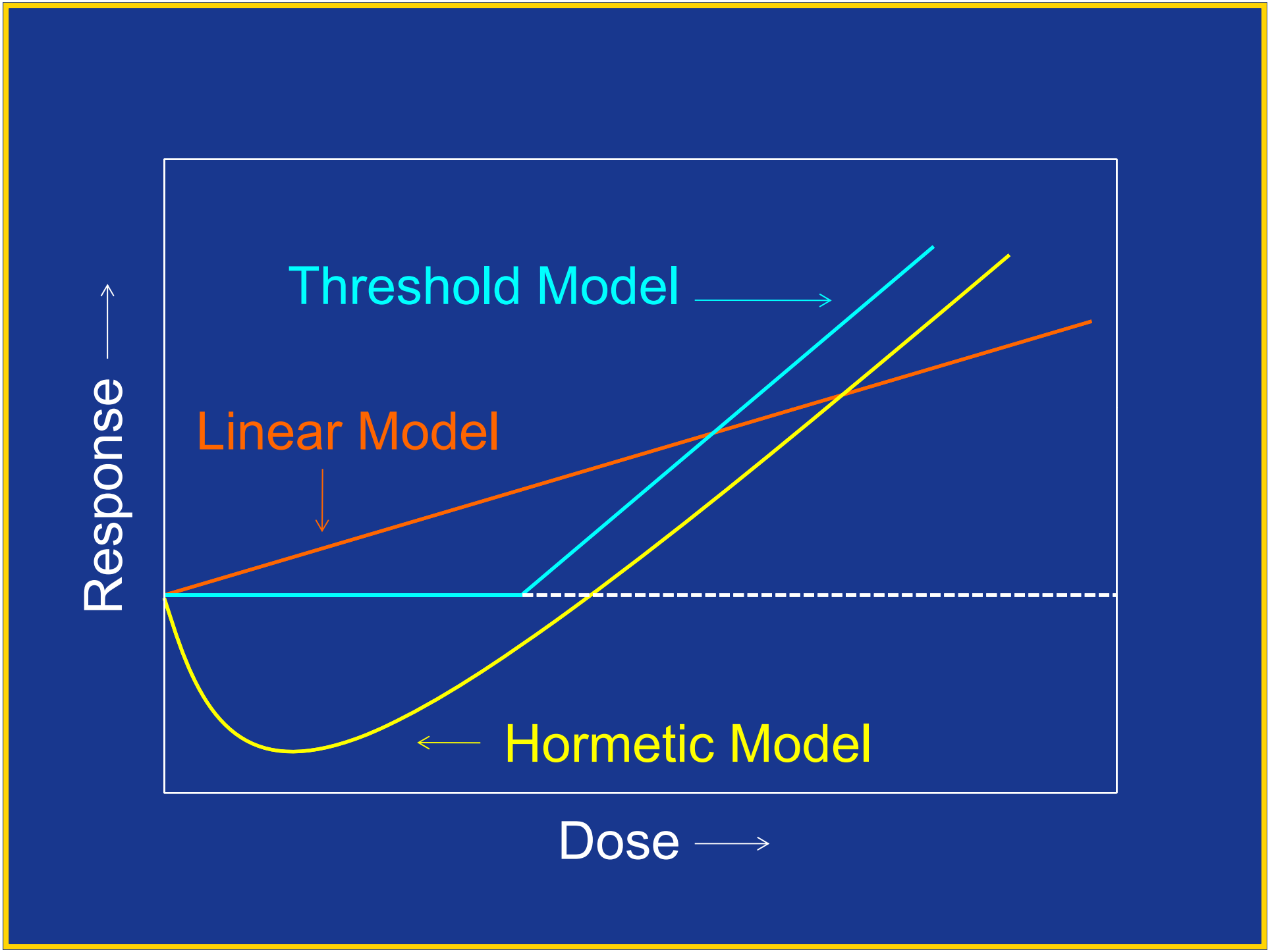
Integration of Hormesis & LNT Optimizes Cancer Risk Assessment

Edward J. Calabrese, Ph.D.

Environmental Health Sciences
University of Massachusetts
Amherst, MA 01003
Phone: 413-545-3164
E-mail: edwardc@schoolph.umass.edu

Hormesis & LNT

This presentation accepts the validity of both hormesis and LNT, that both models deserve an equal seat at the risk assessment table and can be integrated to estimate the optimal public health response.


Threshold Model
Linear Model
Hormetic Model
Response
Dose

Reconciling Hormesis & LNT

It is possible to integrate these two apparently opposing/divergent dose response models.

Integrating Hormesis & LNT

Even though I am an advocate of the hormesis model, it is not the intention of this presentation to make the scientific case for hormesis or to criticize LNT.

Integrating Hormesis & LNT

I will present a brief description of the hormetic dose response model for background purposes and to facilitate the subsequent integration of LNT and hormesis.

Hormesis

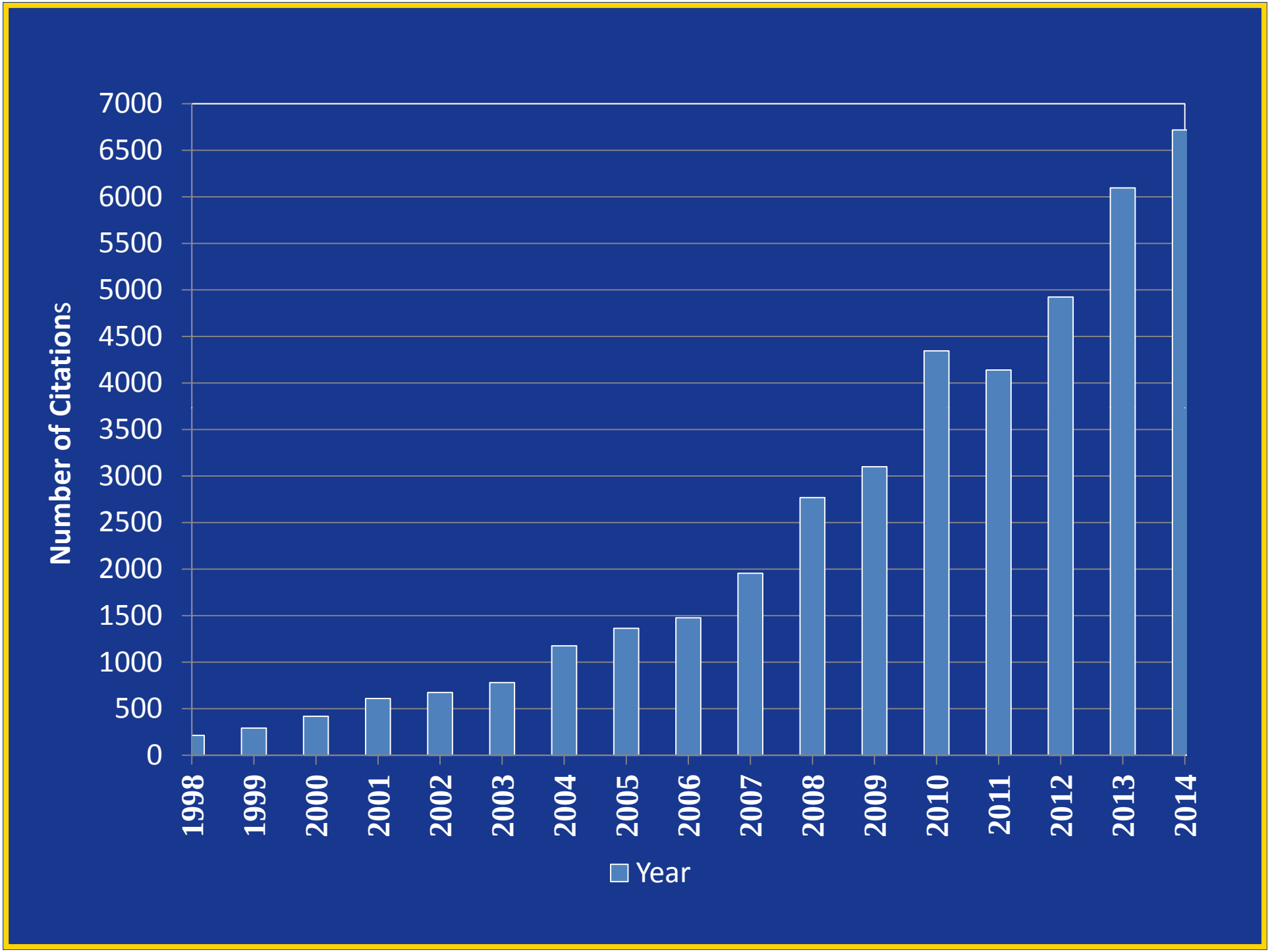
Dose-response phenomenon characterized by a low-dose stimulation and a high-dose inhibition.

