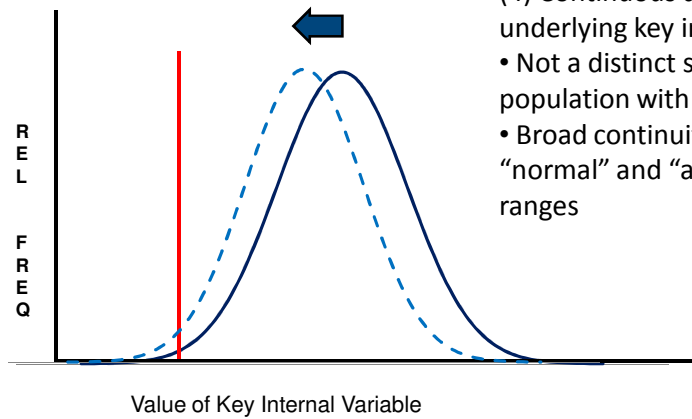
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## What *Biological* Assumptions Does Such Additivity-to-BG Implicitly Make?



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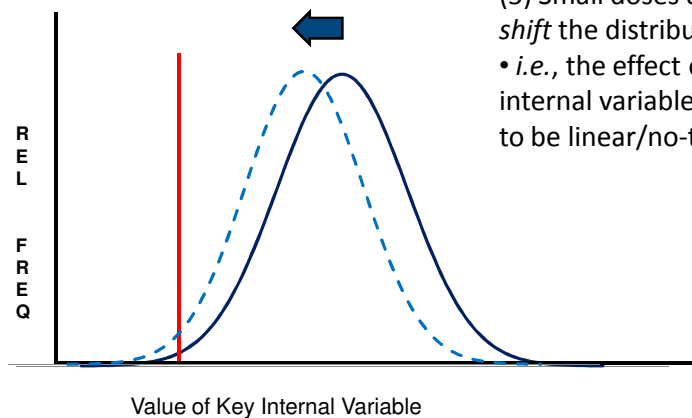


- (4) Continuous distribution of underlying key internal factor
- Not a distinct sub-population with other causes
  - Broad continuity between “normal” and “abnormal” ranges

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

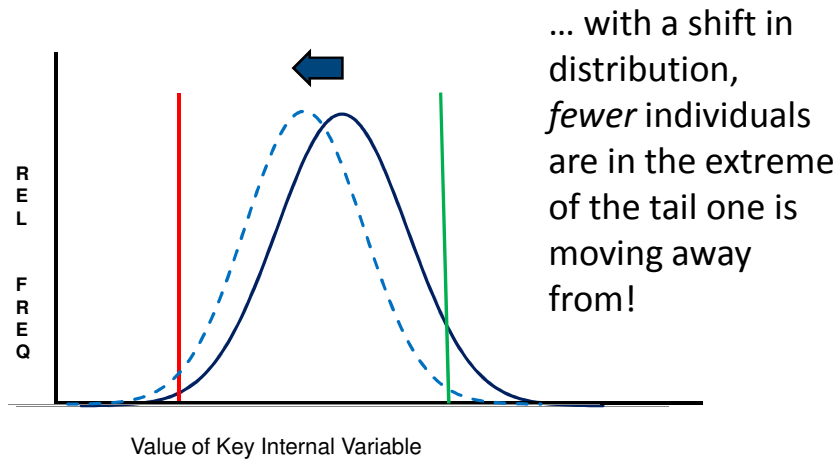


- (5) Small doses do indeed *shift* the distribution
- *i.e.*, the effect on the internal variable is assumed to be linear/no-threshold!

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## The *OTHER* tail!



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1. EP = BG
2. BG in Humans
3. Threshold within Existing Variation
4. Continuity of Mainstream and Affected
5. Small Doses Shift Distribution

*Are usual IRIS endpoints observed as (uncommon) occurrences in natural populations?*

*What human disease states are equivalent to animal endpoints?*

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1. EP = BG
2. BG in Humans
3. Threshold within Existing Variation
4. Continuity of Mainstream and Affected
5. Small Doses Shift Distribution

*What human disease states are equivalent to animal endpoints?*

*How common?*

*Is the MoA for background human disease the same as high-dose animal adverse effects?*

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1. EP = BG
2. BG in Humans
3. Threshold within Existing Variation
4. Continuity of Mainstream and Affected
5. Small Doses Shift Distribution

*MoA? How does just crossing the threshold precipitate disease? What is biologically necessary? Sufficient?*

*Is it unhealthy merely to be on the edges of normal variation?*

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1. EP = BG
2. BG in Humans
3. Threshold within Existing Variation
4. Continuity of Mainstream and Affected
5. Small Doses Shift Distribution

*Is there a gradual gradation between normal and abnormal states? How does this gibe with our notions of "healthy" "normal" and "disease" as distinct states?*

*In view of pathophysiological progression of toxicity, what evidence for widespread intermediate states?*

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1. EP = BG
2. BG in Humans
3. Threshold within Existing Variation
4. Continuity of Mainstream and Affected
5. Small Doses Shift Distribution

*Why does the dose shift the distribution in a linear/no-threshold way? Are we just assuming linearity at a lower level of biological organization?*

