Thresholds: Discontinuities in a Continuous World

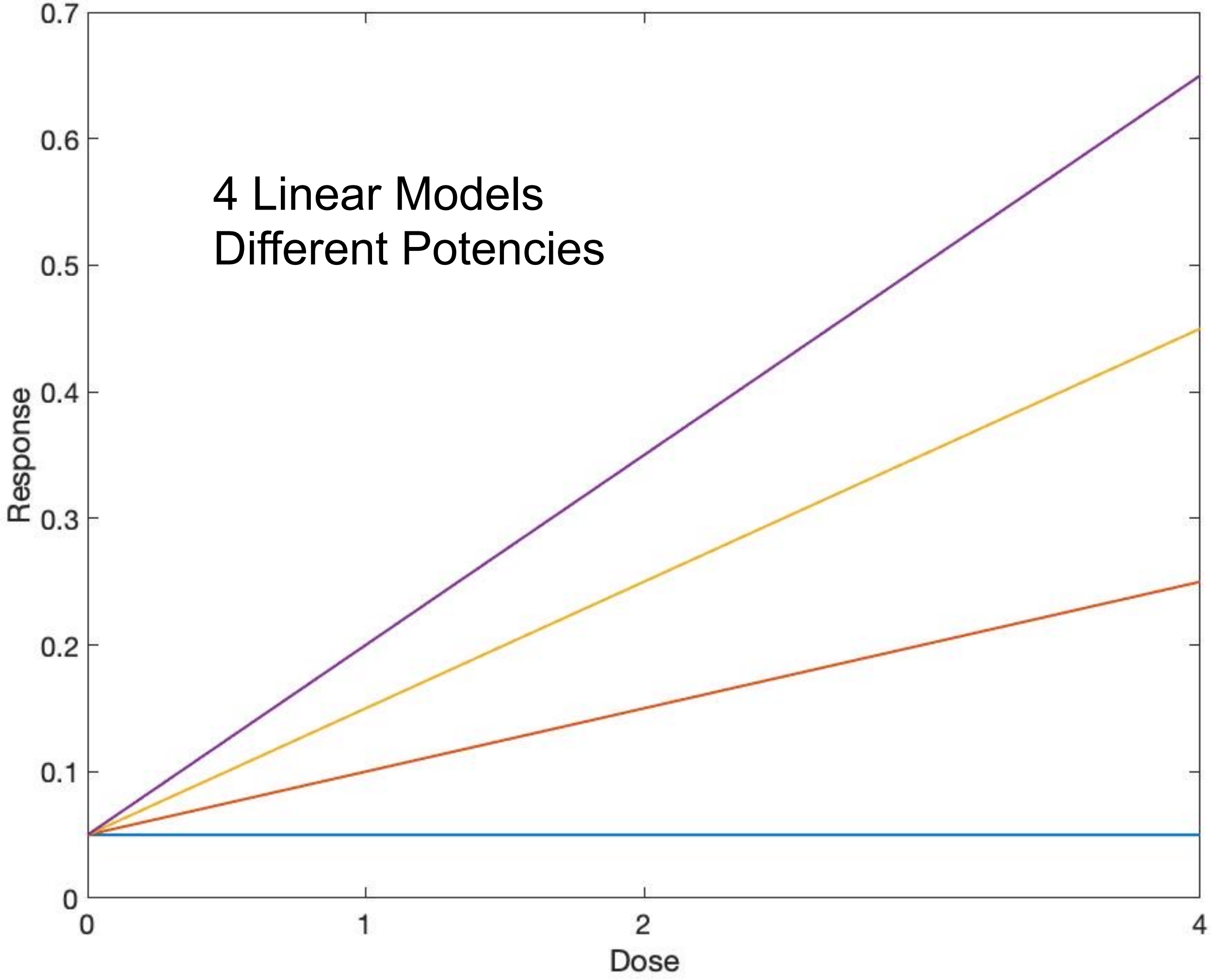
Christopher J. Portier, Ph.D.

27 May, 2021

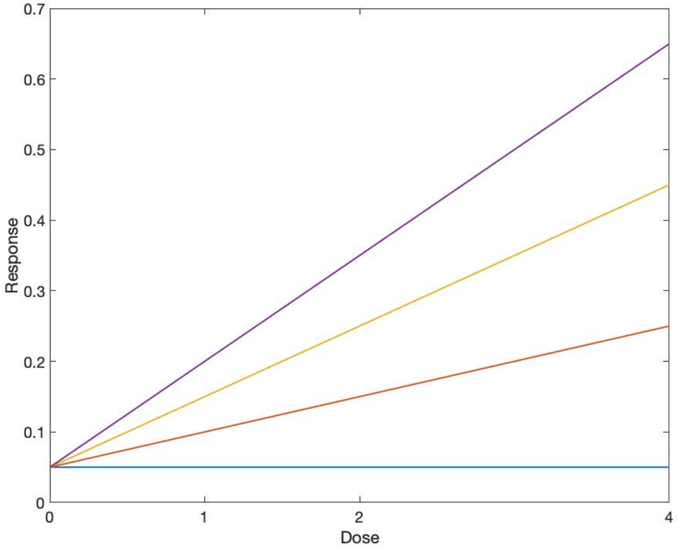
Contents

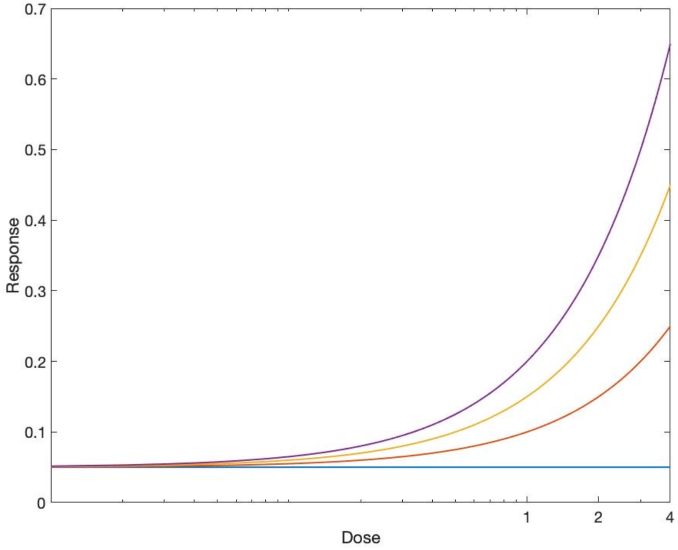
- Definitions
- Additivity
- Theoretical Considerations
- Empirical Considerations
- Practical Considerations