It is a non-monotonic/biphasic dose response, with specific dose response features.

Evidence of Hormesis

Hormesis databases:

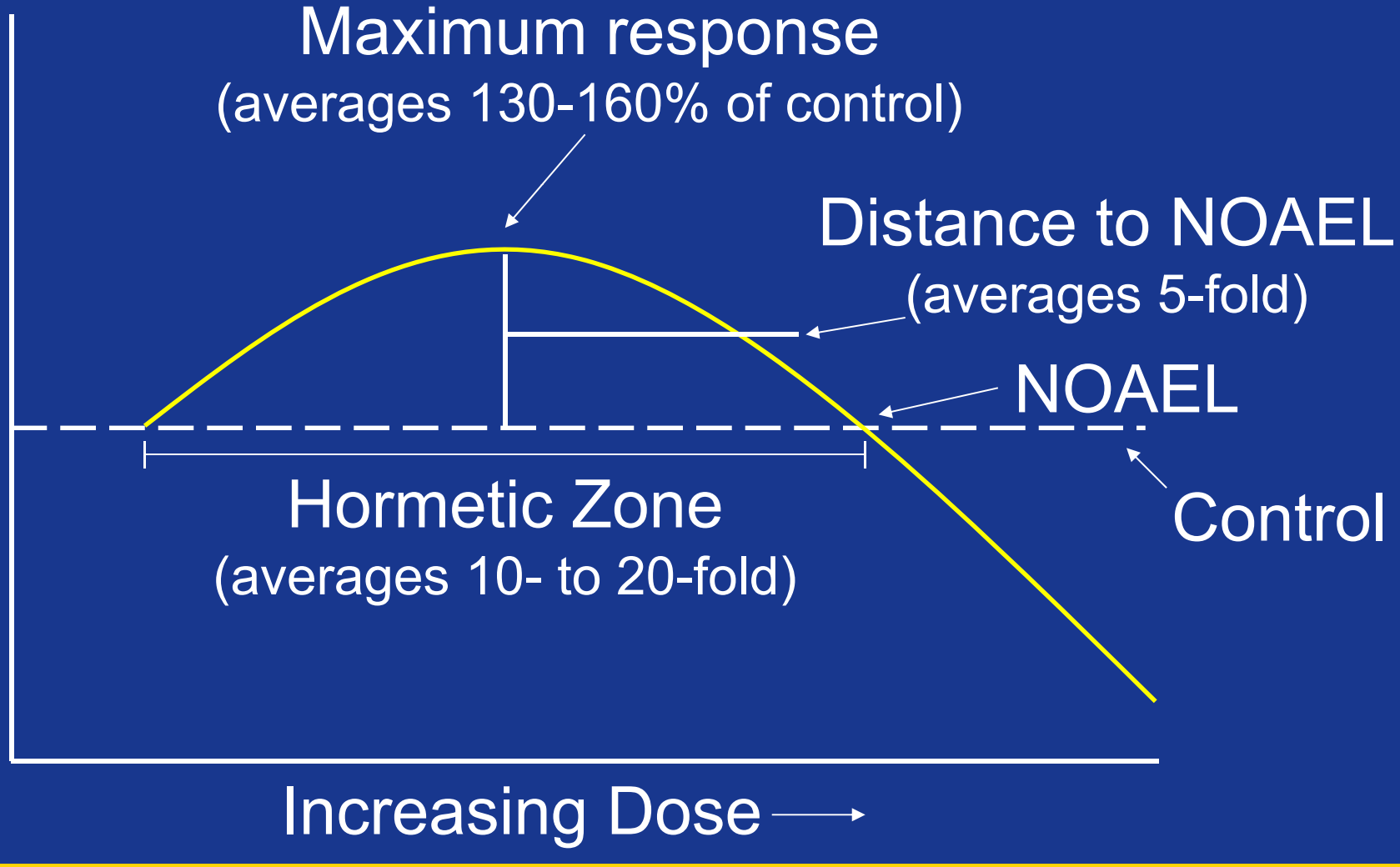
many thousands of dose responses are indicative of hormesis using rigorous entry/evaluative criteria.


Number of Citations
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
Year

Hormesis: a very general phenomenon

Independent of model (e.g., plant, microbial, invertebrate, vertebrate, human, in vitro/in vivo), endpoint, agent, level of biological organization (i.e. cell, organ, individual) and mechanism.

The Quantitative Features of Hormesis



Generally, similar quantitative features with respect to amplitude and range of the stimulatory response.

Hormesis & Stimulation

Modest amplitude;

30-60% Greater than control;

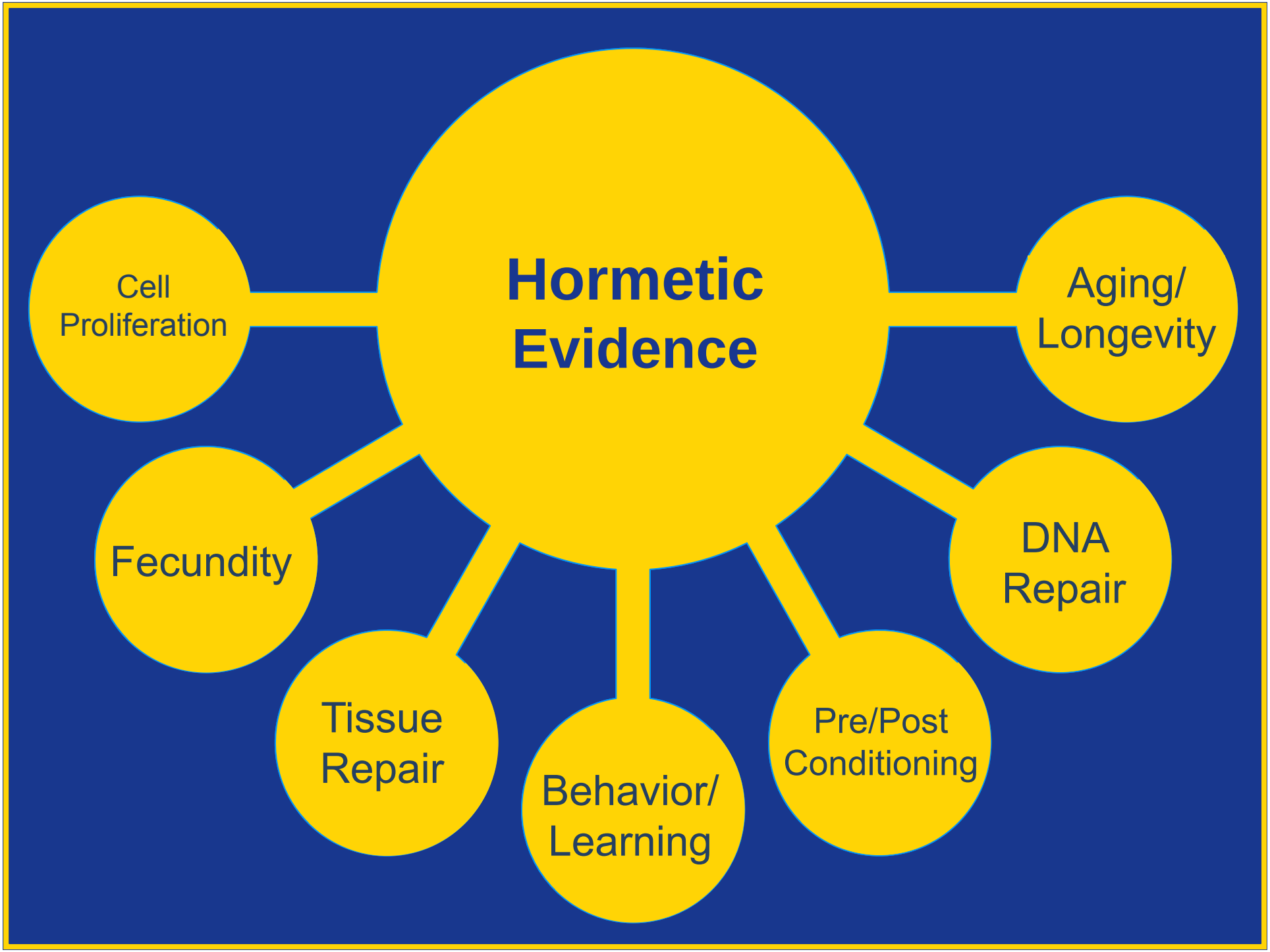
Usually, not more than 100% greater than the control.

