

# Hormesis: Biological Foundations, Medical and Public Health Implications

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# HORMESIS CONCEPT

- Low doses of numerous stressors (e.g. exercising, intermittent fasting, hypoxia, heat, cold, ionizing/non-ionizing radiation, electricity, toxins, chemicals/drugs) can stimulate a wide range of adaptive responses.

- These induced adaptive responses have the potential to profoundly affect the success of public health practices and medical interventions (e.g., surgeries, chemo/radiation therapies) for numerous disorders (e.g., heart attack, stroke, shock, brain traumatic damage, organ transplant).

- Stressors that trigger adaptive responses also offer ways to enhance healthy aging, improve human performance and prevent damage to tissues exposed later to a wide range and levels of injurious stressors.

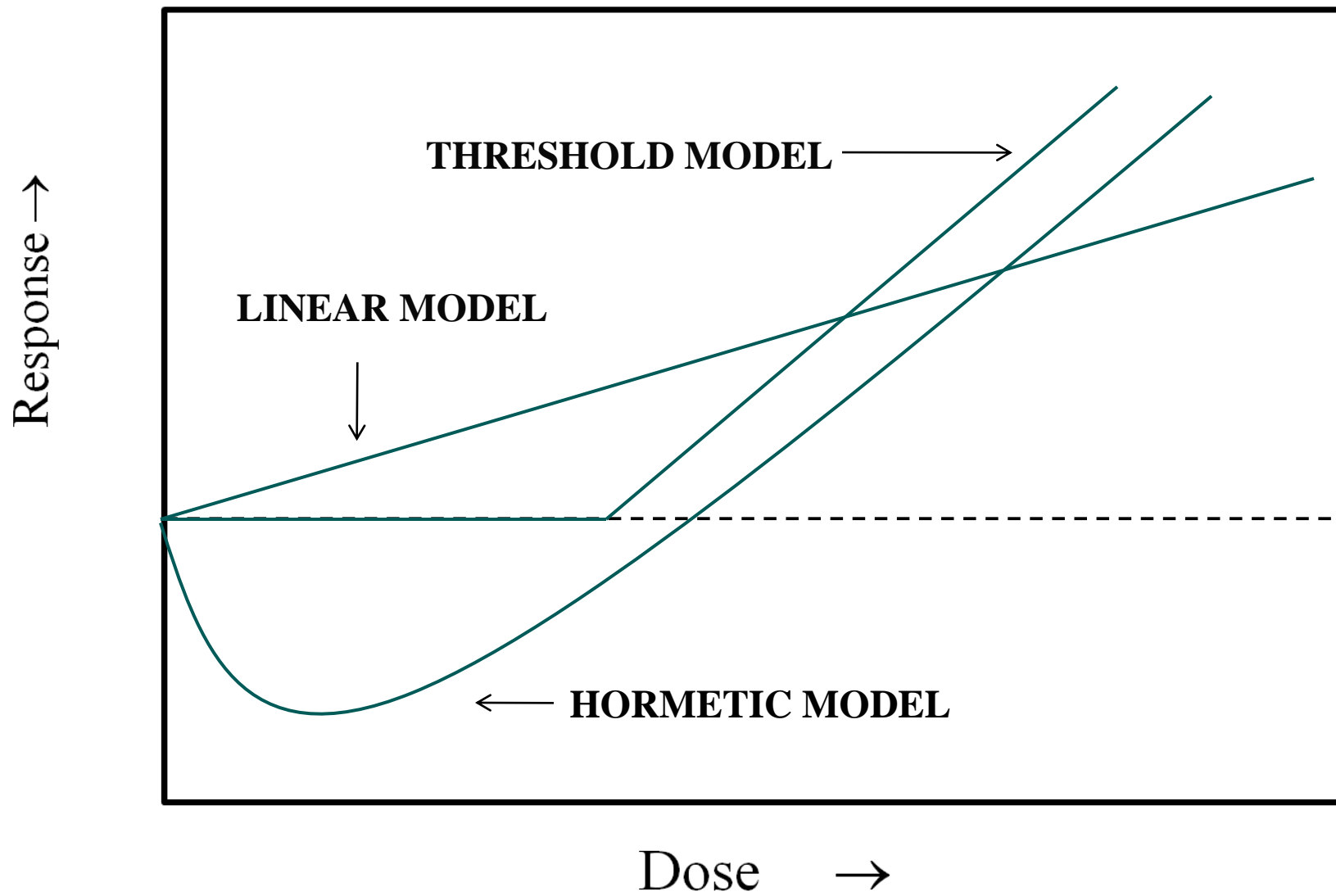
- At the center of this adaptive response concept is the phenomenon of hormesis, a biphasic dose response that mediates processes by which human adaptation and performance may be improved.