Dose-Response Potency

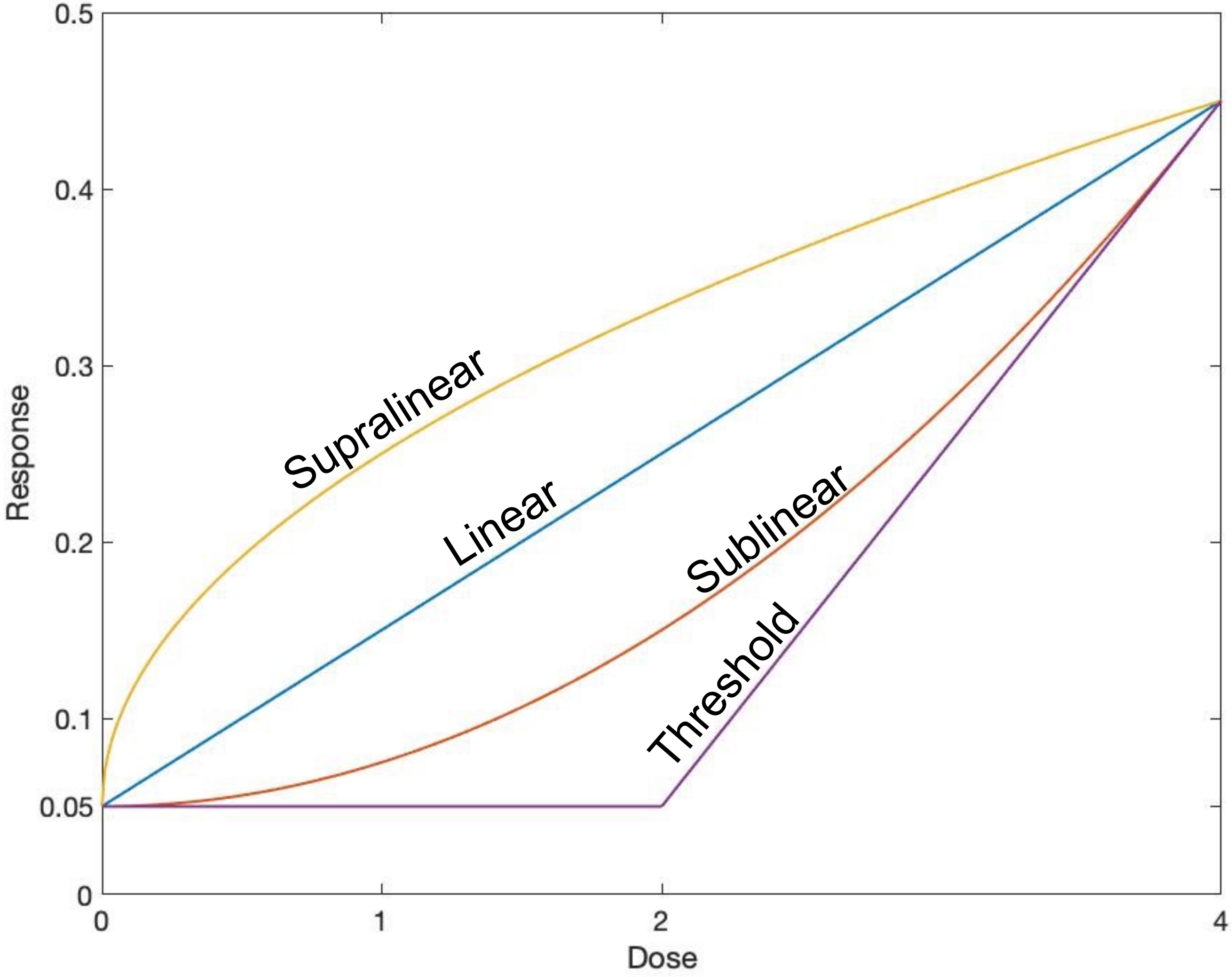


Log-Transformed Dose

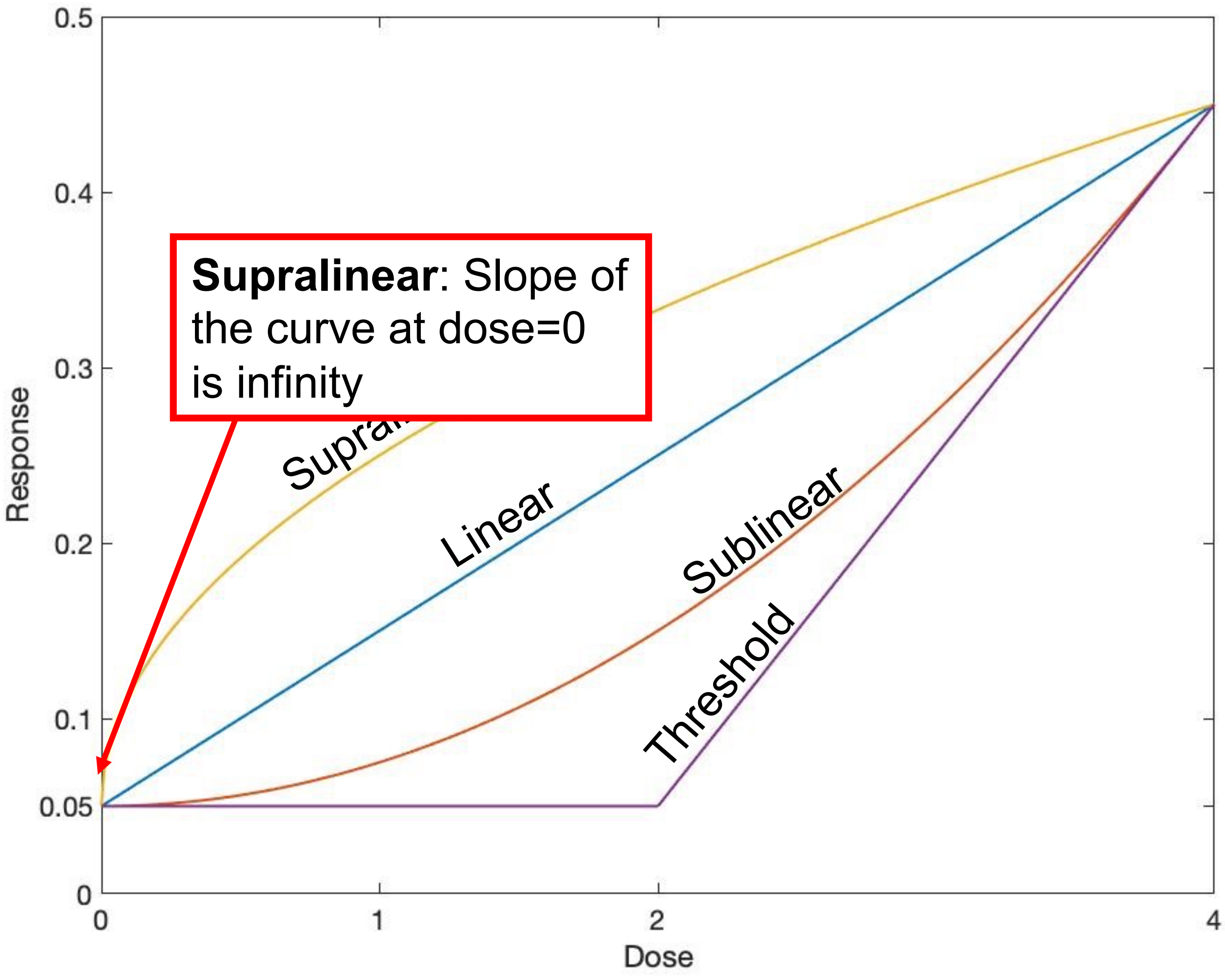




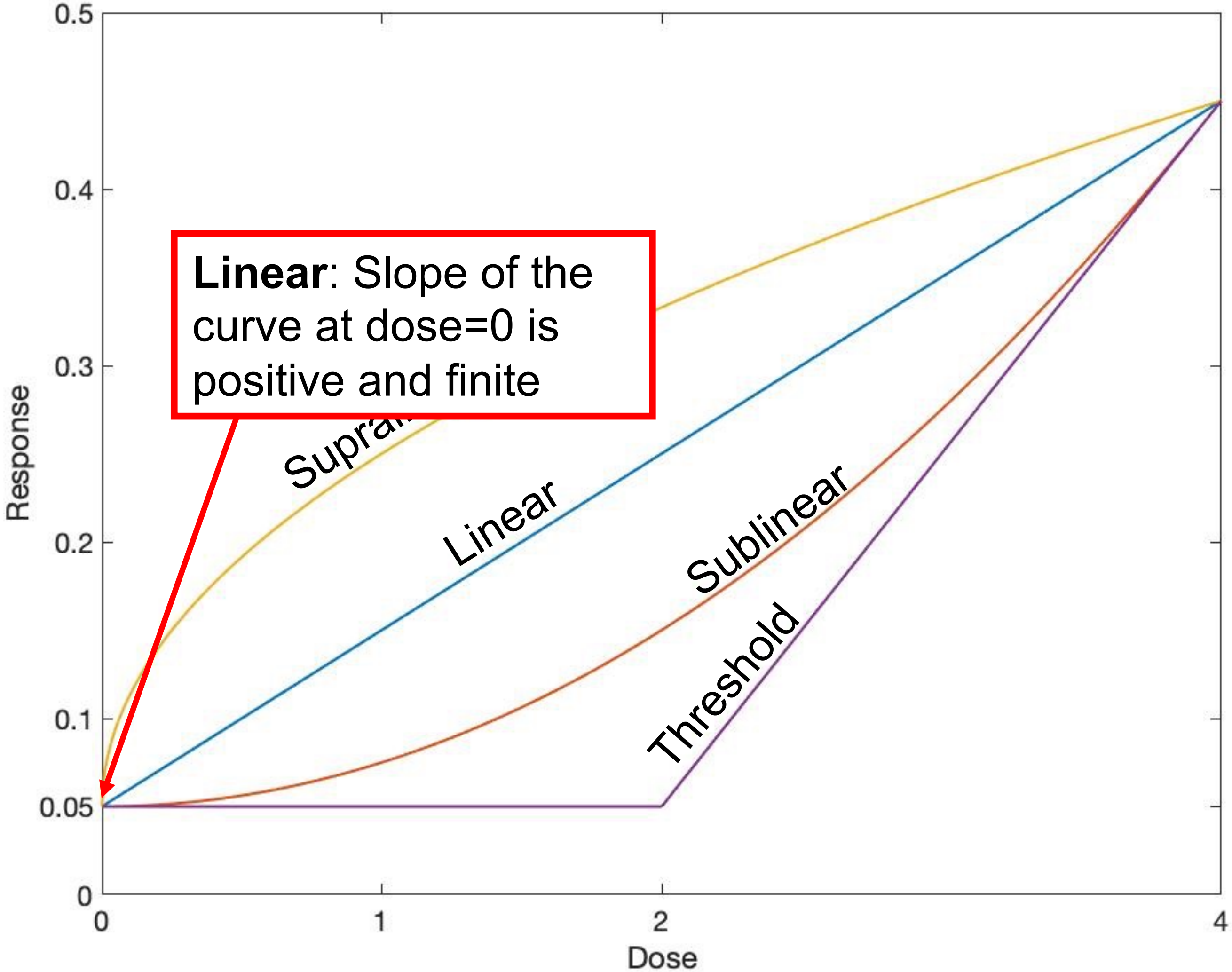
Dose-Response Shape (Monotonic)