Stimulatory Range

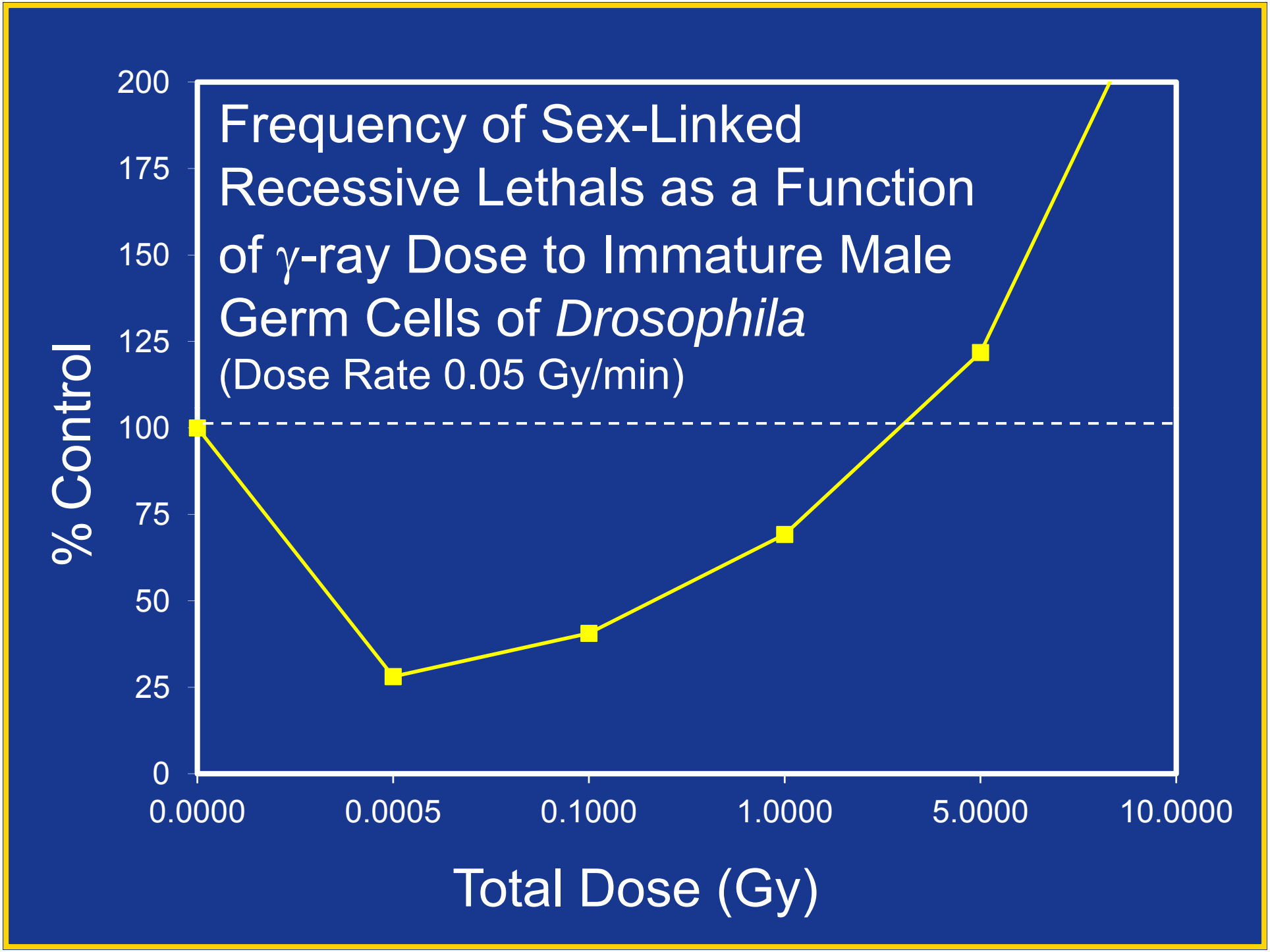
~75 % of the dose responses;