- What is hormesis, how can it be used to achieve these public health and medical advances?
- When and how should hormesis be taught to undergraduates and medical students?

# HORMESIS

## Definition:

- 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.

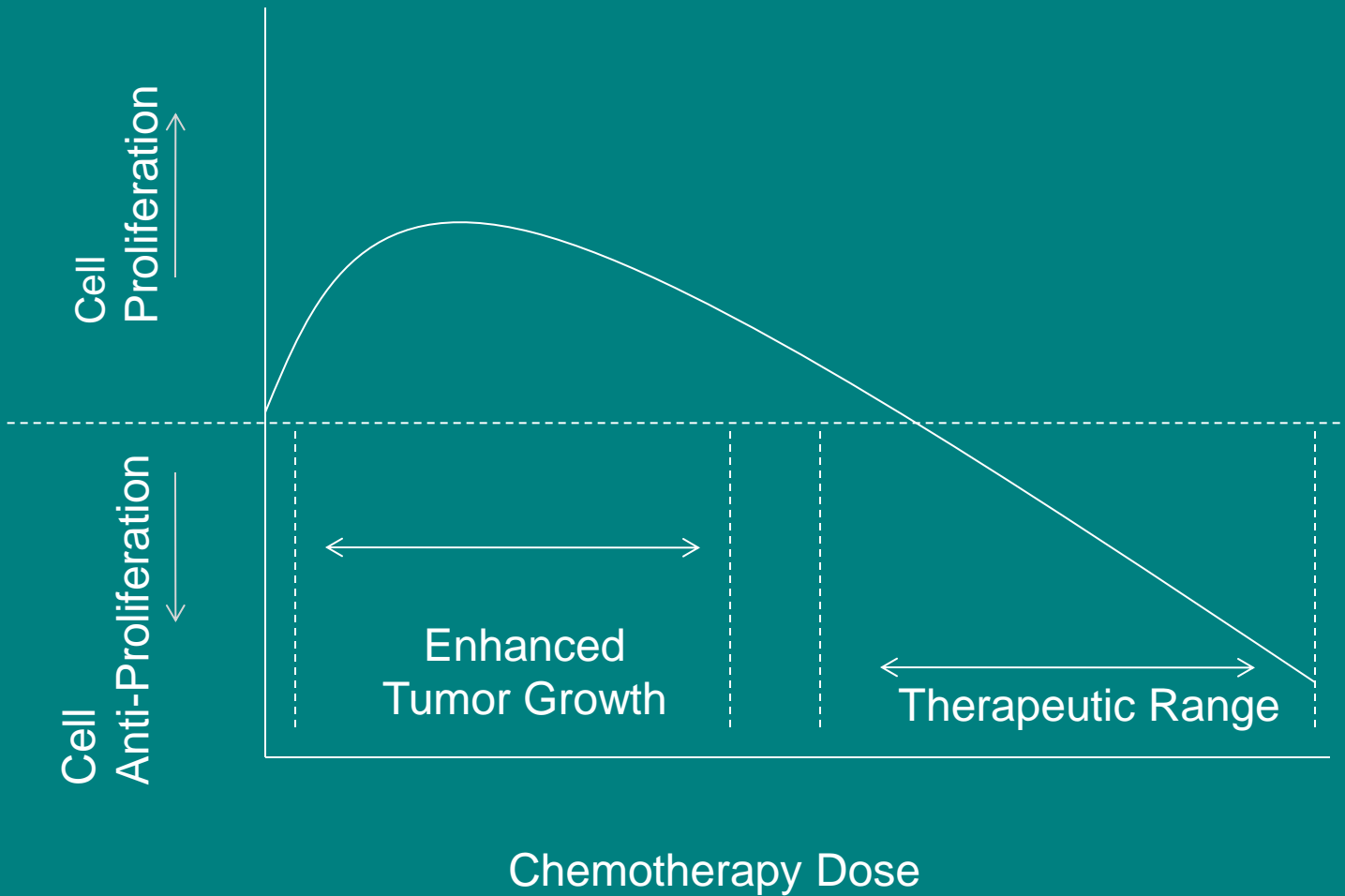


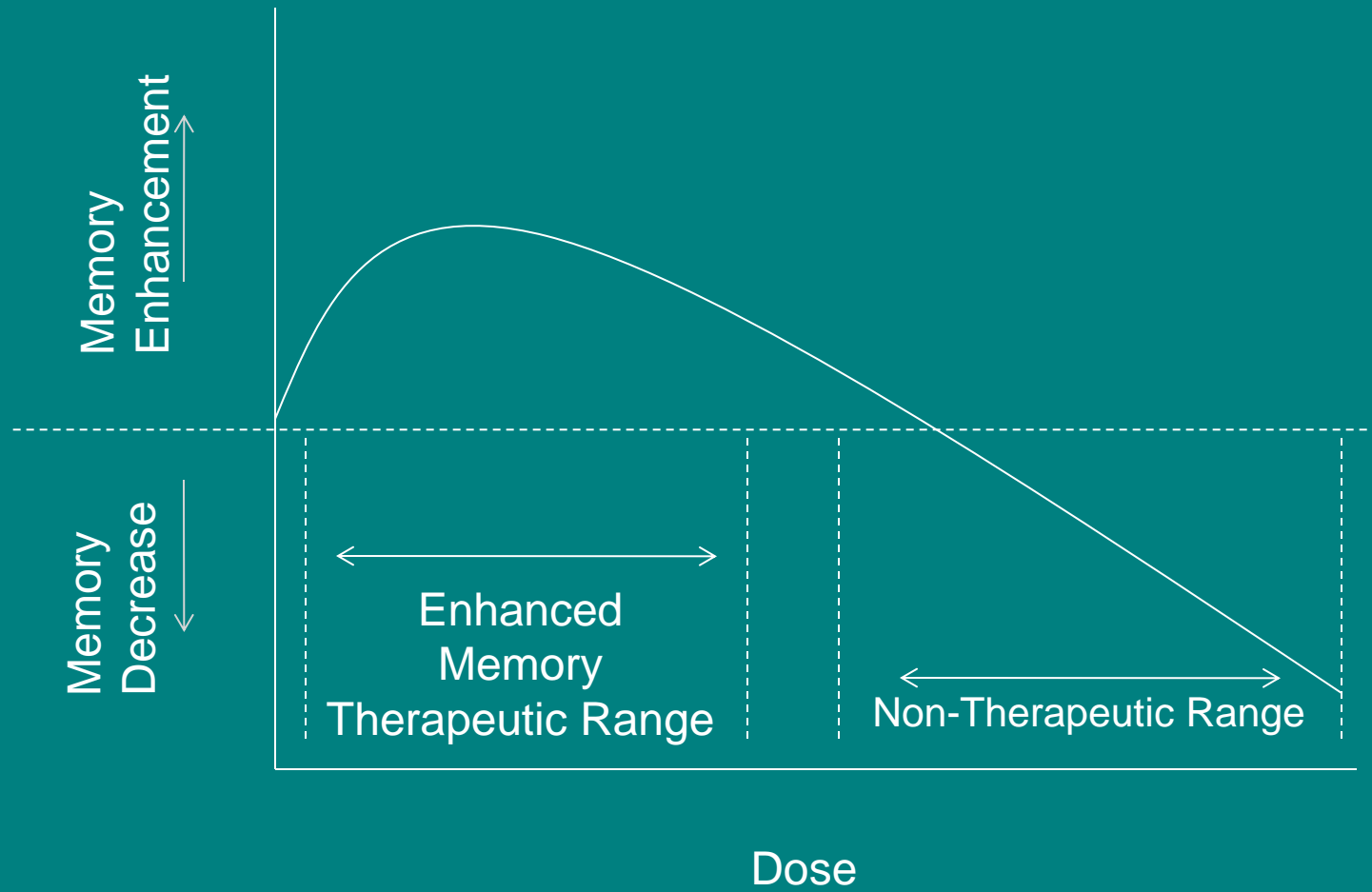


- Generally similar quantitative features with respect to amplitude and range of the stimulatory response.
- Directly induced or the result of compensatory processes following an initial disruption in homeostasis.
- Regardless of the means of induction the quantitative features are similar.

## Interpretation:

- Issue of beneficial/harmful effects should not be part of the definition of hormesis.
- This assessment should be reserved for a subsequent evaluation of the biological and ecological context of the response.





# HORMESIS AND ASSESSMENT CRITERIA

- Dose Response Patterns
- Statistical Significance
- Replication of Findings
- Mechanism Documentation
- Simulation Studies

# EVIDENCE OF HORMESIS

## General Summary:

- Hormesis databases: many thousands of dose responses indicative of hormesis using rigorous entry/evaluative criteria.

# EVIDENCE OF HORMESIS

## General Summary:

- Hormesis is a very general phenomenon: independent of model (e.g. plant, microbial, invertebrate, vertebrate, human) (e.g. in vitro/in vivo), endpoint, agent and level of biological organization (i.e. cell, organ, individual).