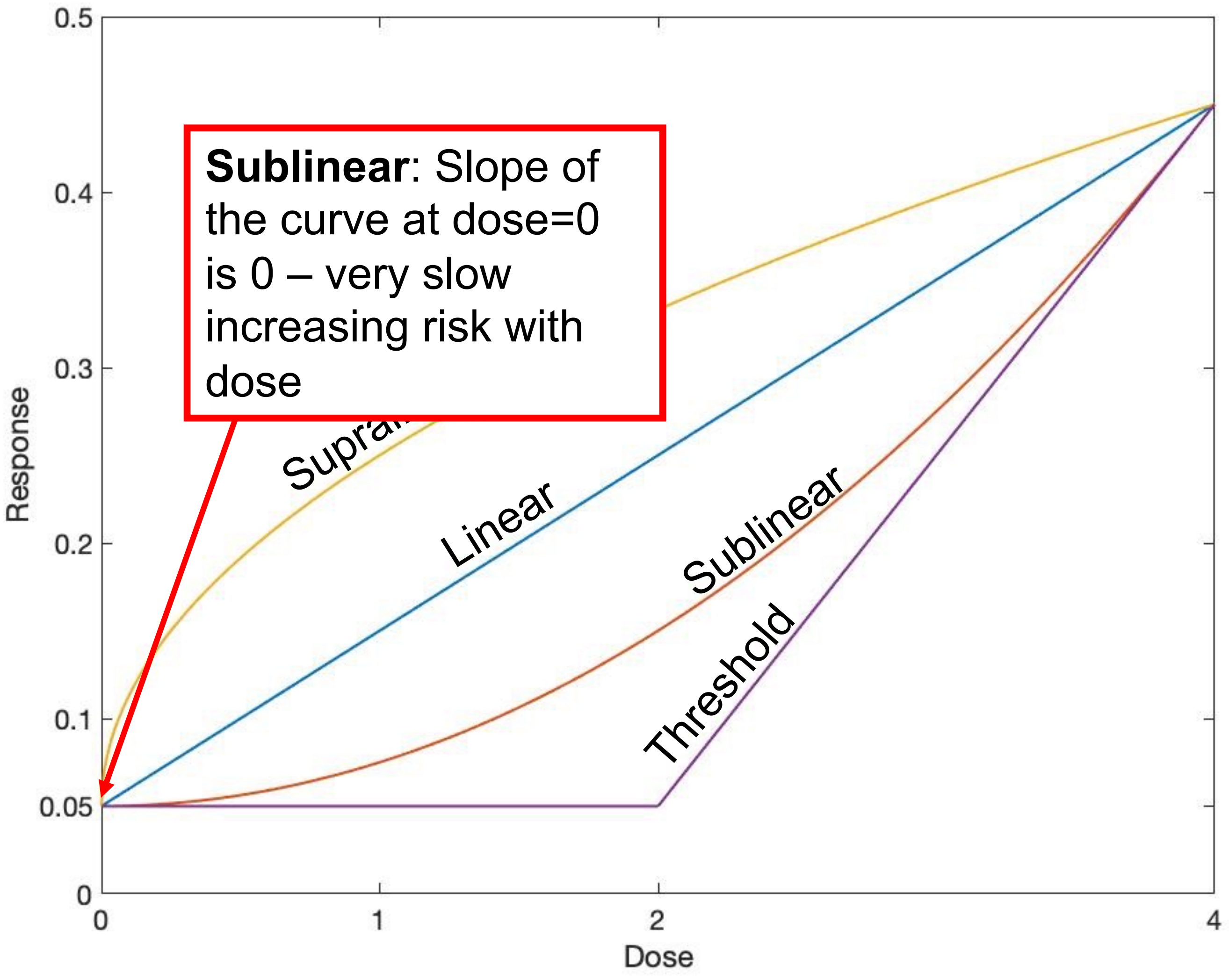
Dose-Response Shape (Monotonic)



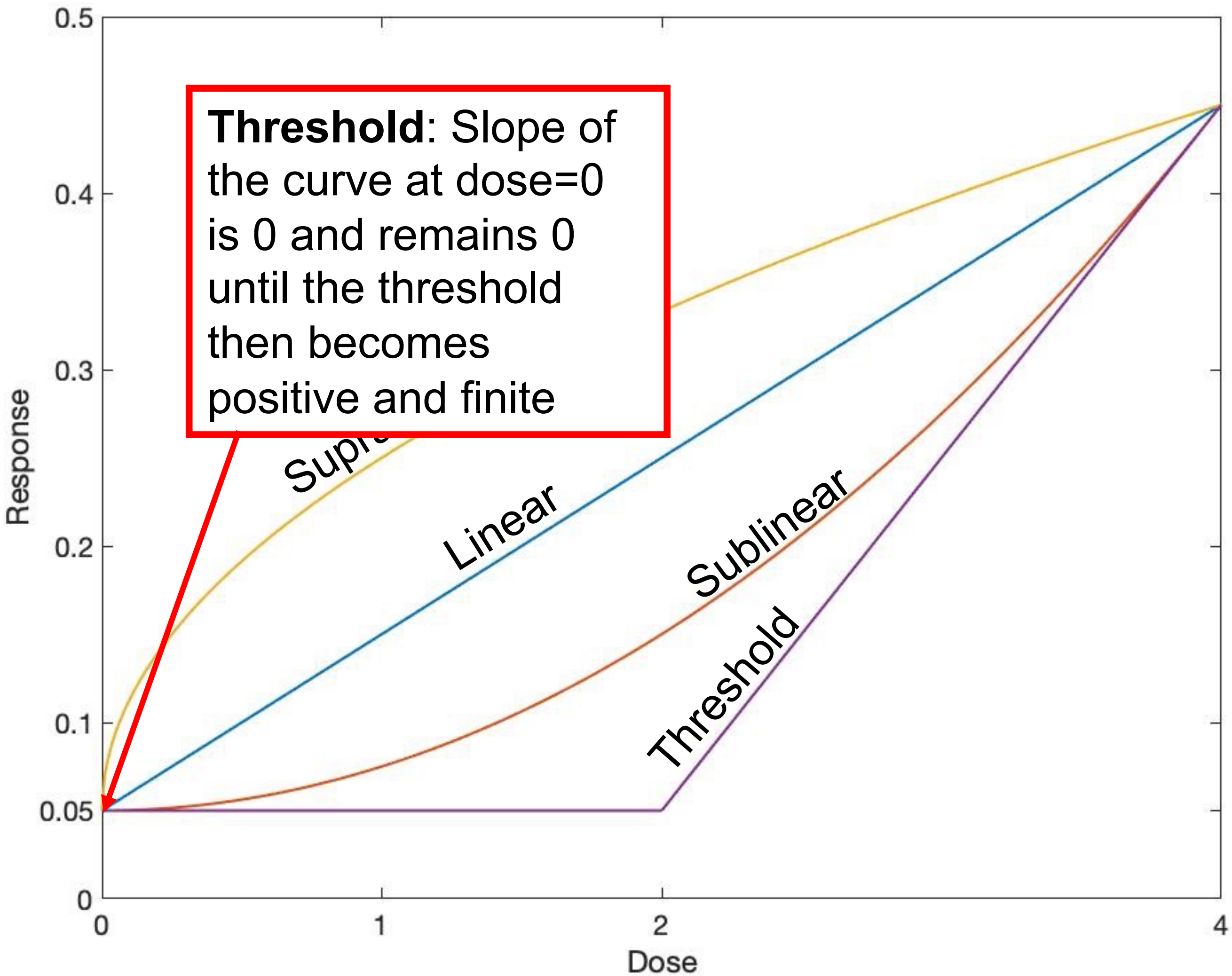
Dose-Response Shape (Monotonic)



Dose-Response Shape (Monotonic)