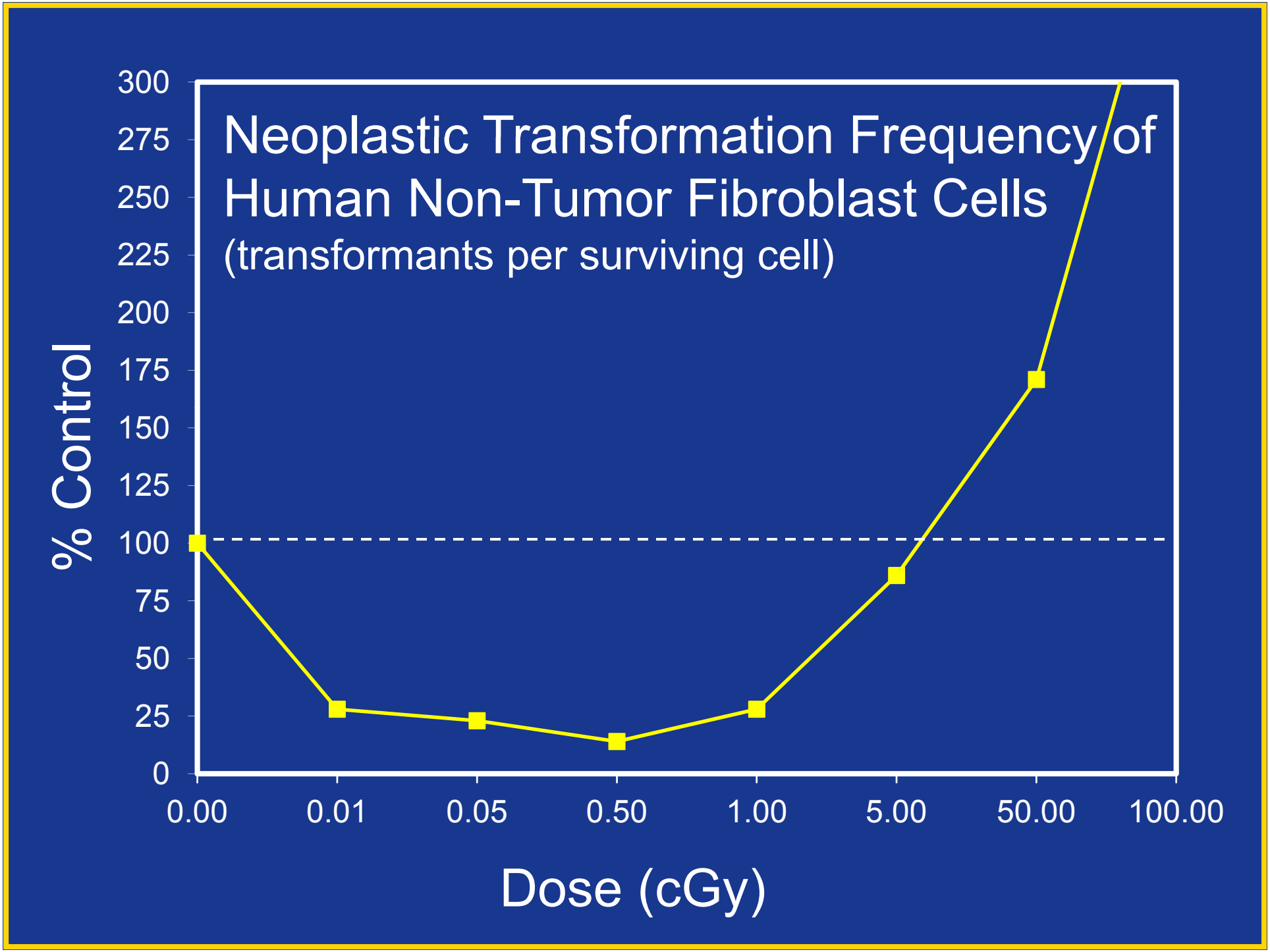
Within 20-Fold of NOEL/NOAEL

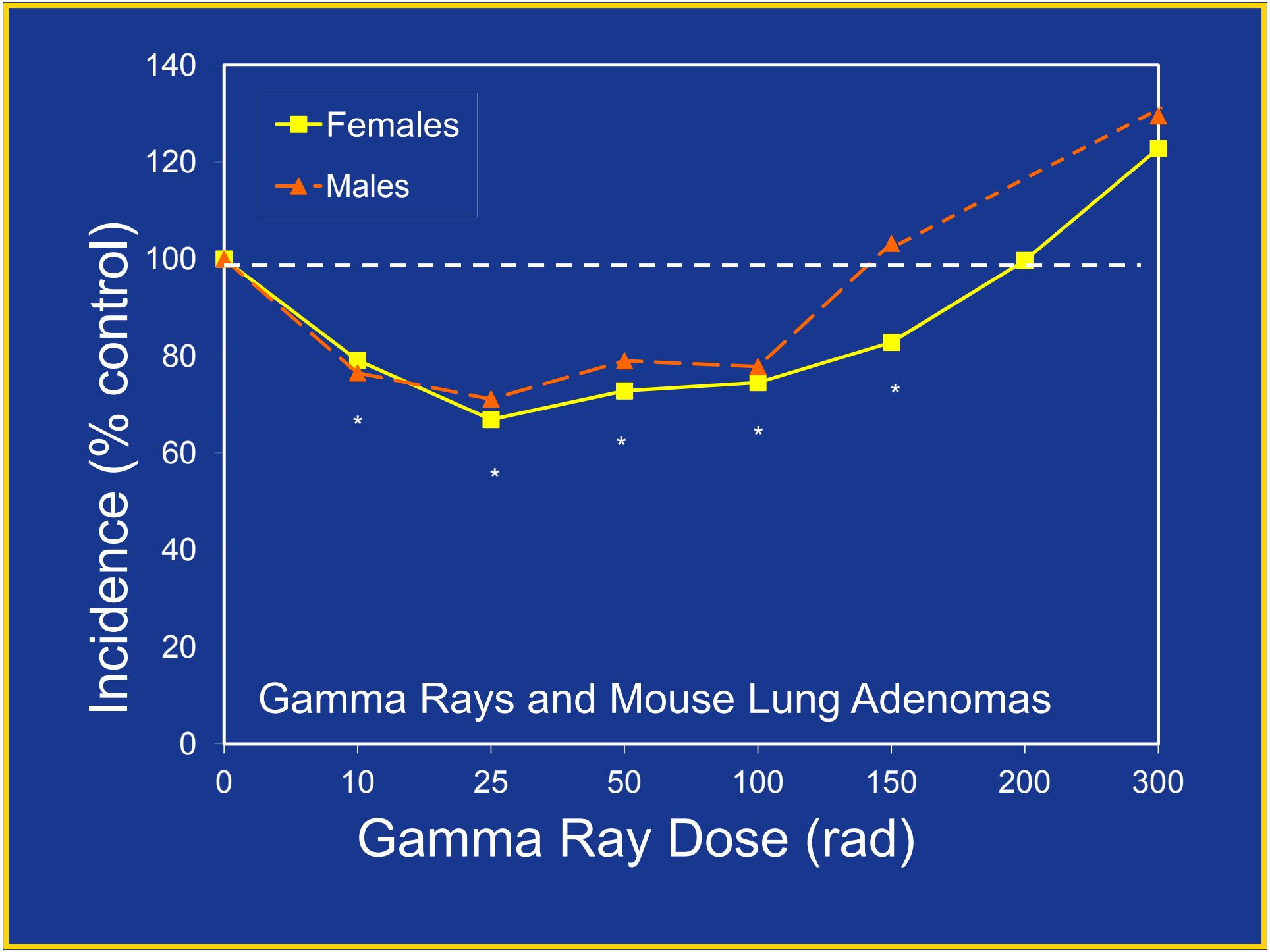
Hormetic responses are integrative endpoints across multiple levels of biological organization

