

(A biologist's perspective on)  
*Estimating Low-Dose Risk from High-  
Dose Data and Its Associated  
Uncertainty*

Rory Conolly

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# *Disclaimer*

*EPA has sponsored Dr. Conolly's attendance at this meeting. This presentation is not a statement of official policy of the United States Environmental Protection Agency.*

# *Outline*

1. Risk at a given exposure is determined by biological processes
  - Reduce uncertainty by characterizing the biology
2. Quantify uncertainty or identify when it is reduced?
  - Qualitative analysis may be sufficient

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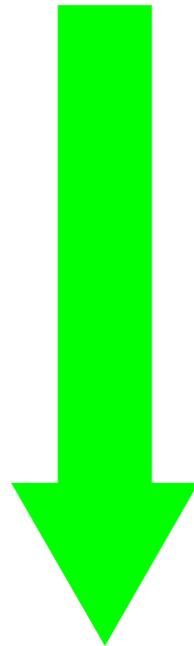
# Uncertainty of a risk estimate

Range of possible risks that contains the actual risk



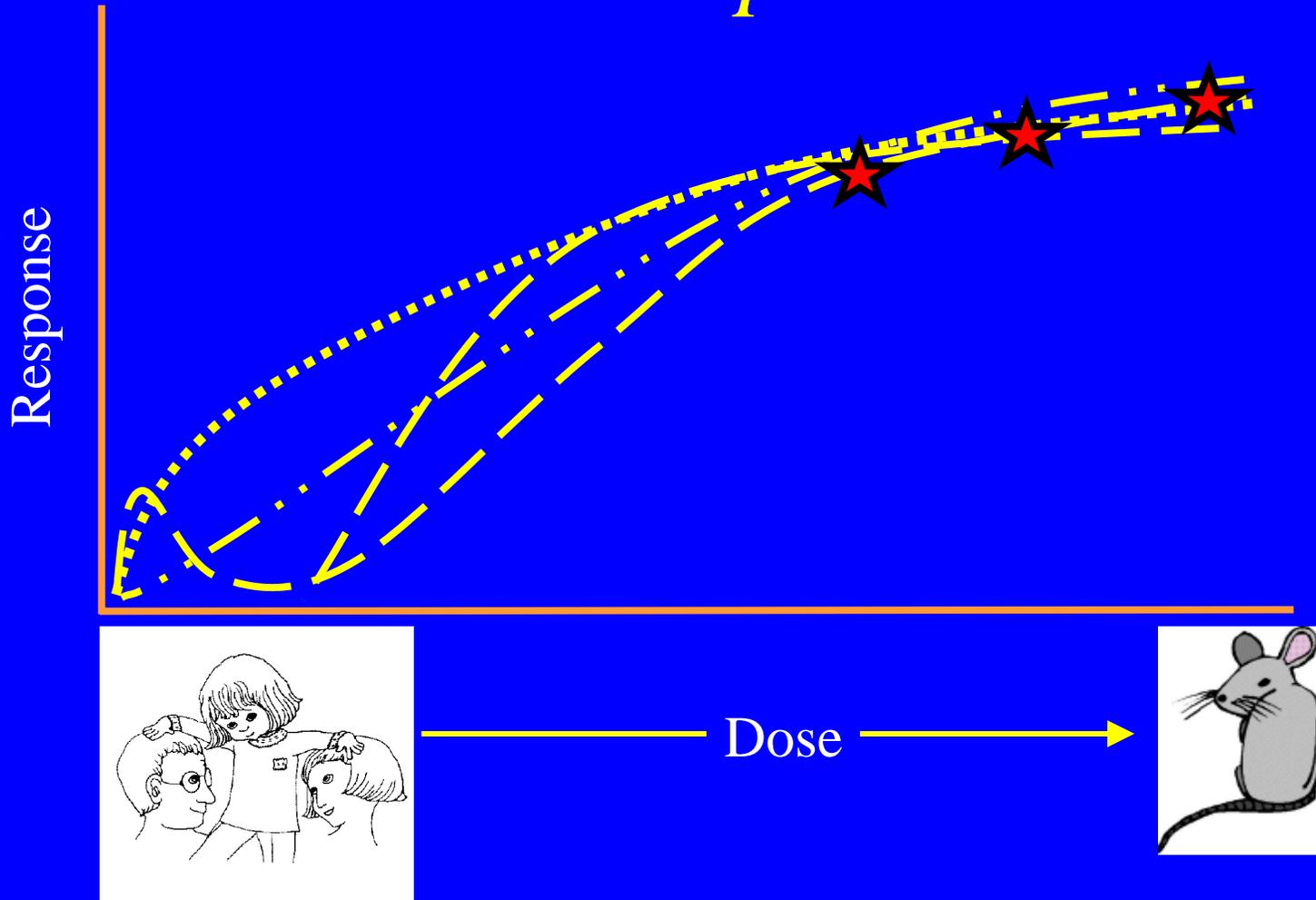
Risk is under-predicted

-----Best estimate of risk-----

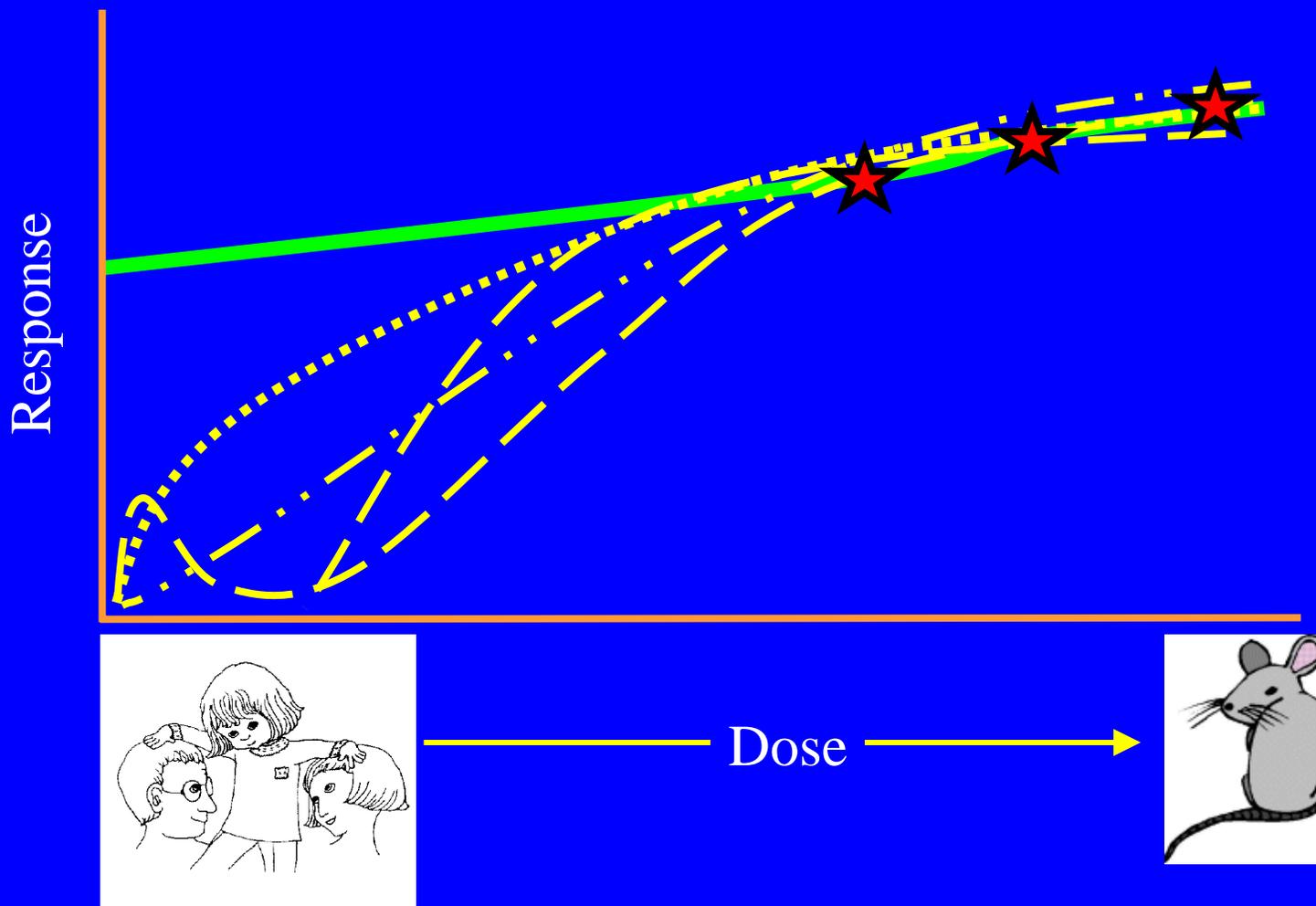


Risk is over-predicted

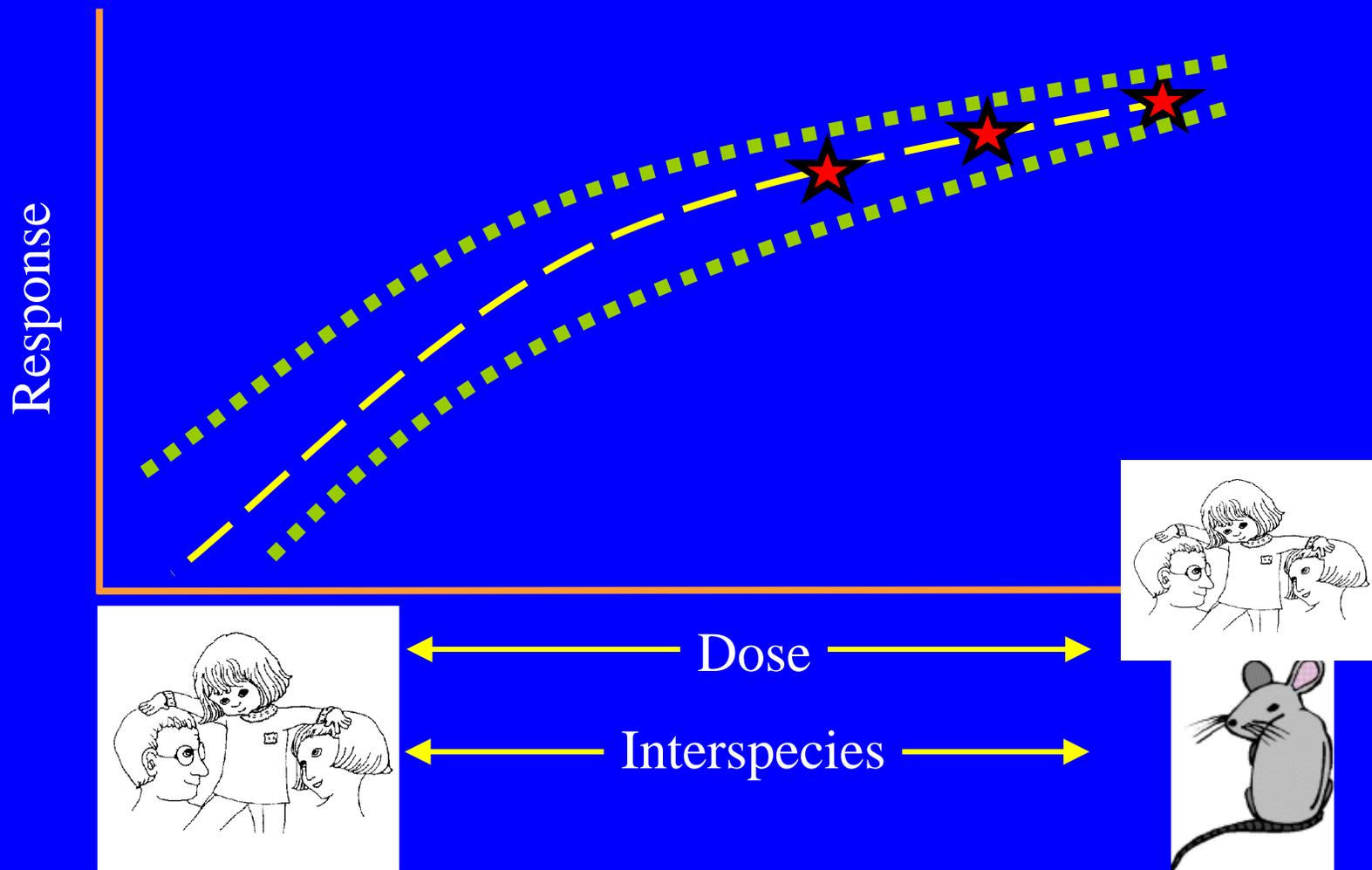
# *Many possibilities for the actual dose-response*