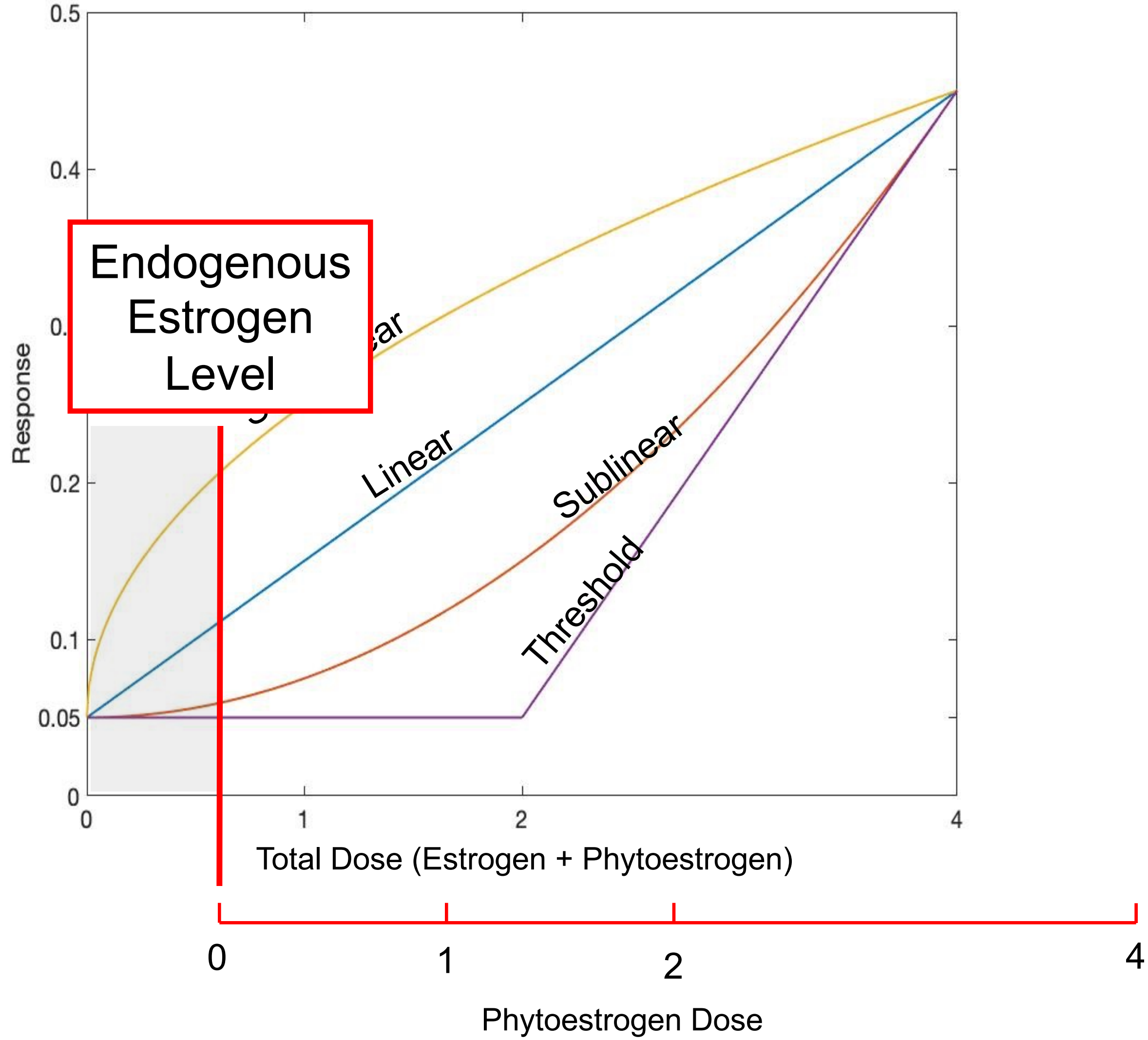


Dose-Response Shape (Monotonic)