# DOSE RESPONSE

## Stimulation Amplitude:

- Modest
- 30-60% Greater Than Control
- Usually Not More Than 100% Greater Than The Control

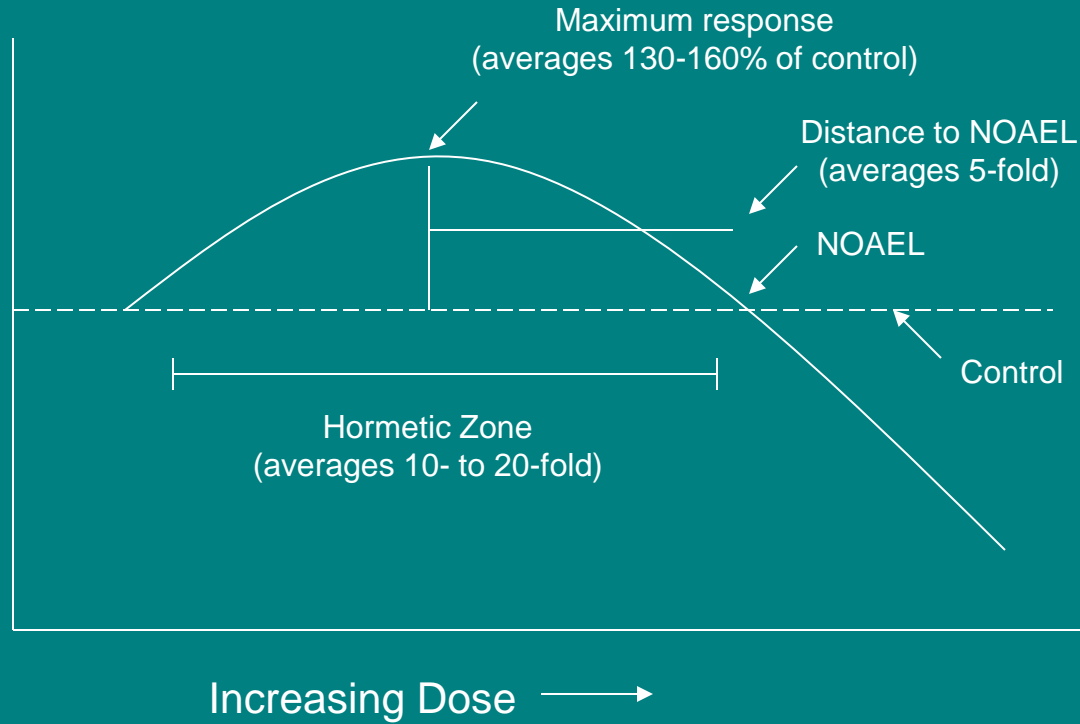


# STIMULATORY RANGE

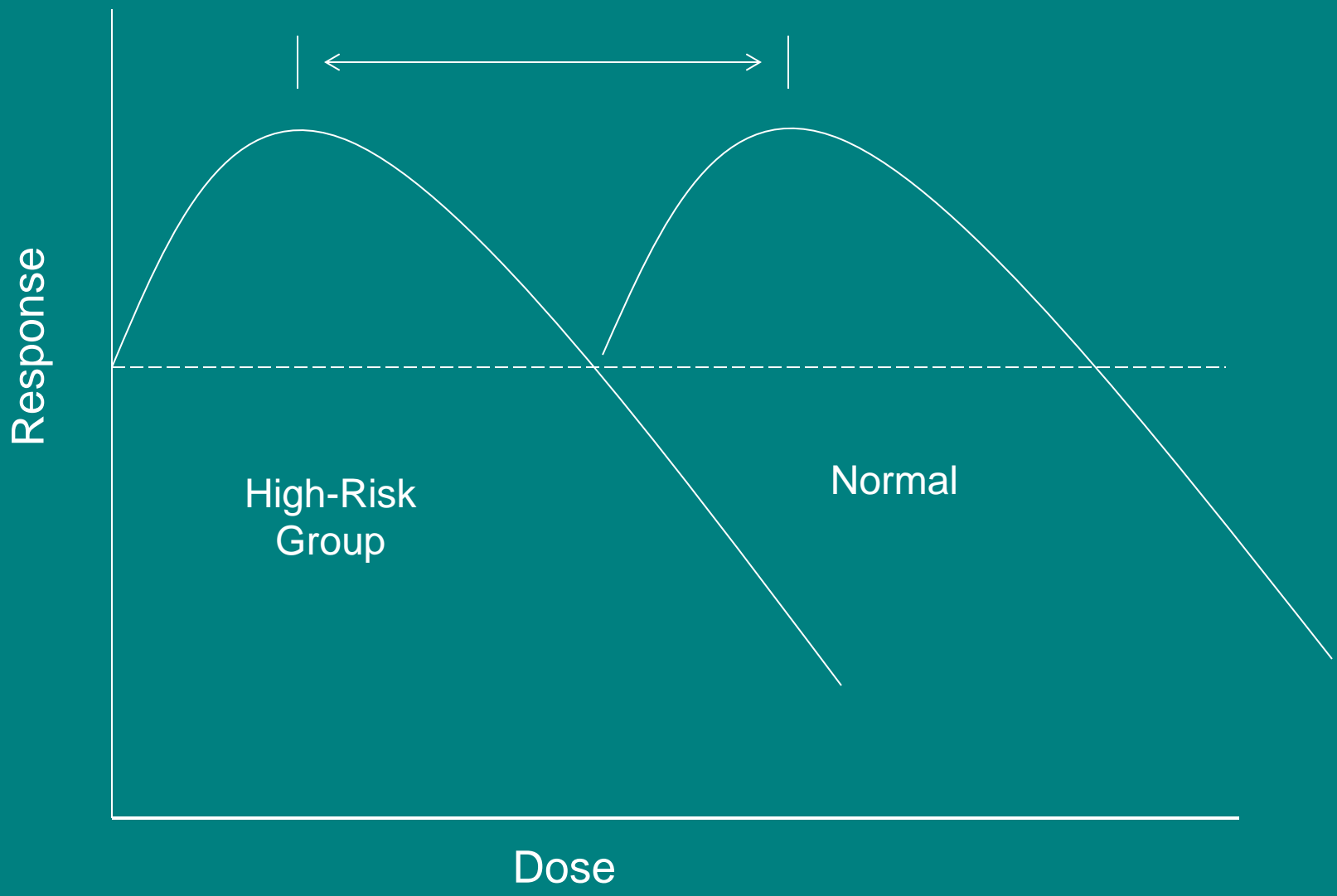
~75 % - Within 20-Fold of NOEL/NOAEL

~20% -  $>20 < 1000$ -Fold of NOEL/NOAEL

~<2% -  $> 1000$ -Fold of NOEL/NOAEL



Dose-response curve depicting the quantitative features of hormesis



Response

High-Risk  
Group

Normal

Dose

# Representative receptor systems displaying biphasic dose-response relationships

Adenosine

Adrenoceptor

Bradykinin

Cholecystokinin

Corticosterone

Dopamine

Endothelin

Epidermal growth factor

Estrogen

5-HT

Human chorionic gonadotropin

Muscarinic acetylcholine

Neuropeptides

Nitric oxide

*N*-methyl-D-aspartate

Opioid

Platelet-derived growth factor

Prolactin

Prostaglandin

Somatostatin

Spermine

Testosterone

Transforming growth factor- $\beta$

Tumor necrosis factor  $\alpha$

# HORMETIC MECHANISMS

- Many studies provide mechanisms to account for hormetic responses;
- Each mechanism is unique to the model, tissue, endpoint and agent;

- Receptor Level Assessment: Use of receptor antagonists to block response;
- Cell Signaling Pathway Assessment: Use of pathway inhibitors;

- Several hundred hormetic dose responses have mechanisms at the receptor/signaling pathway level.