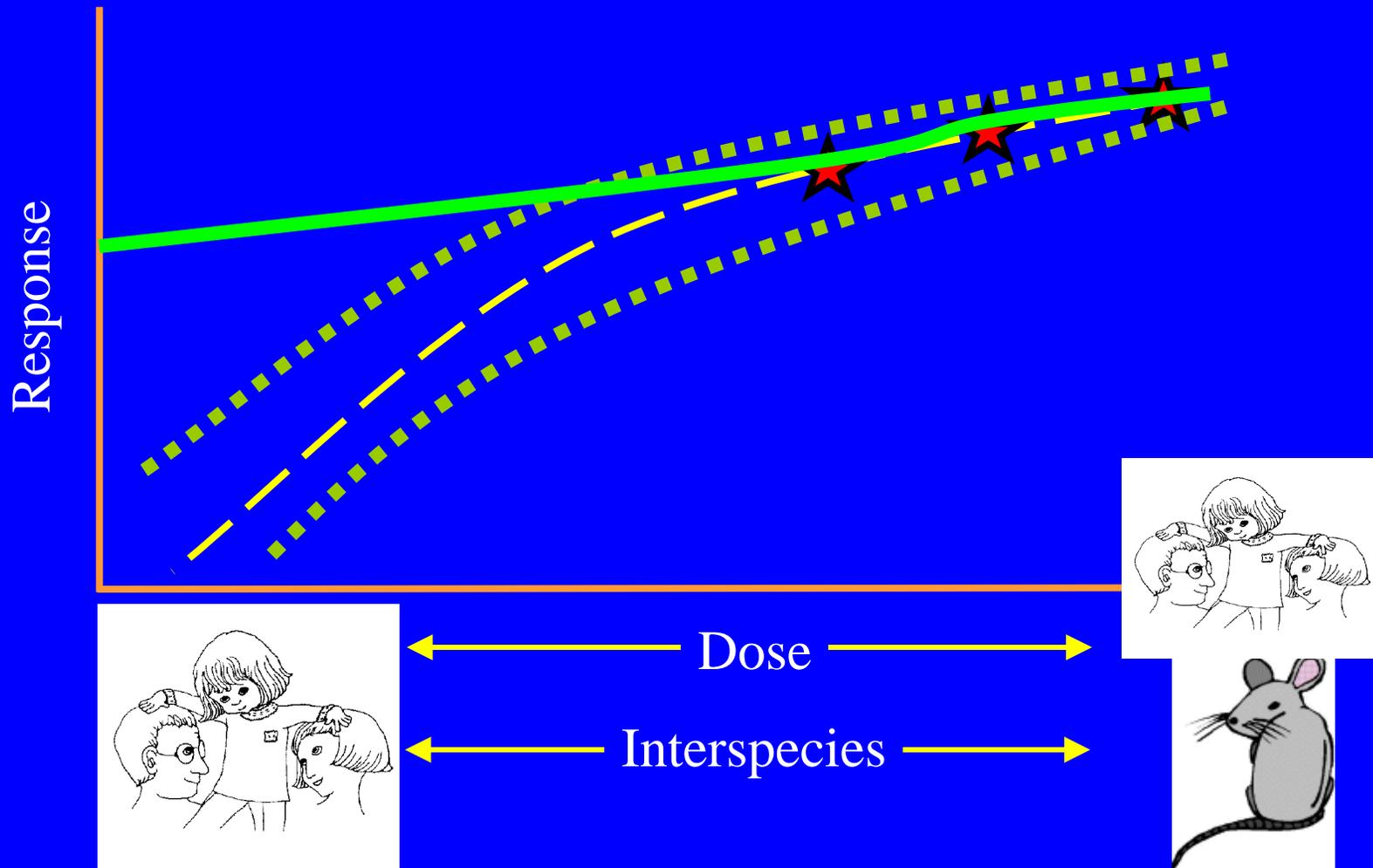
# *Default-driven, health-protective extrapolation*



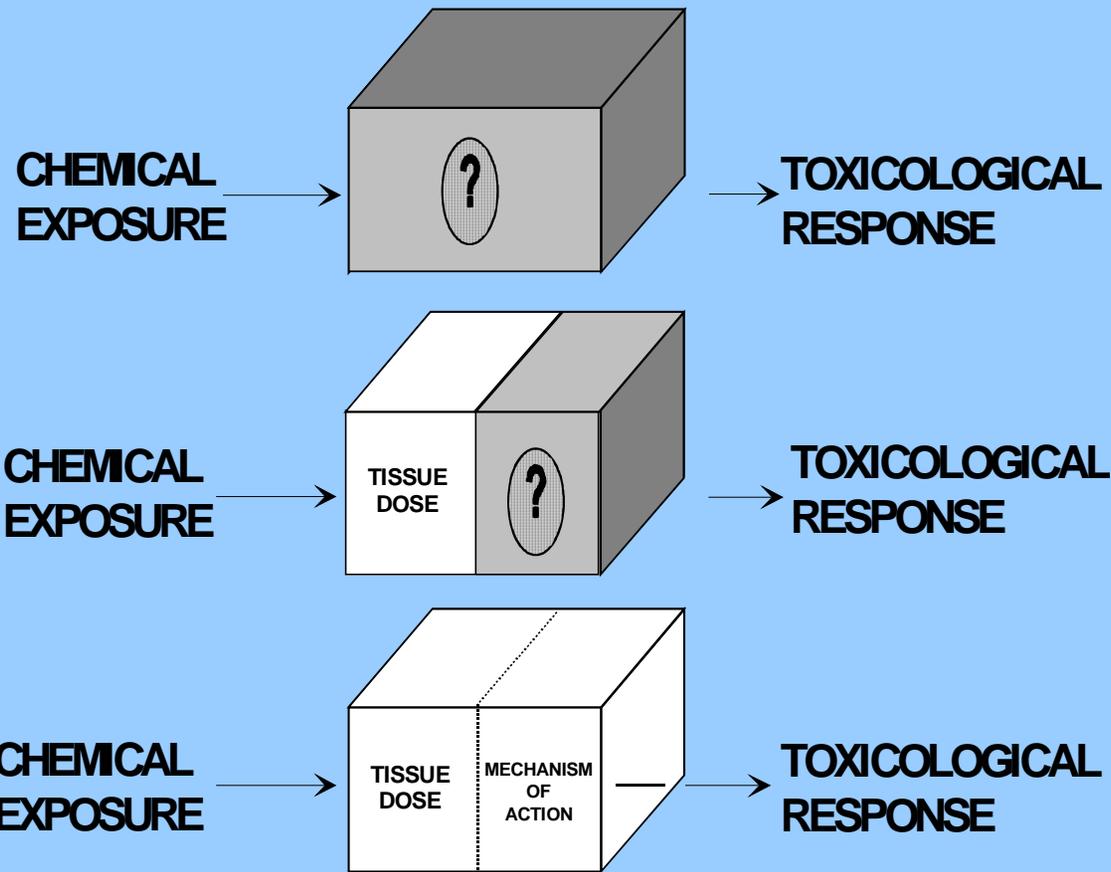
# *Theoretical mode of action based extrapolation with minimal uncertainty*