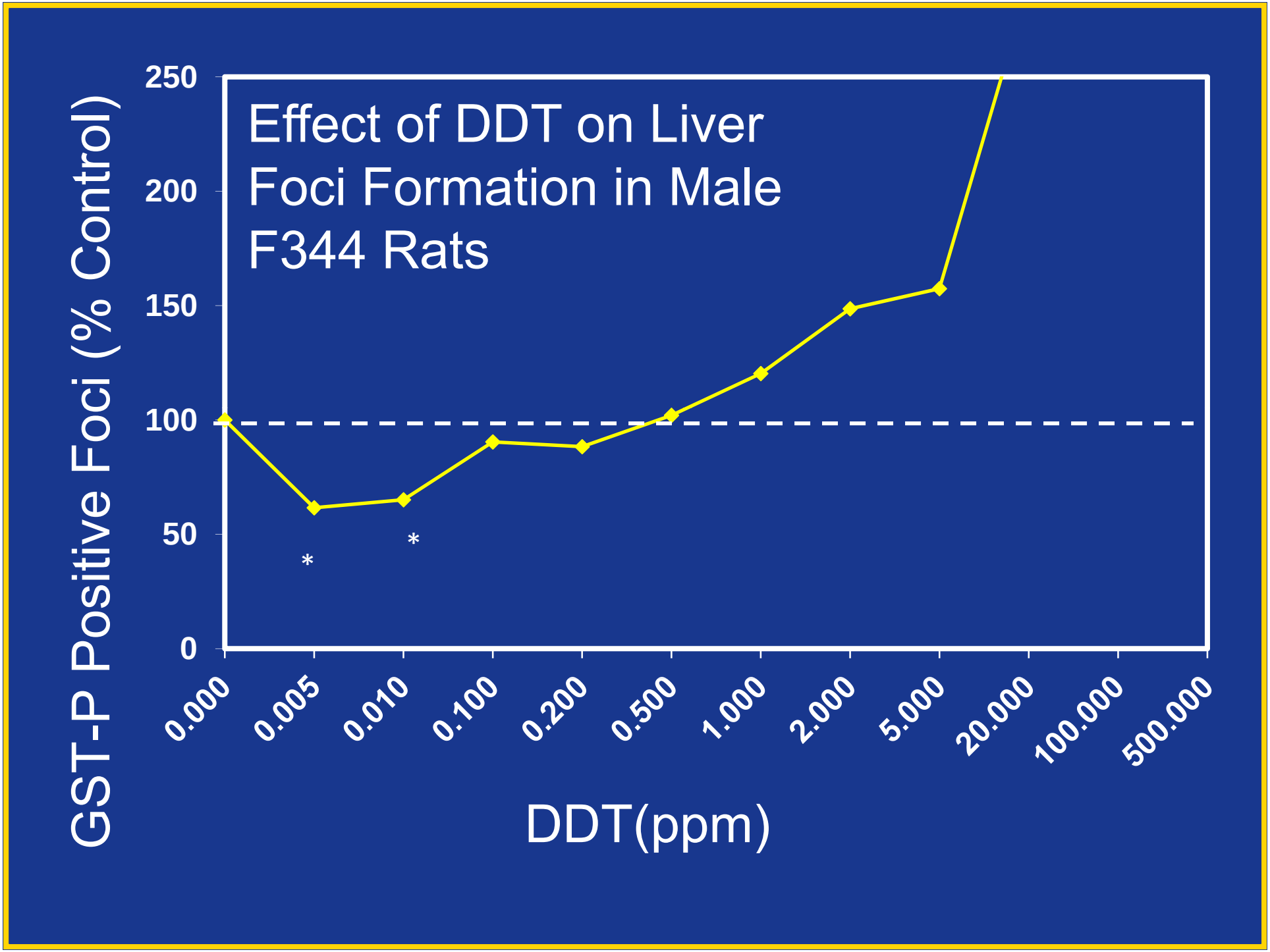

Hormetic Evidence
Cell Proliferation
Aging/ Longevity
Fecundity
DNA Repair
Tissue Repair
Behavior/ Learning
Pre/Post Conditioning

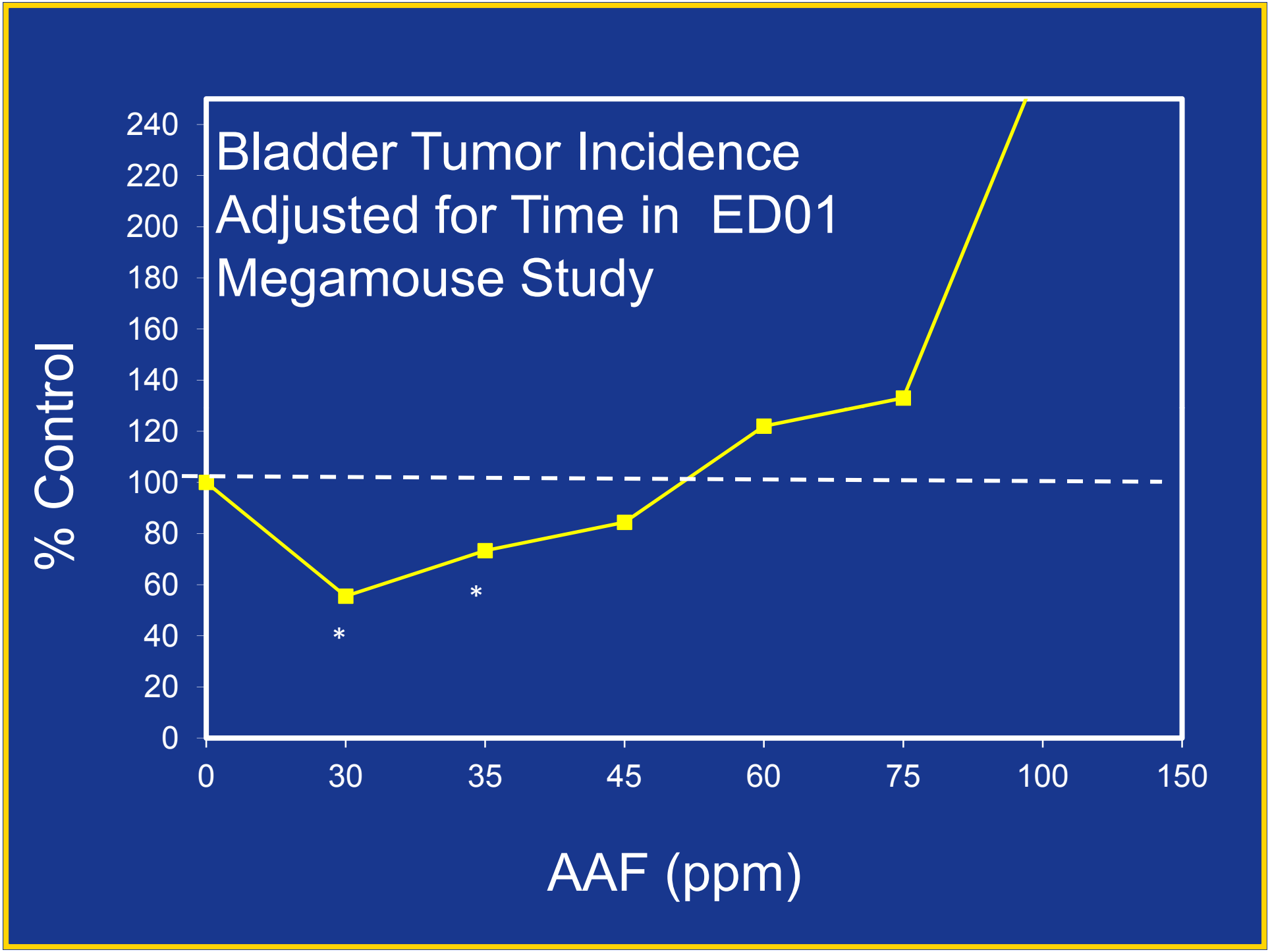
Hormetic Dose Responses Relating to the Process of Carcinogenesis


Frequency of Sex-Linked Recessive Lethals as a Function of γ-ray Dose to Immature Male Germ Cells of *Drosophila*
(Dose Rate 0.05 Gy/min)
% Control
200
175
150
125
100
75
50
25
0
0.0000
0.0005
0.1000
1.0000
5.0000
10.0000
Total Dose (Gy)