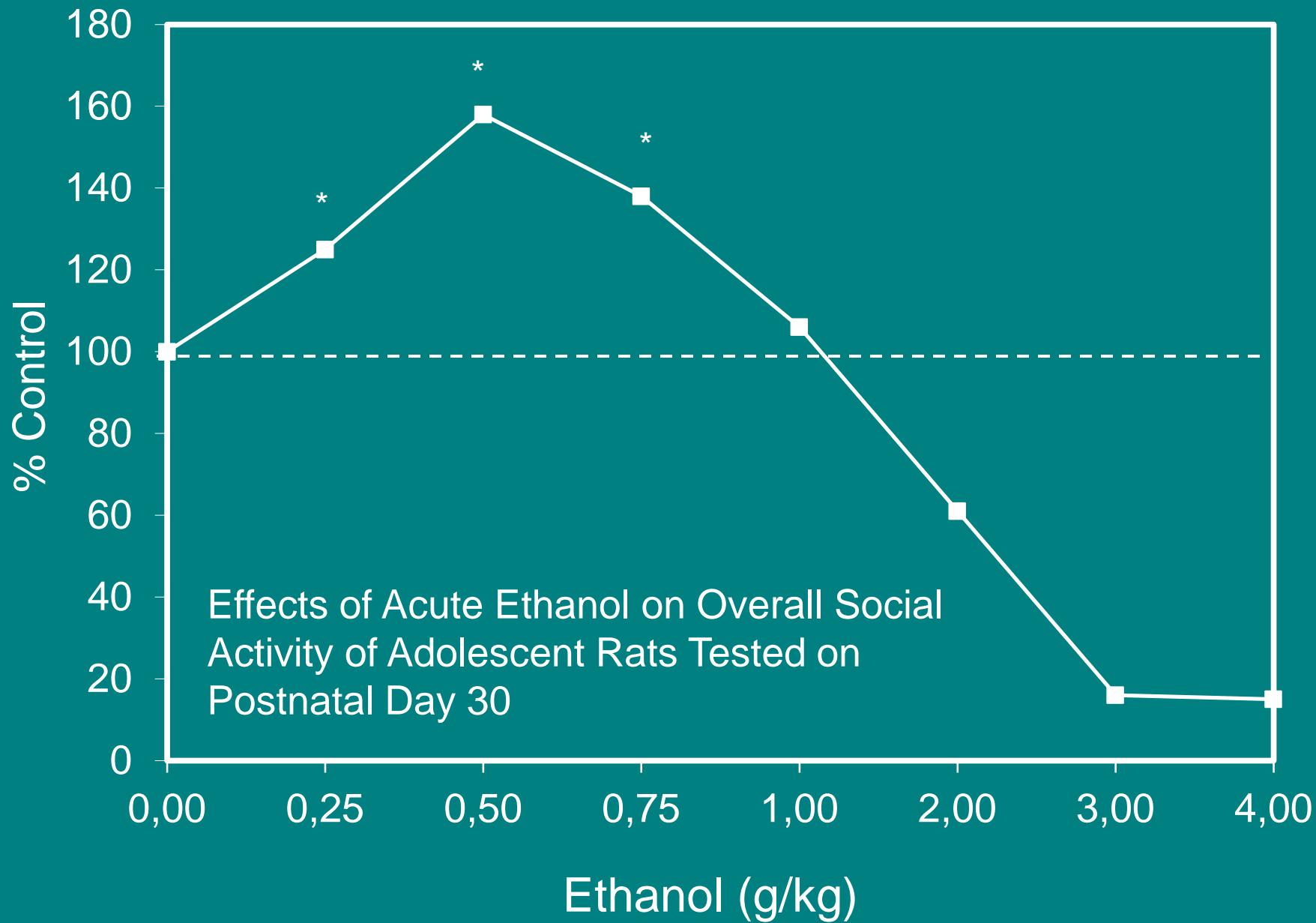
# KEY OBSERVATIONS

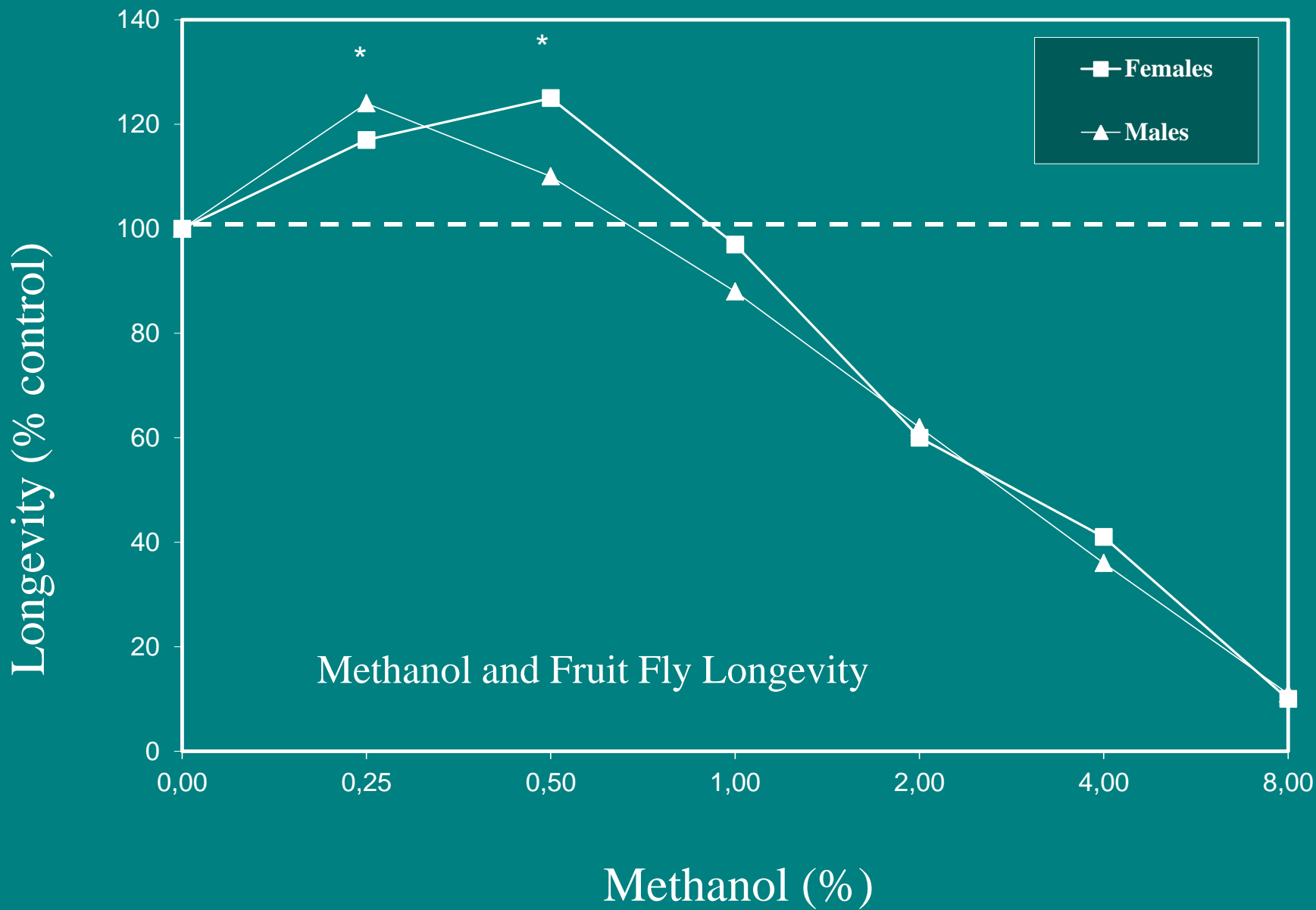
- Regardless of mechanism (e.g. receptor-signaling pathway, non-receptor mediated, direct or compensatory stimulation), the quantitative features of the dose response are similar.