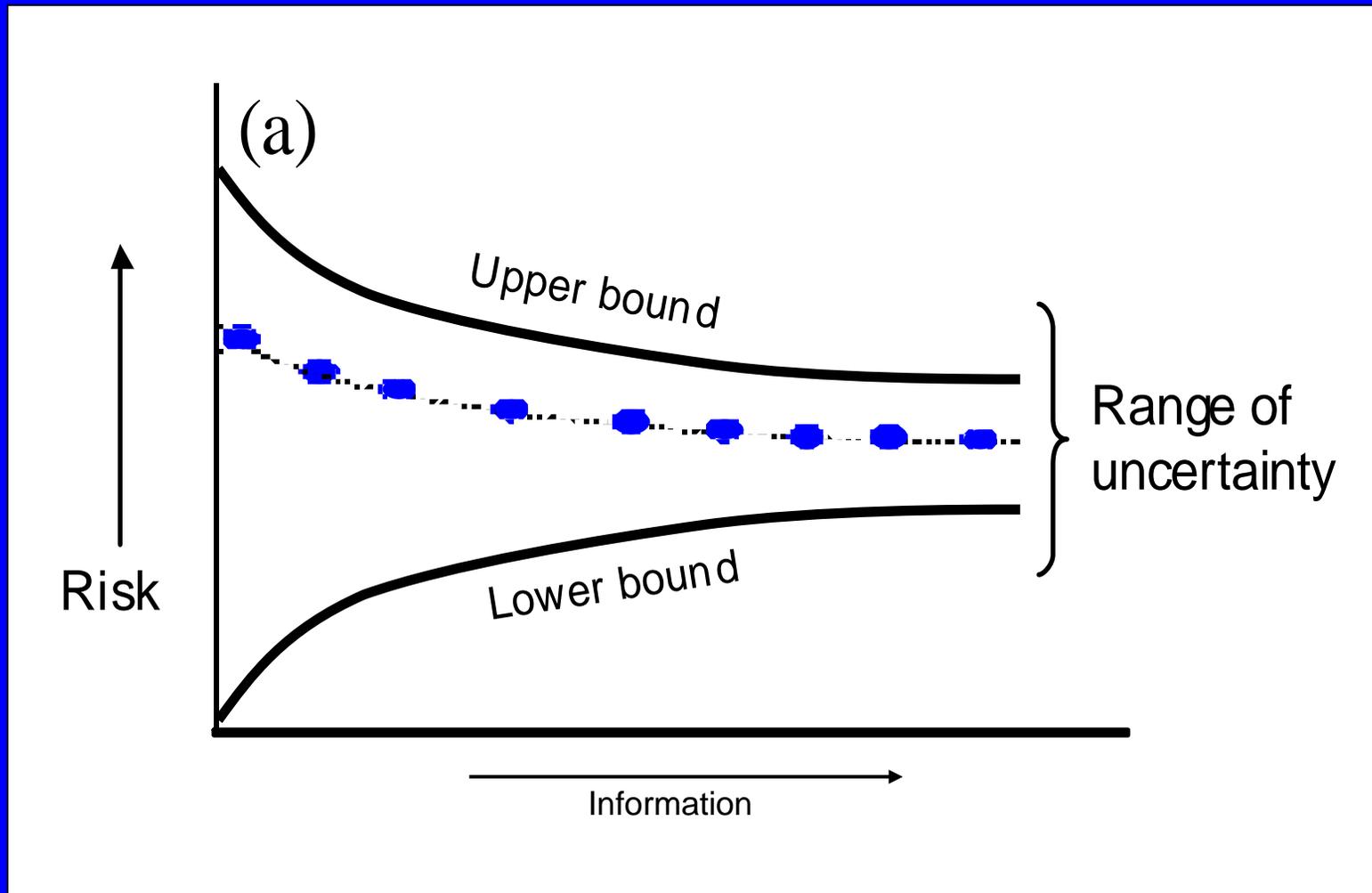
# *Reducing uncertainty: How to close the gap?*