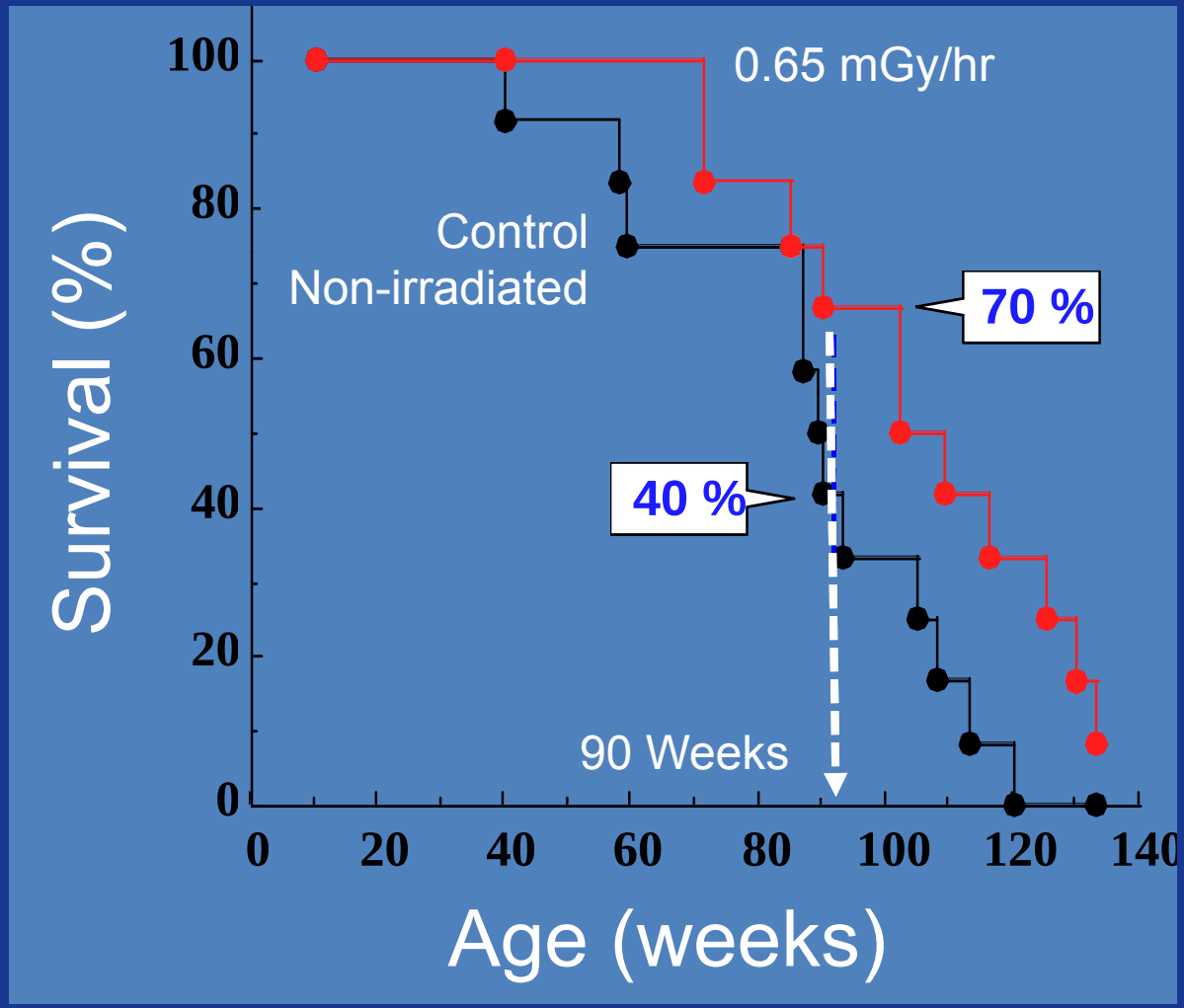

Neoplastic Transformation Frequency of Human Non-Tumor Fibroblast Cells
(transformants per surviving cell)
% Control
300
275
250
225
200
175
150
125
100
75
50
25
0
0.00
0.01
0.05
0.50
1.00
5.00
50.00
100.00
Dose (cGy)


Females
Males
Incidence (% control)
140
120
100
80
60
40
20
0
Gamma Rays and Mouse Lung Adenomas
0
10
25
50
100
150
200
300
Gamma Ray Dose (rad)


Effect of DDT on Liver Foci Formation in Male F344 Rats
GST-P Positive Foci (% Control)
250
200
150
100
50
0
*
*
0.000
0.005
0.010
0.100
0.200
0.500
1.000
2.000
5.000
20.000
100.000
500.000
DDT(ppm)


Bladder Tumor Incidence
Adjusted for Time in ED01
Megamouse Study
% Control
240
220
200
180
160
140
120
100
80
60
40
20
0
0
30
35
45
60
75
100
150
*
*
AAF (ppm)

Prolongation of Life Span by Low Dose Irradiation



Appearance of db/db mice at 90th week of age

Irradiated Group

Control Group

Model Uncertainty & Response Optimization

The integration of hormesis and LNT responses can provide lower & upper bounds of population-based responses for cancer risk assessment.

Model Uncertainty & Response Optimization

The goal would be to identify the dose which yields the most favorable public health response (i.e., lowest proportion of adversely affected people) across the dose response continuum.

How would this be done?

Identify an optimal public health response within a framework of dose response model uncertainty.

Hormesis/LNT Convergence

Hormetic Method

- *Calabrese & Cook, 2005*
- *Calabrese et al., 2015a, b*

LNT Method

- *Gaylor, 1989*
- *Based on Howe and Crump (1982)*

Convergence Steps

Hormetic Method	LNT Method
Step 1: Same	**Step 1:** Estimate 1% response from animal bioassay via a BMD
Step 2: Apply UF of 10-fold	**Step 2:** Divide BMD_{01} by 100-fold (two UFs)
Step 3: Estimate optimized hormetic response	**Step 3:** Estimate risk at $BMD_{01}/100 \cong 10^{-4}$
Best estimate ~10-fold below human BMD_{01} (could range from 5-≥100-fold)	

Hormesis/LNT Convergence

Hormetic Method LNT Method

Both approaches converge at the same dose;

Achieve optimized hormetic benefit (30-60% lower disease incidence than control) at dose where LNT shows a 10^{-4} risk

This provides the bounds of model uncertainty.