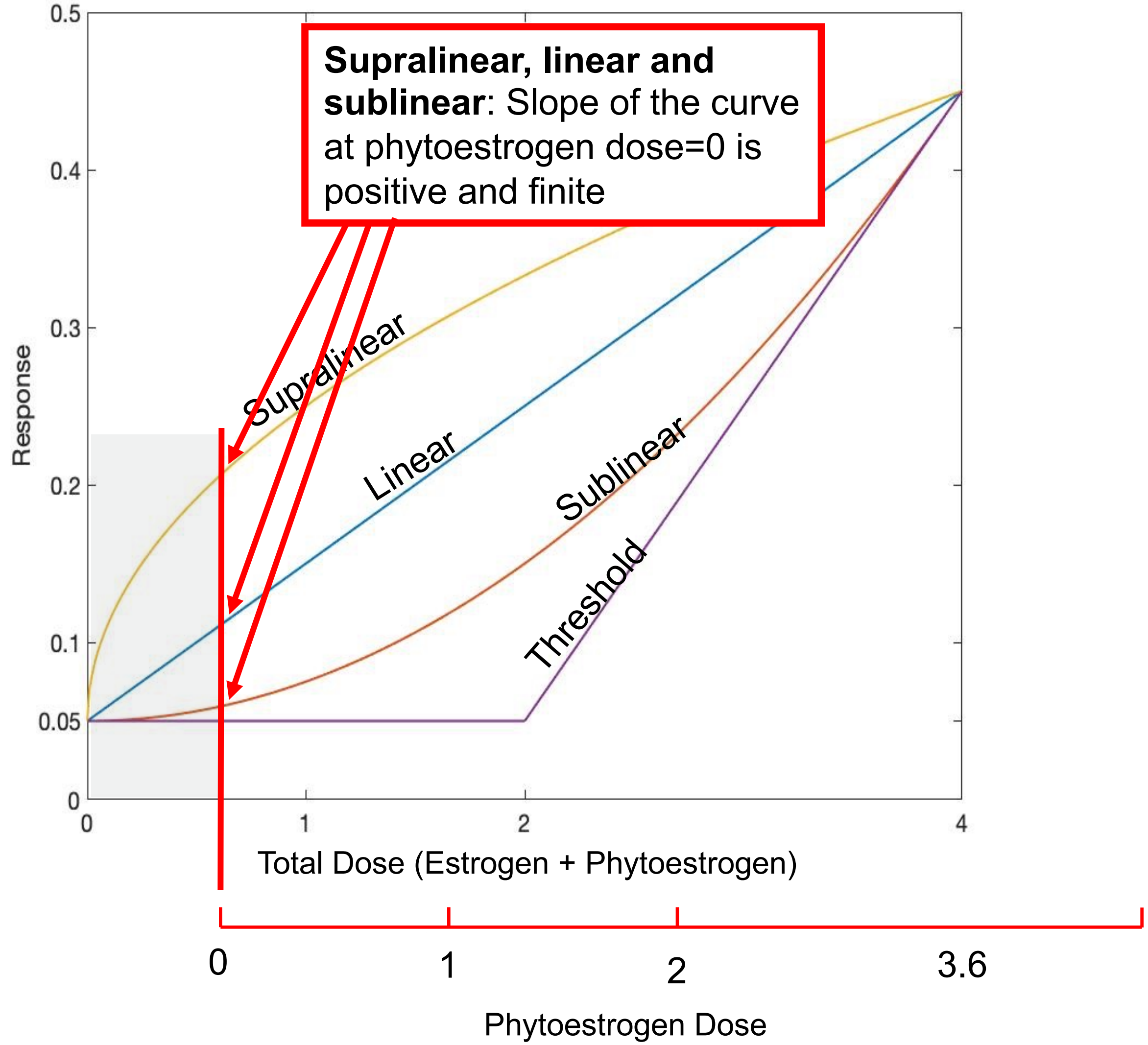
Additivity to Background

Example: Estrogen/Phytoestrogen



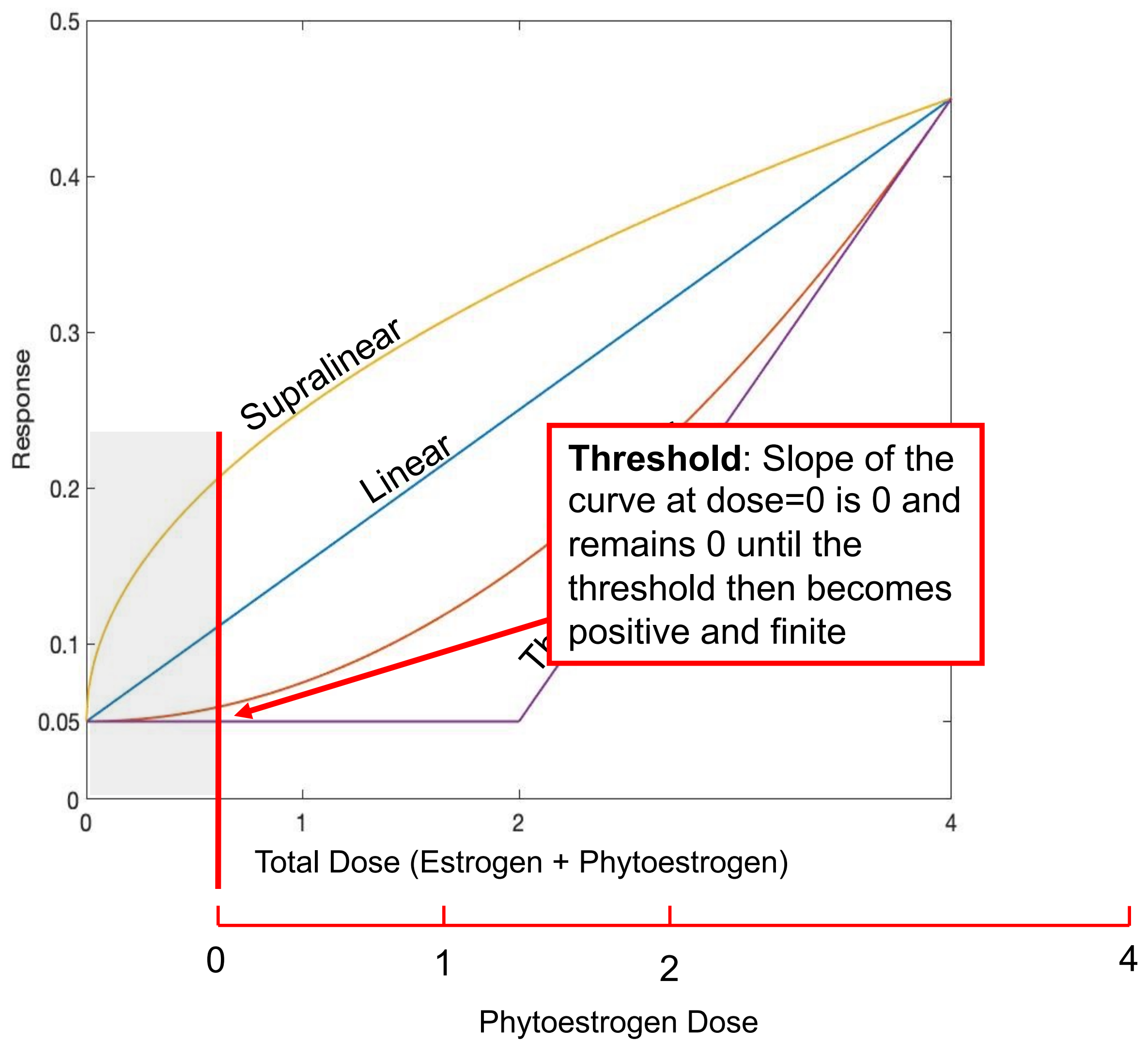
Additivity to Background

Example: Estrogen/Phytoestrogen



Additivity to Background

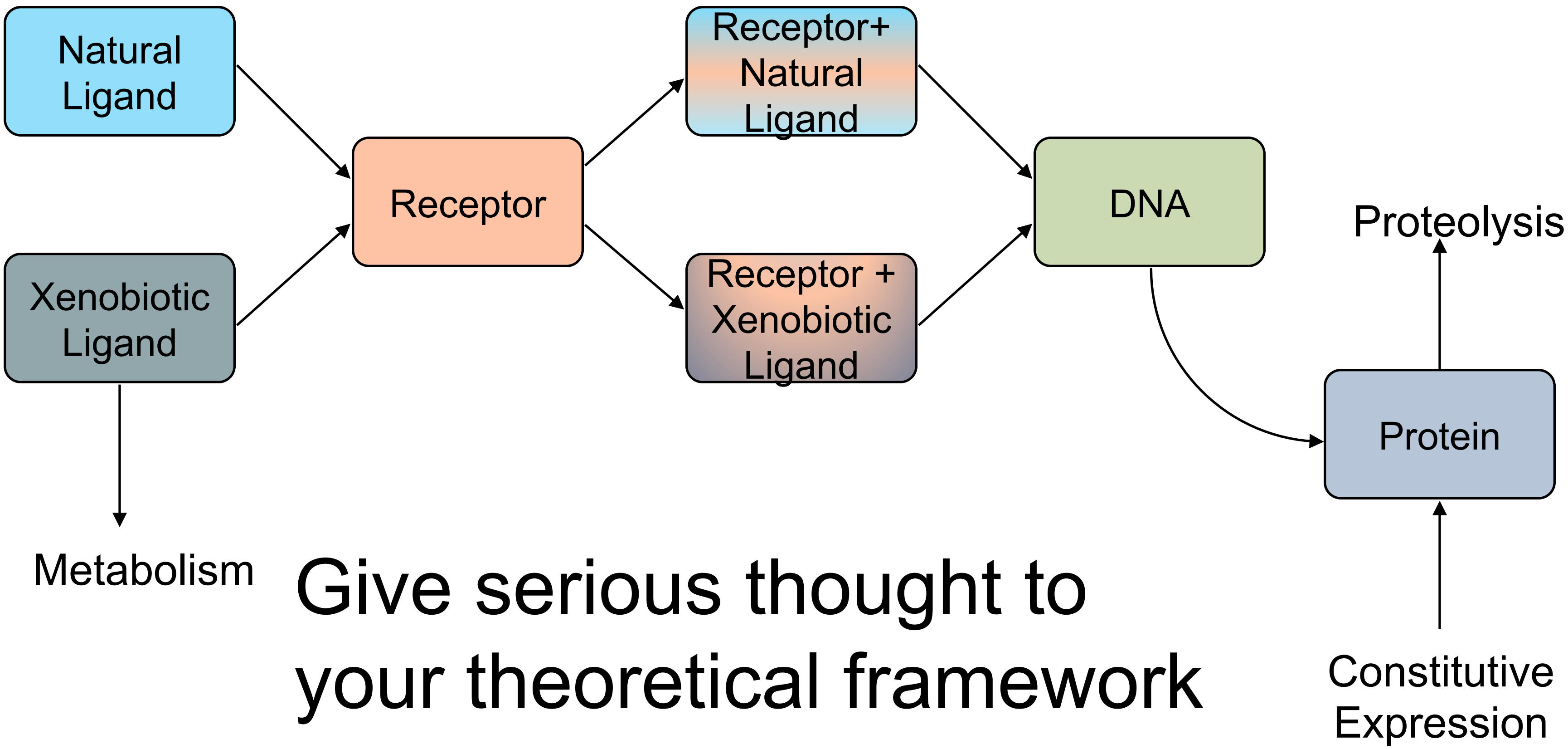
Example: Estrogen/Phytoestrogen



Consequences of Additivity

- Non-Threshold Models
  - At low doses, the dose-response can be modelled by a linear function (Taylor's Theorem)
  - Thus, even small doses increase risk
- Threshold Models
  - The existence of a threshold is a strong assumption
  - Can it be proven?

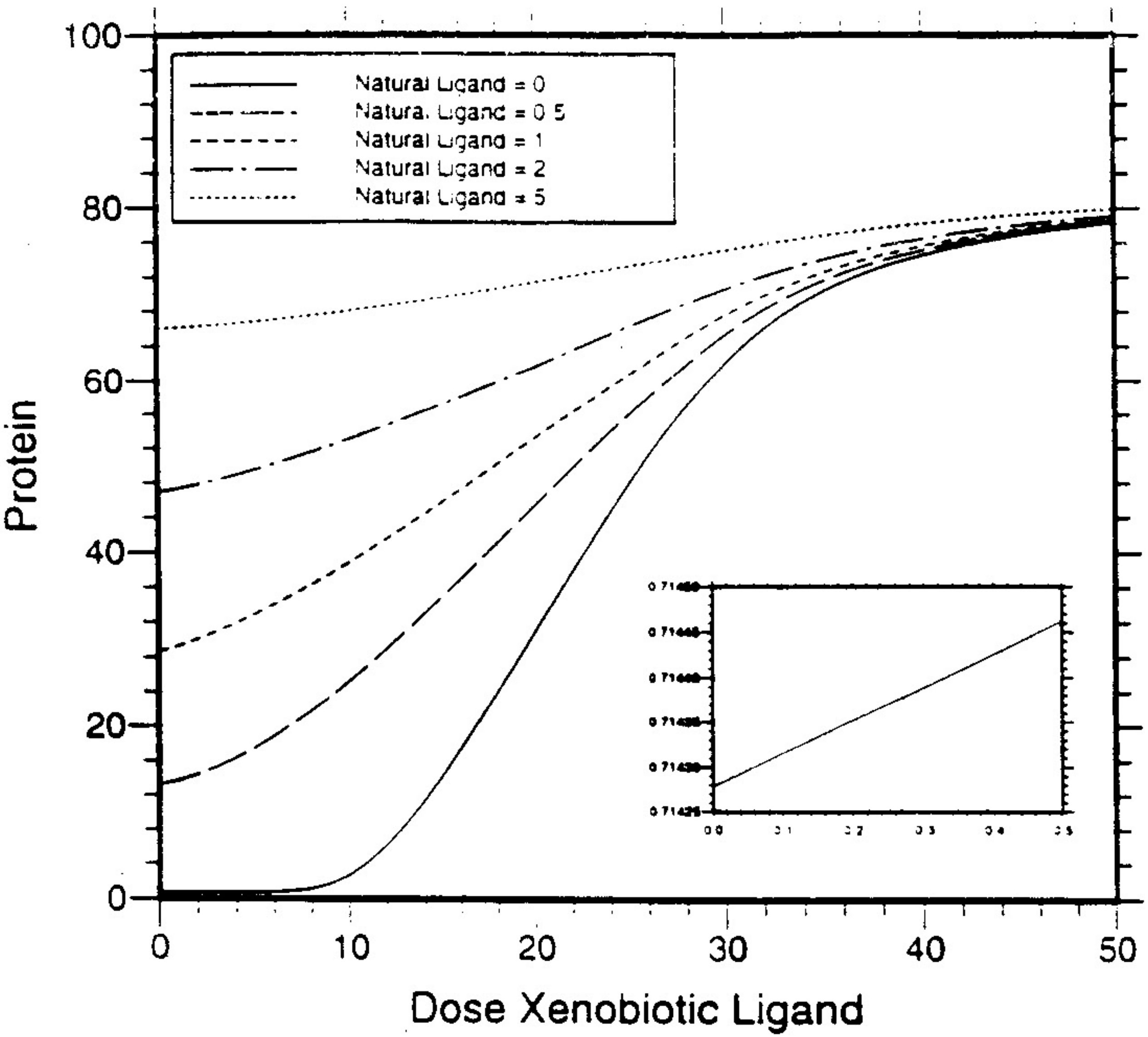
Unquantified Theory Can be Misleading: Minimal Receptor-Mediated Gene Expression