# *Biological mechanisms determine dose-response*



# *Reduce uncertainty by describing the system more accurately*



# *Outline*

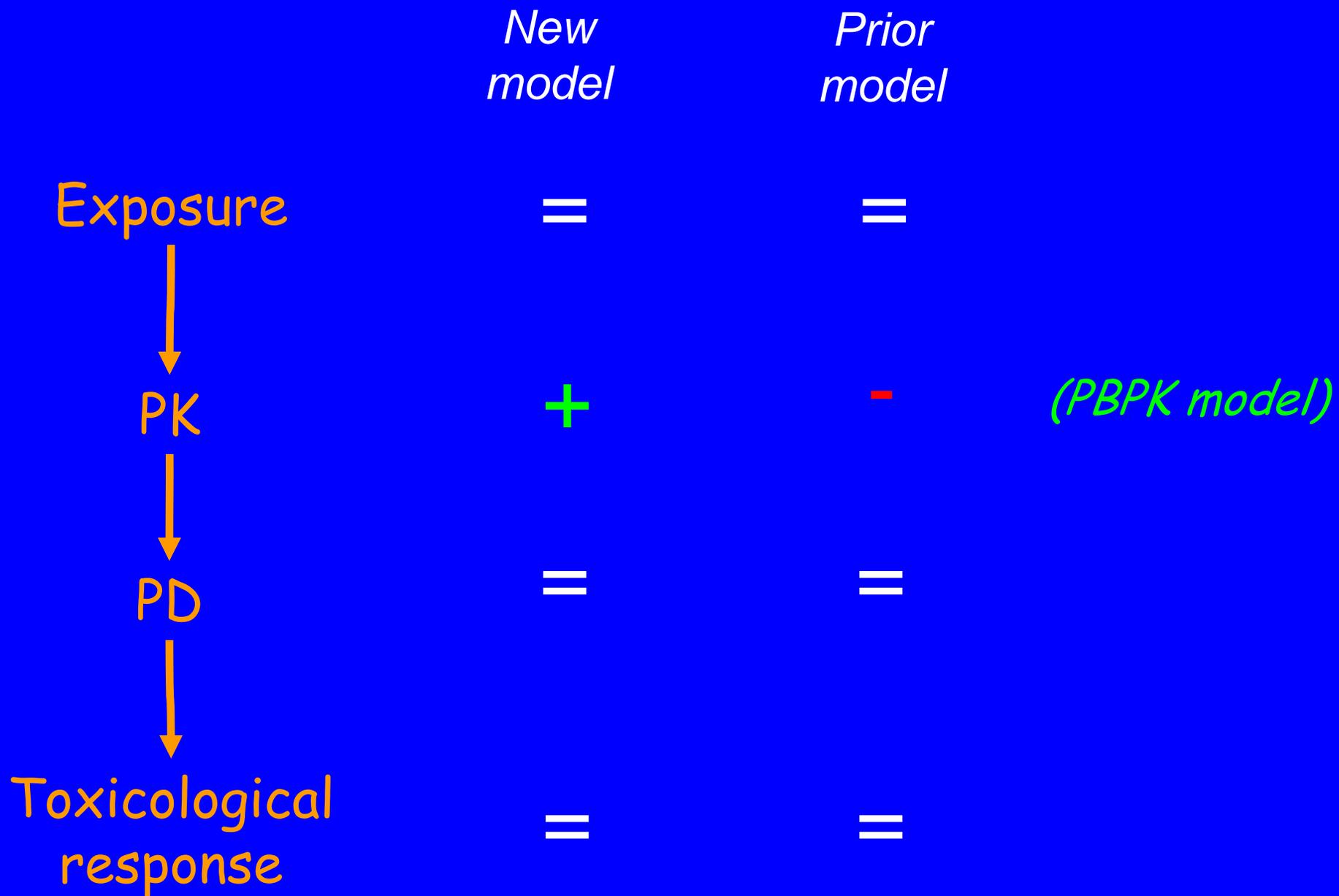
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# *Quantify uncertainty or reduce it?*

- What is the motivation for quantifying uncertainty?
  - To identify the appropriate level of confidence in predicted risk.
- As a practical matter, is it enough to simply know that a new assessment is less uncertain than its forerunner?