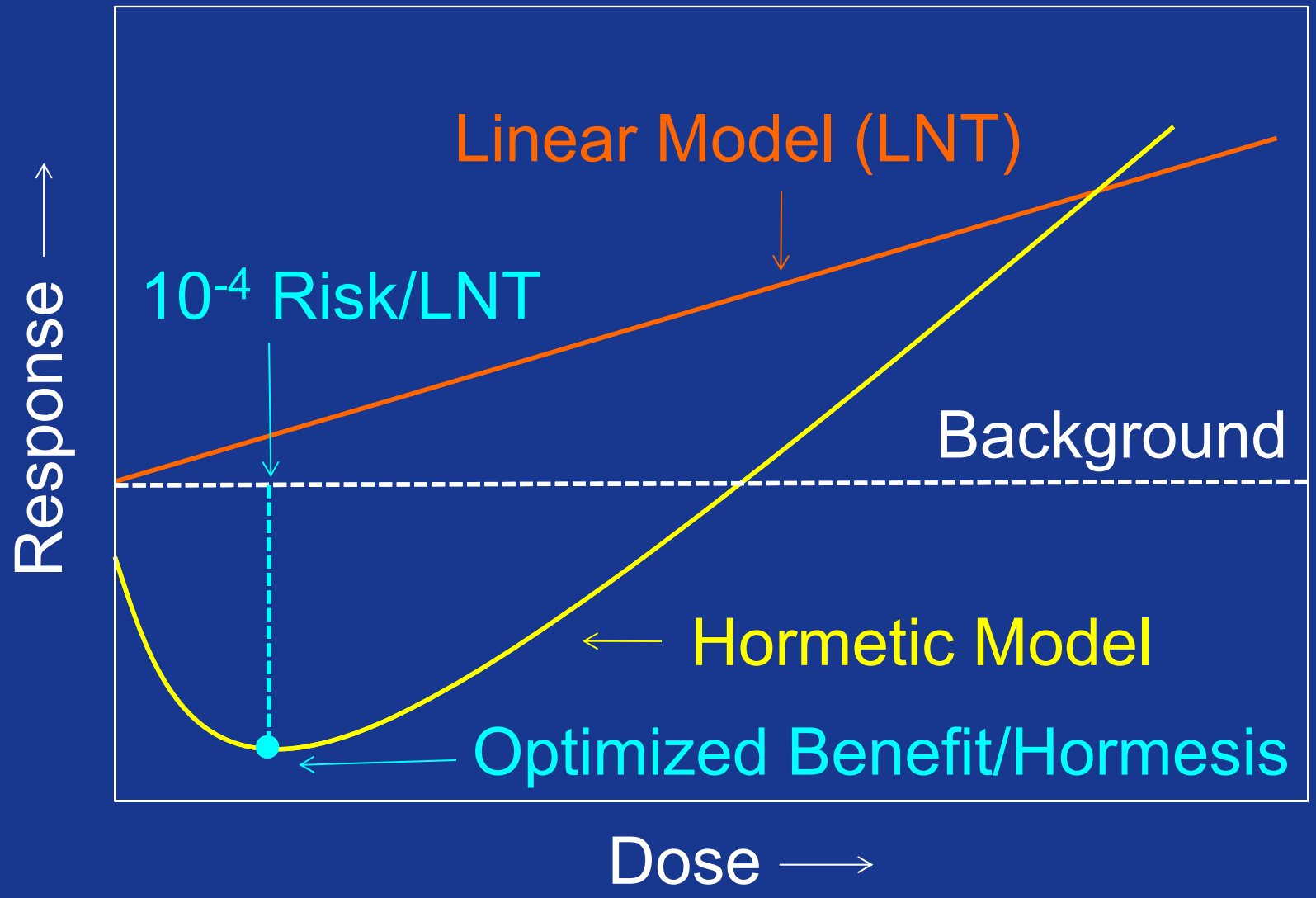
Proposal

Adopt an acceptable risk of 10^{-4} using the LNT model since this dose also yields the optimal hormetic dose-response benefit with the lowest cancer incidence in the population.

10^{-4} = Regulatory "Sweet Spot"

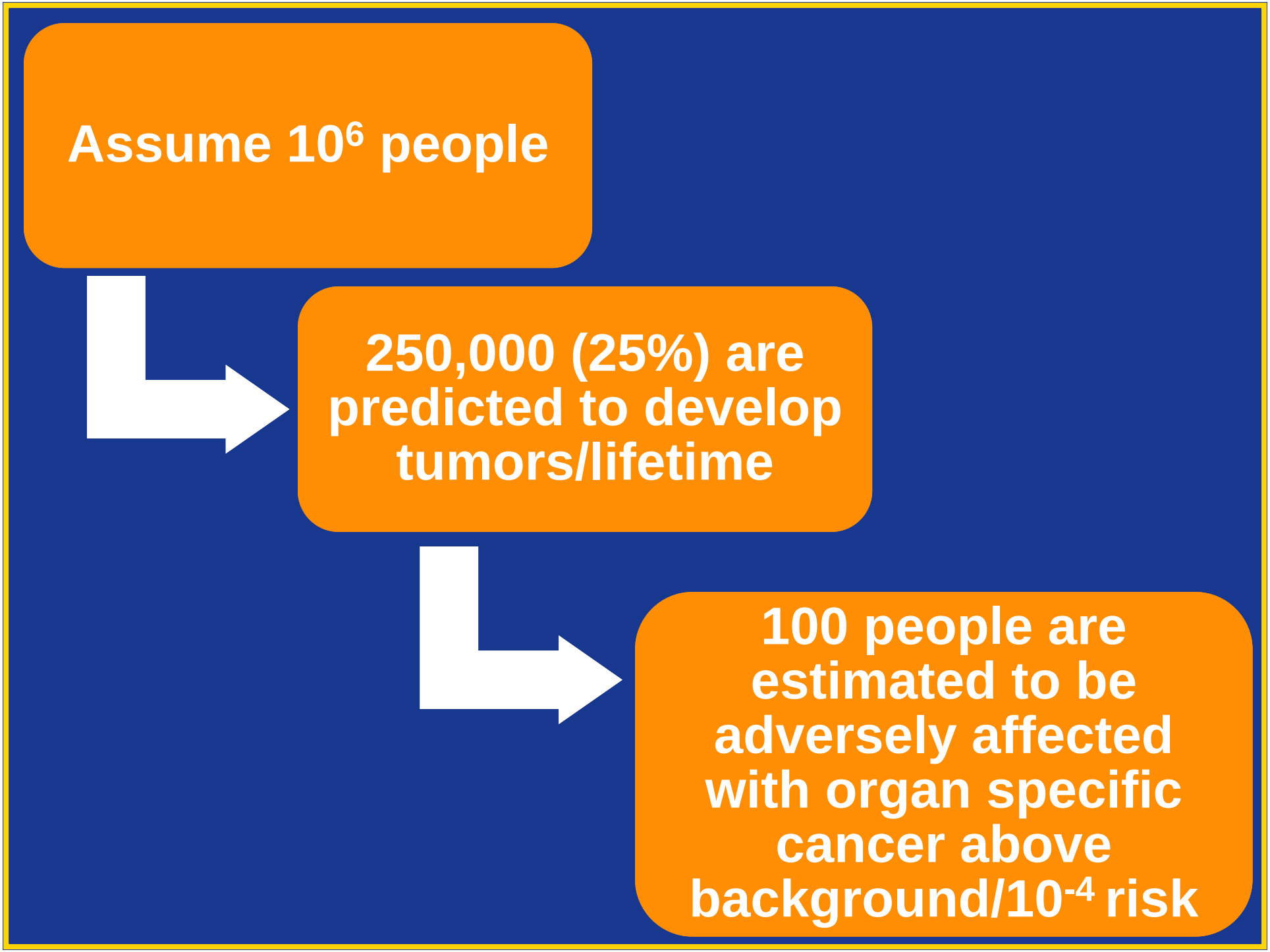
10^{-4} provides substantial protection against theoretical low dose risks (10^{-6}) that are below the detection of epidemiological and toxicological studies/methods, while including potential benefits predicted by the hormetic dose-response model.