Give serious thought to your theoretical framework

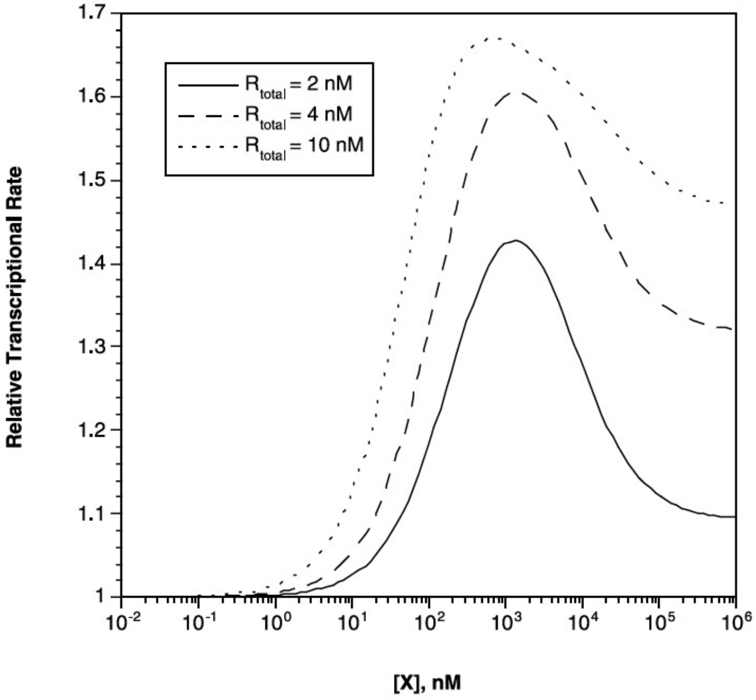
Kohn et al, 1993

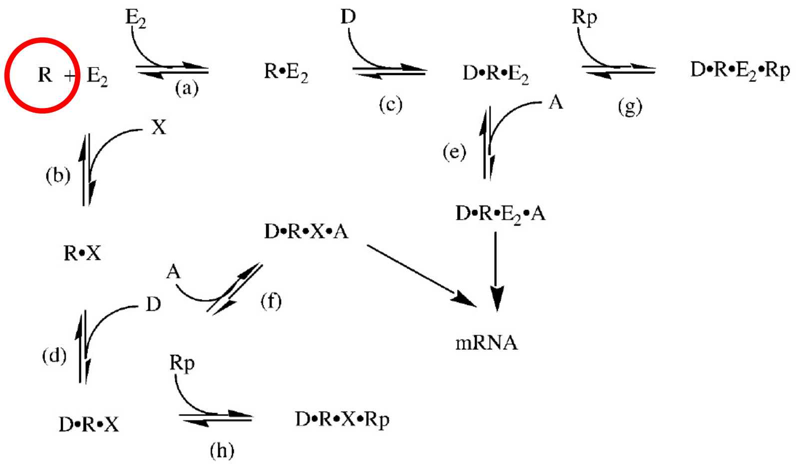
Additivity and Natural Ligands
no cooperative binding to receptor



Inset: low-dose behavior for no natural ligand

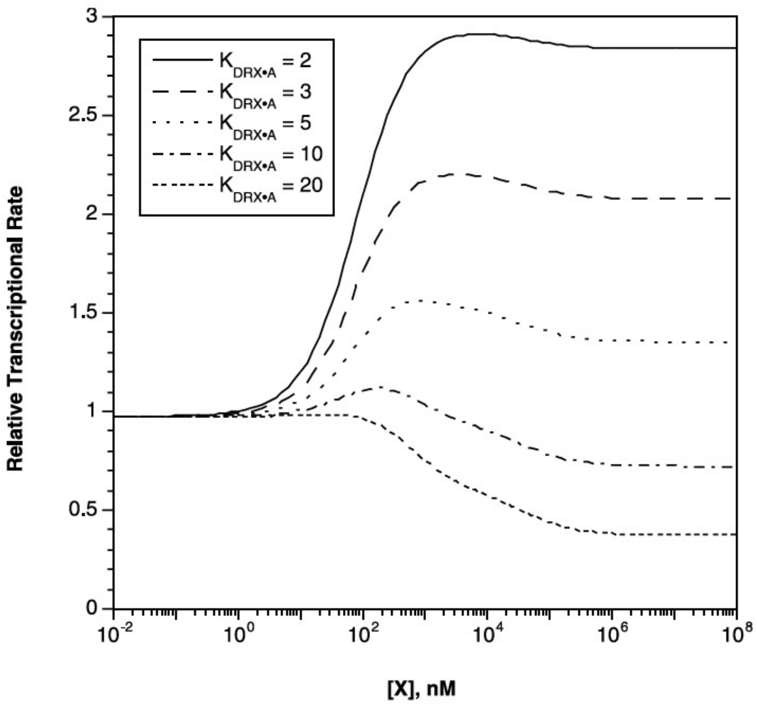
Changing the Amount of Receptor

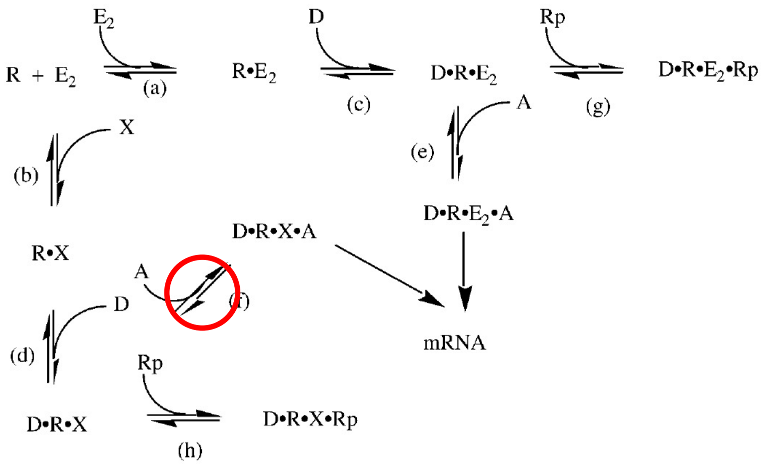




Kohn and Melnick, 2002

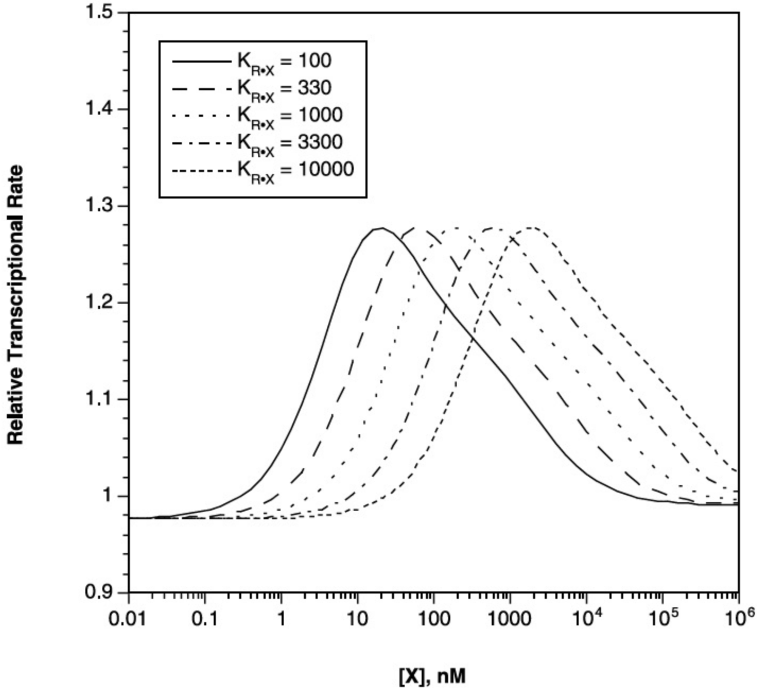
Changing the reaction rate for the co-activator