# *Approach*

- Partition the exposure  $\rightarrow$  dose  $\rightarrow$  response relationship into its component parts
  1. Exposure
  2. Pharmacokinetics
  3. Pharmacodynamics
    - Mode of action
  4. Toxicological response

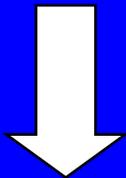


*Example: Formaldehyde dosimetry*

# *Dosimetry in EPA and CIIT assessments*

*CIIT, 2003*

Inhaled ppm



CFD modeling



Tissue dose  
(DPX)

*EPA, 1991*

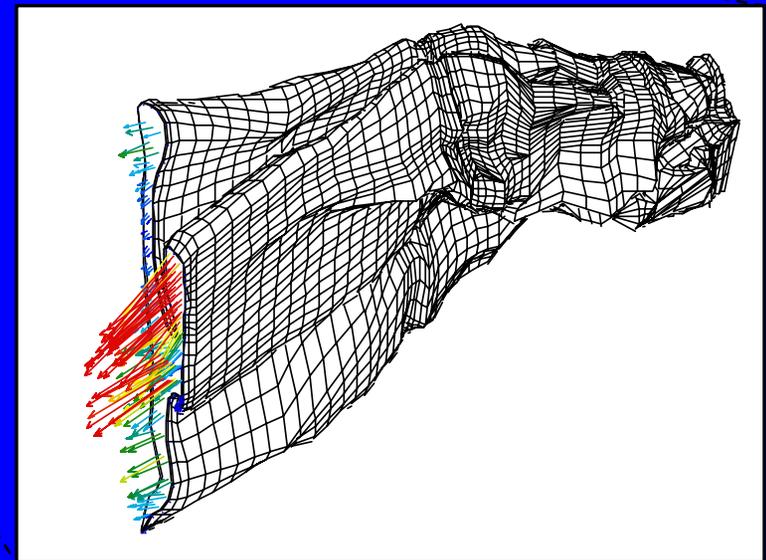
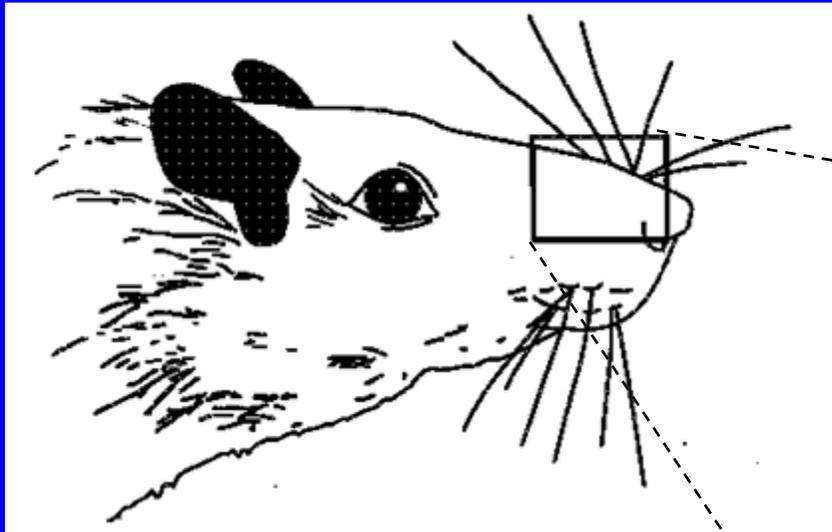
Inhaled ppm



Tissue dose  
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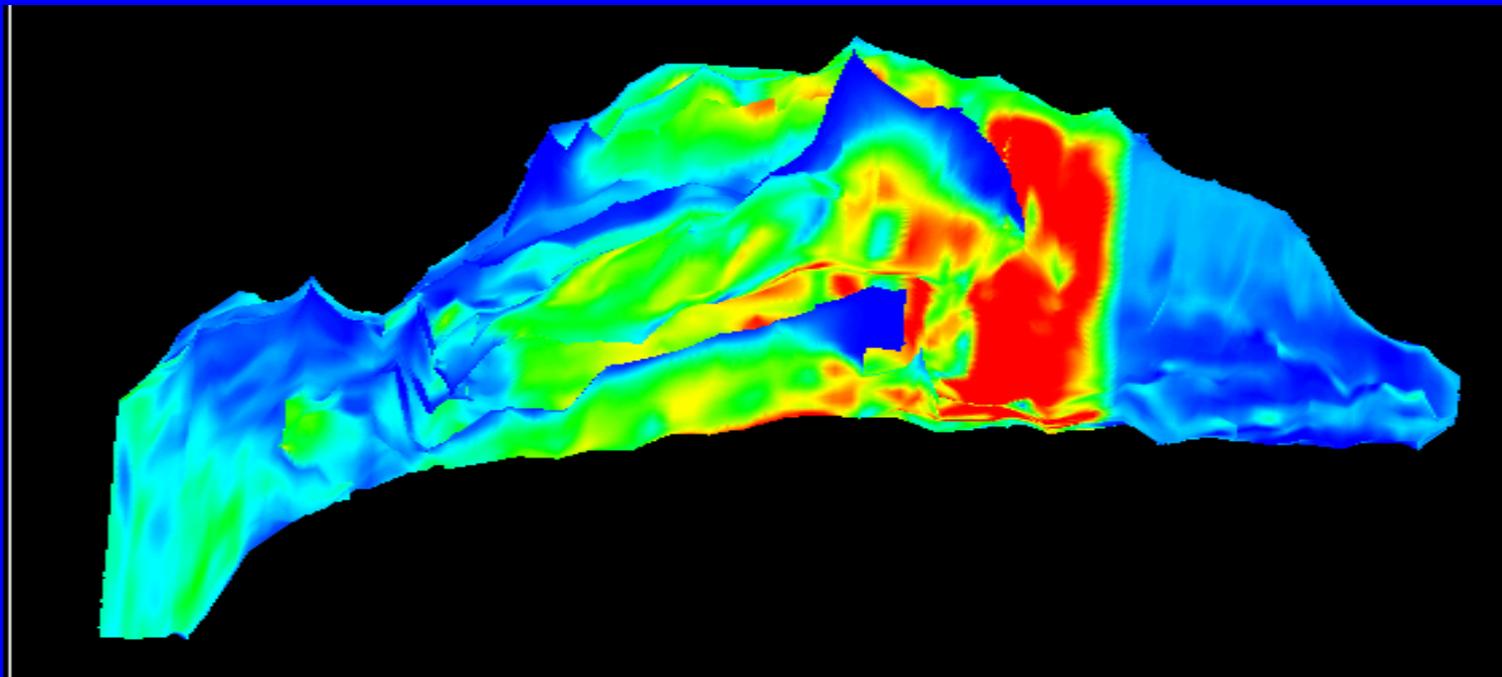
# *CFD Simulation of Nasal Airflow*