*Role of homeostasis, control processes, and defenses?*

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## Counterarguments

- High-dose toxicity is usually qualitatively distinct from background disease
- Disease state is discrete and distinct from health – don't see continuous gradation of underlying pathology
- Progression of severity with dose – disease is only final stage

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## Counterarguments

- Variation does not mean tails cross thresholds
- Variation does not mean that internal states are easily perturbed
- Effects from small doses is counter to a vast body of experience

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## Counterarguments

- Homeostasis is characteristic of life
- Nature of living system is to be robust to changing environments – to maintain desirable states (and orderly, discrete transitions among states) *despite* such fluctuating circumstances

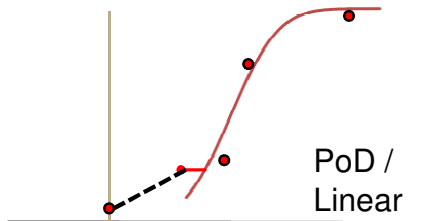
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## In short:

- Small doses don't necessarily shift distribution
- Distribution of sensitivities probably has a population threshold
- Background processes are usually mechanistically distinct from high-dose toxicity
- “Overwhelming defenses” is still a valid model for noncancer toxicity

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## 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*

## 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

## Low-Dose Linearity for Noncancer Toxicity?

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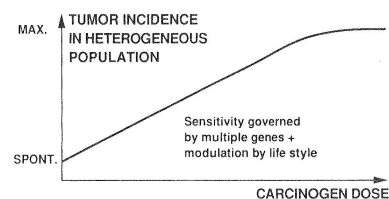
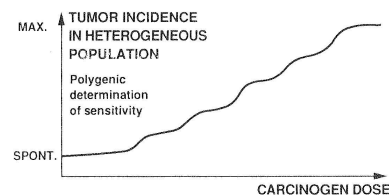
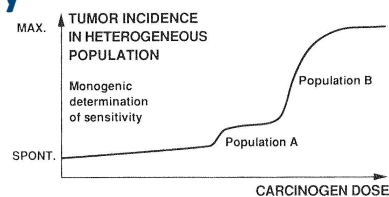
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## Population Heterogeneity

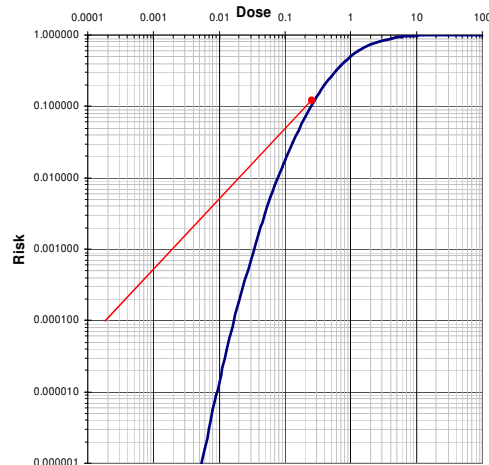
- White *et al.* (2009) assert heterogeneity in sensitivity to chemicals in the population linearizes the dose-response curve
- Based on incorrect interpretation of an argument put forth by Lutz, *Carcinogenesis* 11(8):1243



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## Population Heterogeneity

- Dose-response curve is *itself* an expression of heterogeneous susceptibility
- Varying sensitivity factors ought to be multiplicative
- Combined action of multiple sensitivity factors makes a dose-response curve lognormal



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## Low-Dose Linearity for Noncancer Toxicity?

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## Exposure Measurement Error

- For many chemicals, mechanistic and toxicity studies demonstrate thresholds, while epidemiology studies do not
- Exposure measurement error is ubiquitous and unavoidable in epidemiology
- Regressions (including D-R curves) are biased toward flattening when there is measurement error in the independent variable (exposure)

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## Exposure Measurement Error in Epidemiology Biases Toward Flat Dose-Response and Obscures True Thresholds

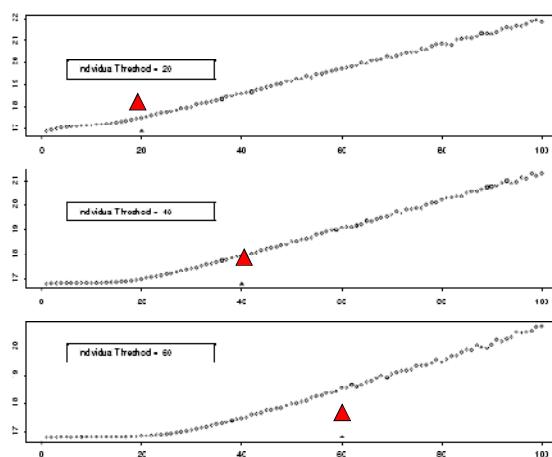


Fig. 4 Expected number of deaths per 1,000,000 (y-axis) versus ambient concentrations ( $\mu\text{g}/\text{m}^3$ ) of  $\text{PN}_{2.2}$  (x-axis). Individual-level thresholds,  $t_i$ , are denoted by  $\blacktriangle$ .

Brauer *et al.*, *Risk Anal* 22(6):1183

## Conclusions

- Additivity to background and population heterogeneity do not linearize D-R curves at low doses
- Exposure measurement error can mask thresholds
- Linear low-dose extrapolation for noncancer health effects is the exception, not the rule

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