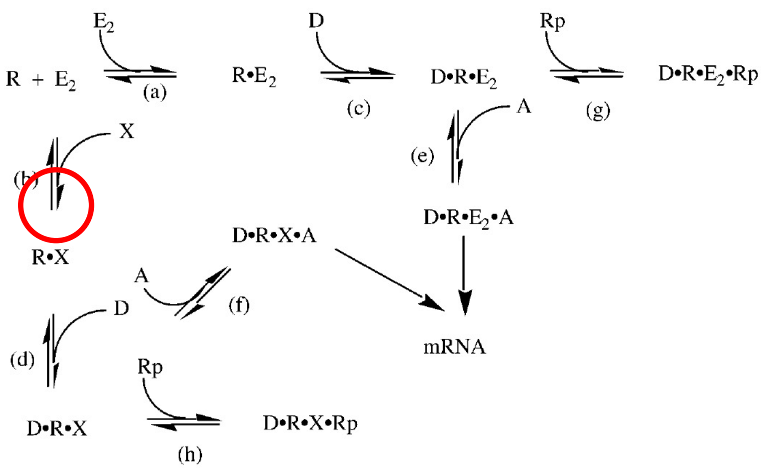




Kohn and Melnick, 2002

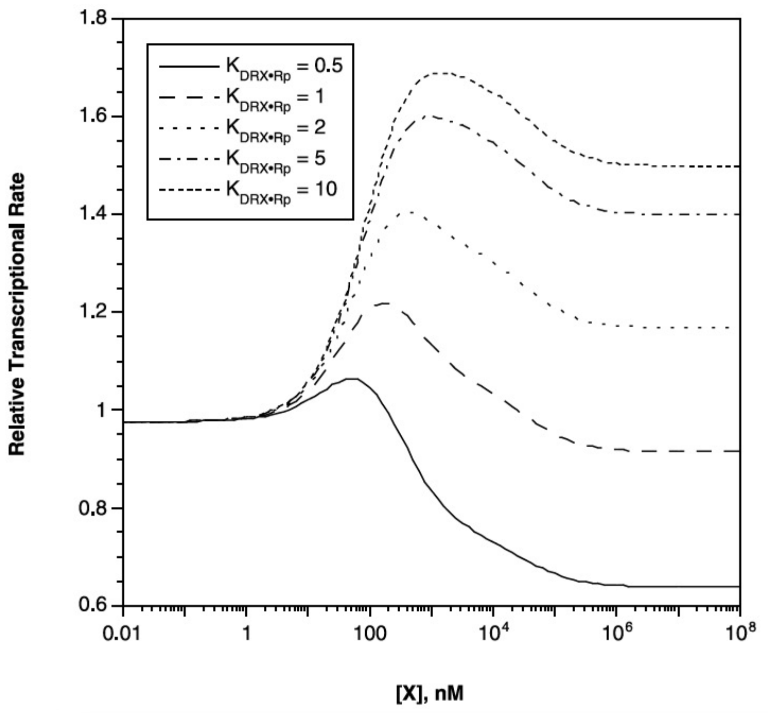
Changing the affinity of the receptor for the xenobiotic ligand

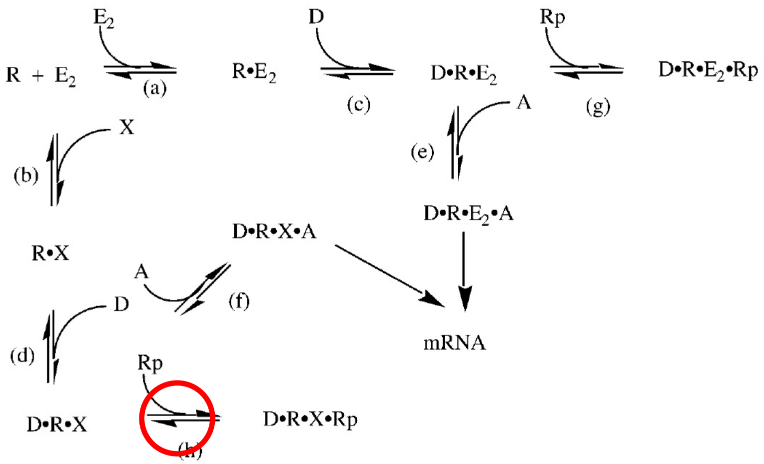




Kohn and Melnick, 2002

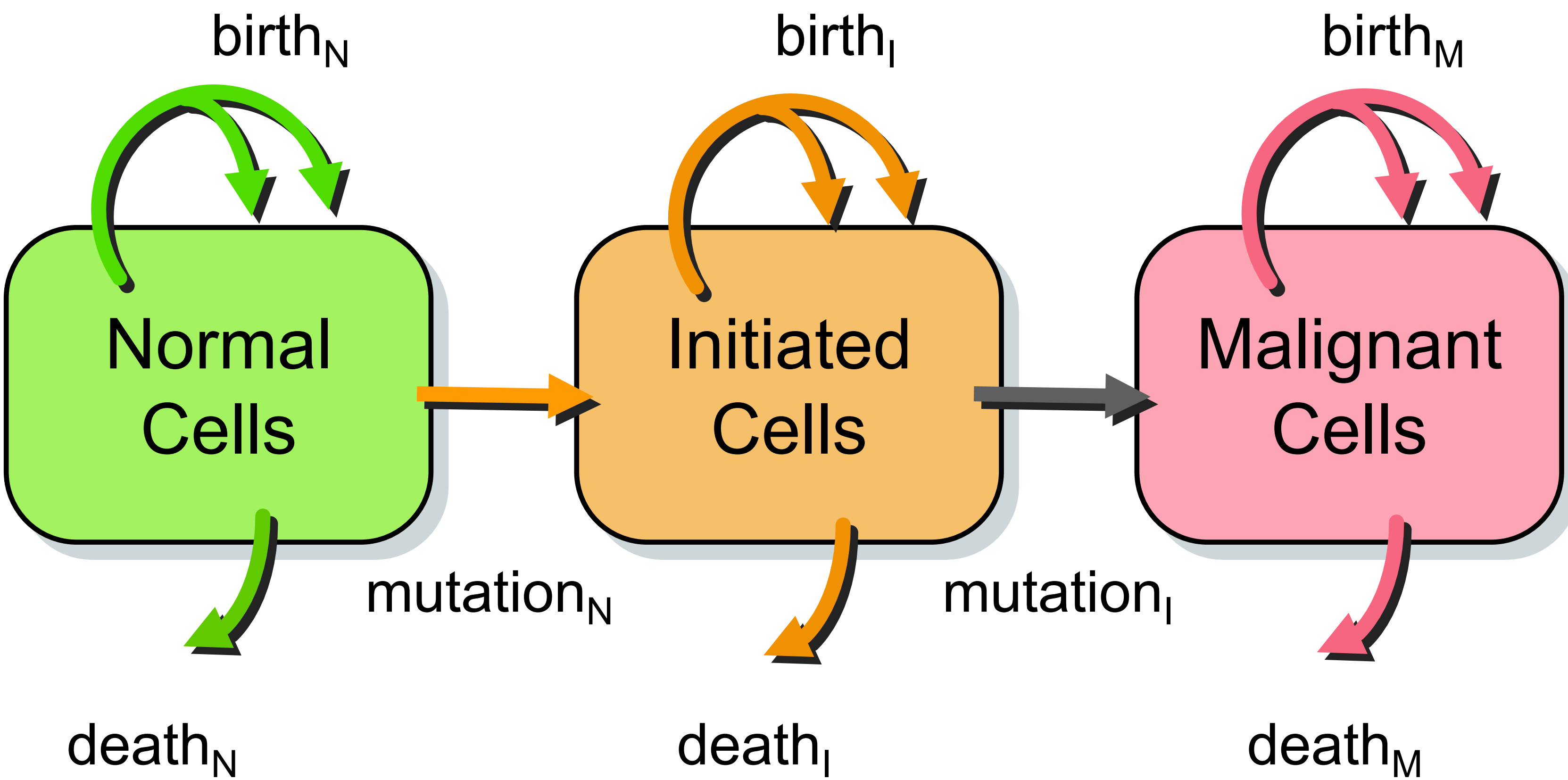
Changing the affinity of the bound xenobiotic/ligand/DNA for the repressor