*(Kimbell et. al)*



## *Flux bins*

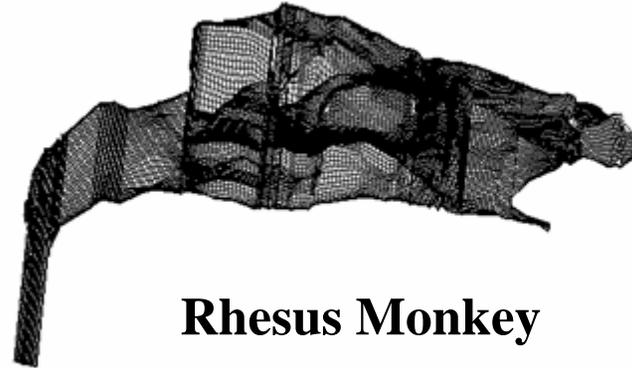
- Nasal surface area partitioned into 20 bins ranked according to flux of formaldehyde predicted by the CFD model



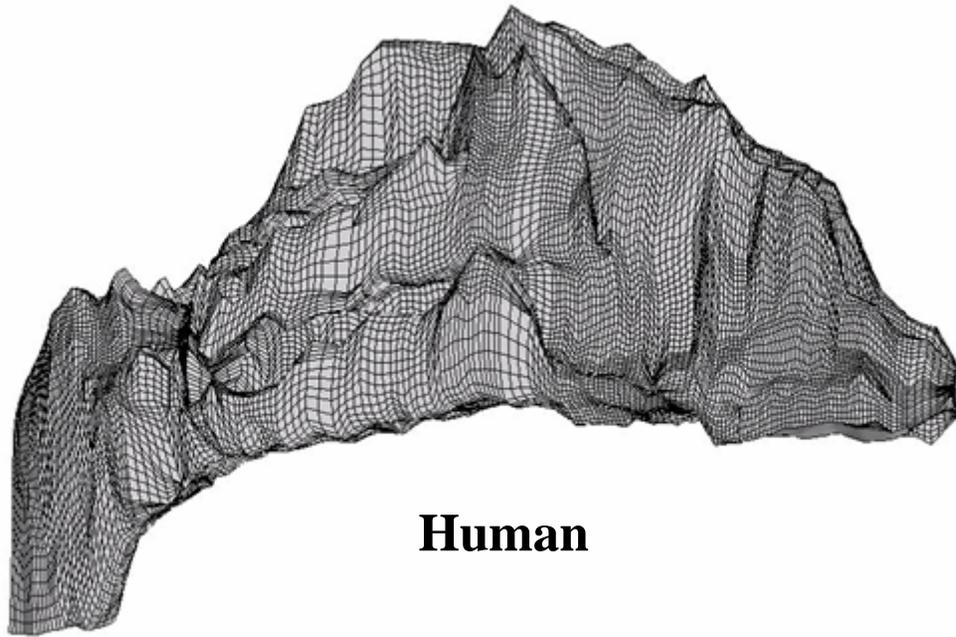
# *Computational fluid dynamics models of the nasal airways*



**F344 Rat**



**Rhesus Monkey**



**Human**

*New  
model*

*Prior  
model*

Exposure

=

=

PK

+

-

*(CFD model)*

PD

=

=

Toxicological  
response

=

=

## *To reduce uncertainty...*

- Incremental characterization, in a manner that is both statistically and biologically rigorous, of
  - Exposure
  - Mechanisms
    - PK
    - PD
- Consider relative uncertainty as opposed to quantitative

*End*