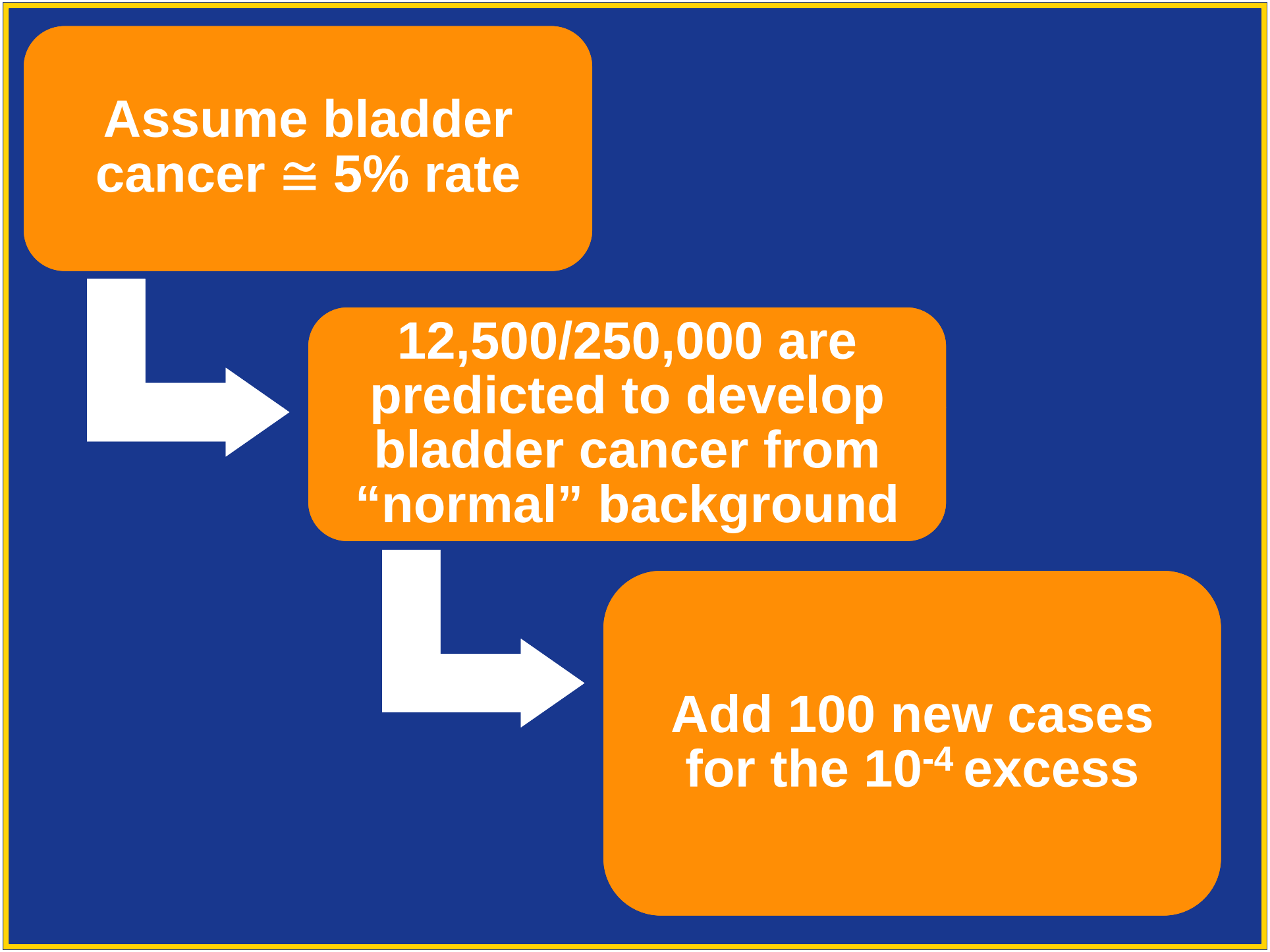
Estimating the Regulatory "Sweet-Spot"



LNT & Hormesis Convergence

Public Health Optimization Application


Assume 10^6 people
250,000 (25%) are predicted to develop tumors/lifetime
100 people are estimated to be adversely affected with organ specific cancer above background/10^{-4} risk

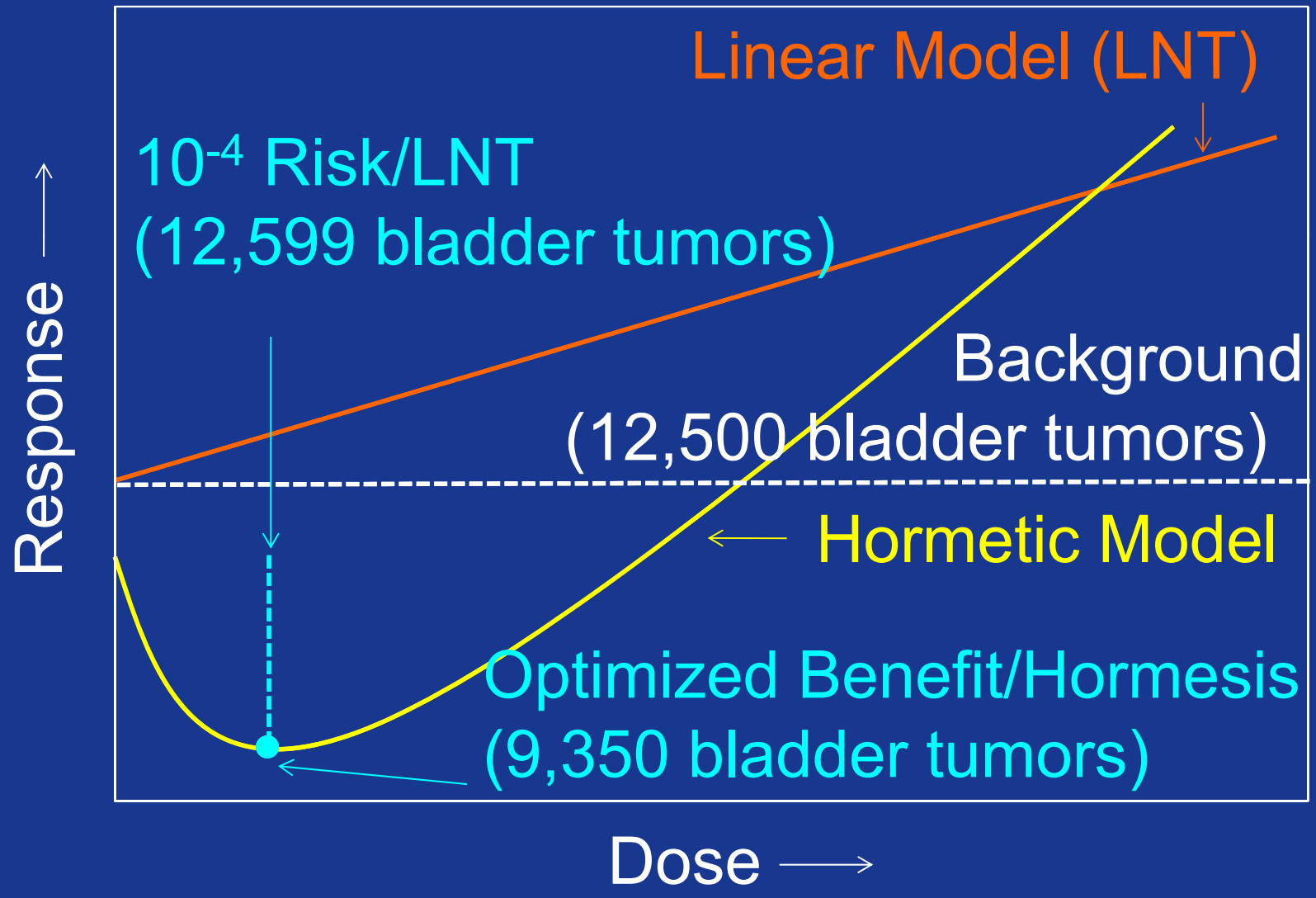

Assume bladder cancer ≅ 5% rate
12,500/250,000 are predicted to develop bladder cancer from "normal" background
Add 100 new cases for the 10^{-4} excess

Subtract 1 case for spontaneous and excess incidence in same person

12,500 + 100 -1 = 12,599 Total

≅25% of cases will not develop bladder cancer via hormetic mechanism → 3,150 cases prevented

The "Sweet-Spot" & Bladder Cancer



Advantages of Integration

Characterizes model uncertainty;

Optimizes exposure standard method;

Provides population based response with lowest integrated risk;

Hormetic prediction can be tested/validated

Advantages of Integration

Minimizes model error by combining optimal features of both models;

LNT is likely to be more accurate at 10^{-4} than 10^{-6} while still being strongly protective

More Advantages of Integration

This strategic compromise of model integration for population health optimization in the presence of considerable uncertainty should also encourage constructive means to test and resolve areas of uncertainty.

Issues with Integration

Only applies to animal bioassays but could be expanded to epidemiology data

LNT risk assessment practice needs the flexibility to accept risks at 10^{-4} rather than "*deminimus*" lower risks (e.g., 10^{-5} or 10^{-6})

Acknowledgments

This presentation is based on:

- Calabrese EJ, Shamoun DY, Hanekamp JC. (2015). Cancer risk assessment: Optimizing human health through linear dose-response models. *Food and Chemical Toxicology* 81:137-140.

- Calabrese EJ, Shamoun DY, Hanekamp JC. (2015). The Integration of LNT and Hormesis for cancer risk assessment optimizes public health protections. *Health Physics Journal* (in press).

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