Kohn and Melnick, 2002

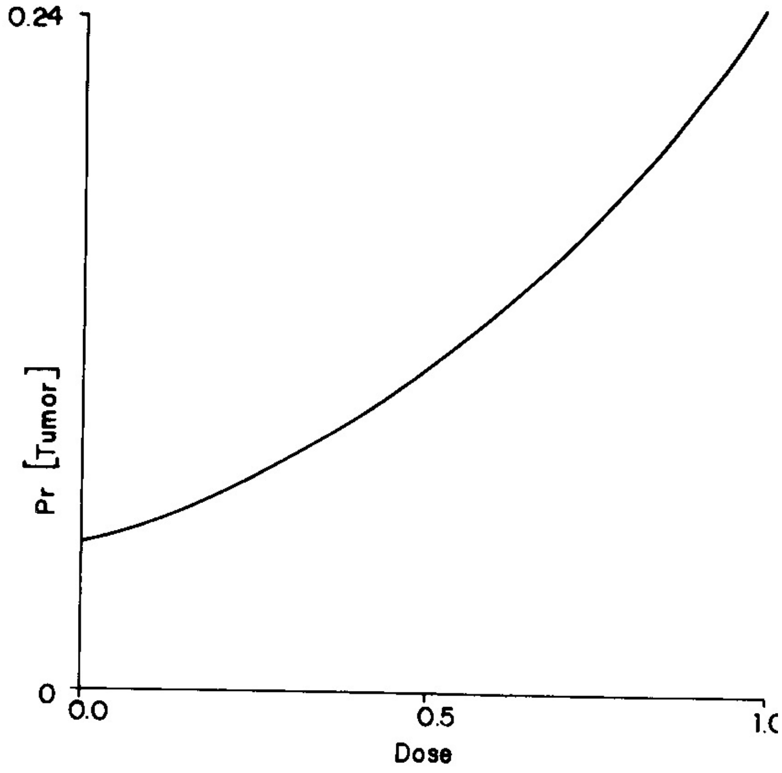
Two Stage Model of Cancer



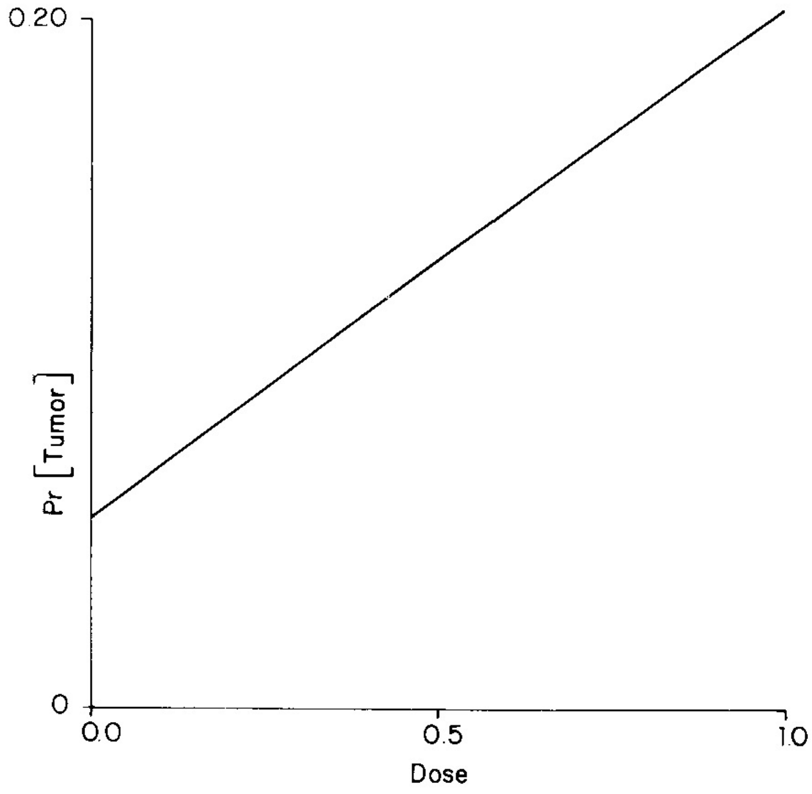
Initiator – Affects mutation rates
Promoter – Affects birth and/or death rates

Initiators versus Promoters

Initiator



Promoter



Conclusions from Theory

- How you handle existing processes relative to a xenobiotic make a big difference
- All types of shapes are possible depending upon the underlying processes
- There is no clear pattern that emerges

Shapes of Cancer Bioassay Dose-Response Curves

- 334 Rodent Bioassays
  - 315 Chemicals studied by NCI and NTP
  - 390 positive dose-response curves
- $P(d) = 1 - e^{\alpha+\beta d^k}$
- k=1 – linear model (L)
- k=2 – quadratic model (Q)
  - sublinear
- k=0.5 n- square-root model (SR)
  - supralinear

Consistency of Cancer Bioassay Data with Different Shapes

Part A: Testing for consistency with various models

L, SR, Q	L, SR	L, Q	SR only	L only	Q only	None <SR	None >Q
260 (67%)	36 (9.2%)	30 (7.7%)	7 (1.8%)	1 (0.3%)	35 (9.0%)	1 (0.3%)	20 (5.1%)

Part B: Comparing to Best Fits

SR	L	Q
129 (33%)	77 (20%)	184 (47%)

Consistency of Cancer Bioassay Data with Different Shapes and Ame's Salmonella Test

Part A: Testing for consistency with various models

Ame's Test	L, SR, Q	L, SR	L, Q	SR only	L only	Q only	None <SR	None >Q
+	150 (65.2%)	18 (7.8%)	18 (7.8%)	5 (2.2%)	1 (0.4%)	21 (9.1%)	1 (0.4%)	16 (7.0%)
-	92 (67.3%)	16 (11.7%)	10 (7.3%)	2 (1.5%)	0 (0.0%)	13 (9.5%)	0 (0.0%)	4 (2.9%)

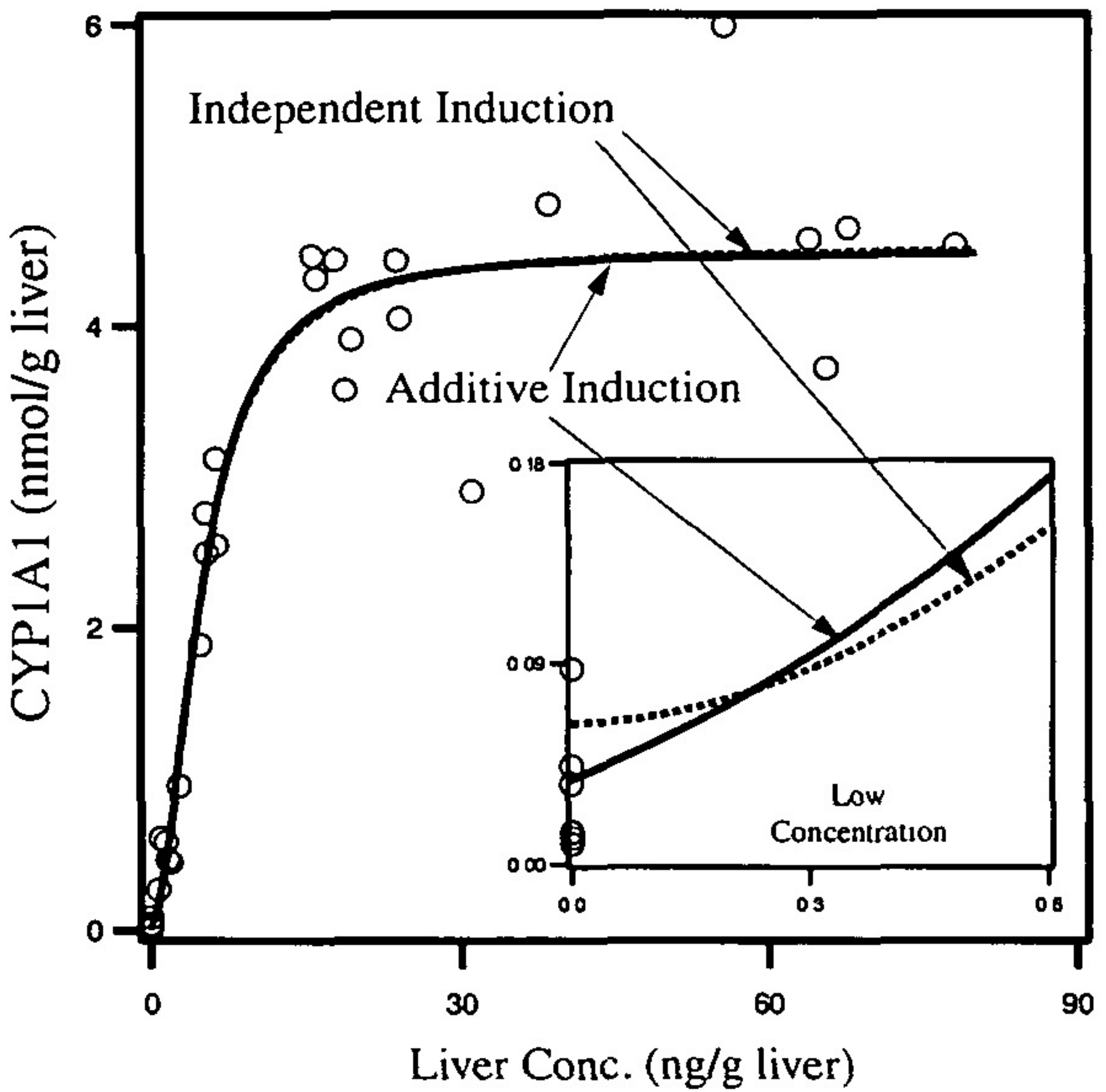
$p=0.605$

Part B: Comparing to Best Fits

Ame's Test	SR	L	Q
+	78 (33.9%)	43 (18.7%)	109 (47.4%)
-	41 (29.9%)	27 (19.7%)	69 (50.4%)

$p=0.732$

Modeling TCDD and CYP1A1 Induction



Portier et al. (1993)

Conclusions from Empirical Evaluations

- You generally do not have sufficient data to differentiate between models
- In general, the data can seldom tell you whether you have a threshold
  - This is an unsubstantiated assumption

Practical Considerations

- Thresholds in Engineering
  - Failure of a structure, machine, system, etc.
  - Safety factors used to account for uncertainty in point or probability of failure
- Thresholds in chemistry
  - Usually associated with state change
    - Liquid to gas or solid
  - Unlikely with continuous biochemical reactions in human cells
  - Most likely approach should be non-linear models that are mechanism-based