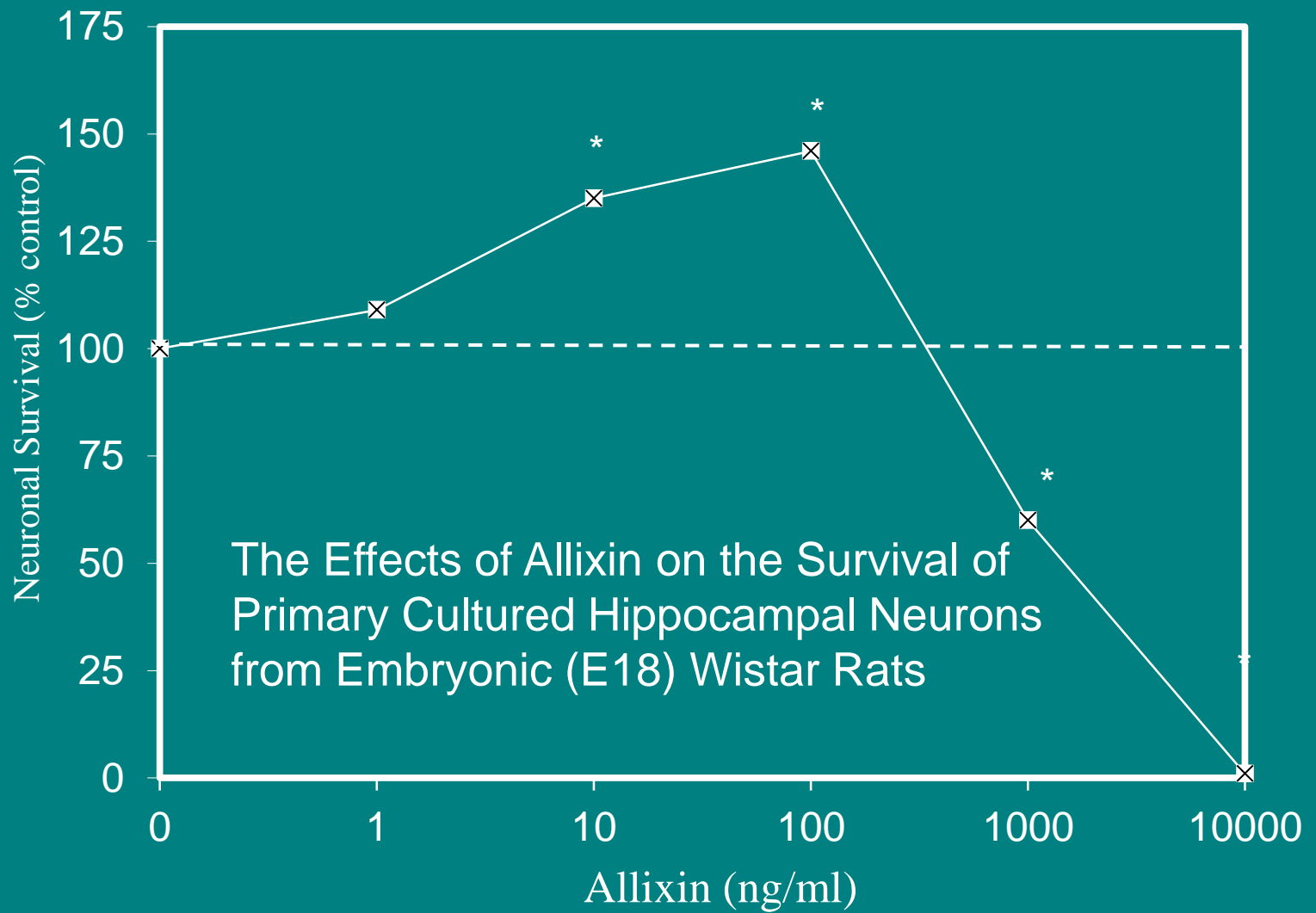


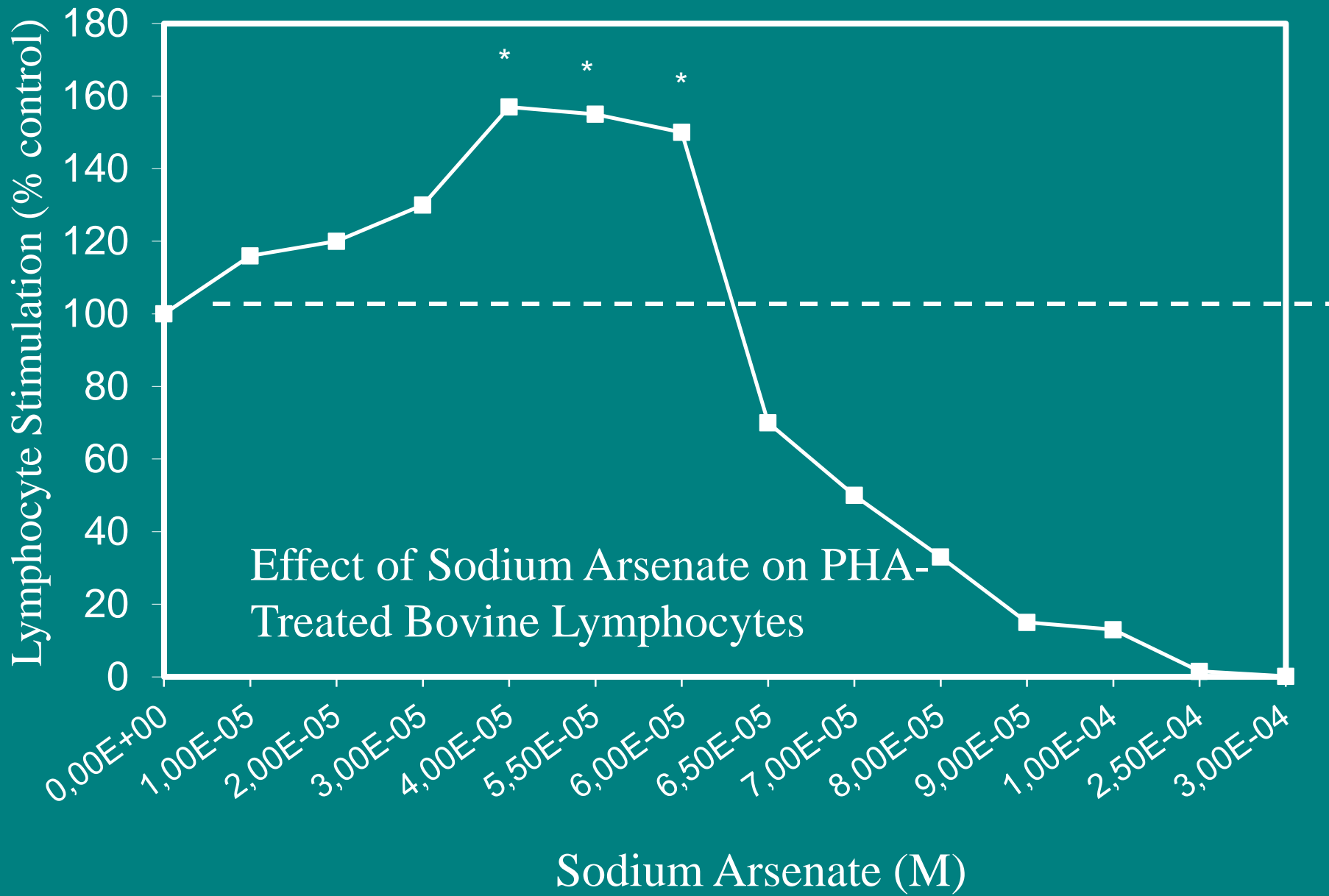
- Hormetic responses are integrative responses across multiple levels of biological organization;

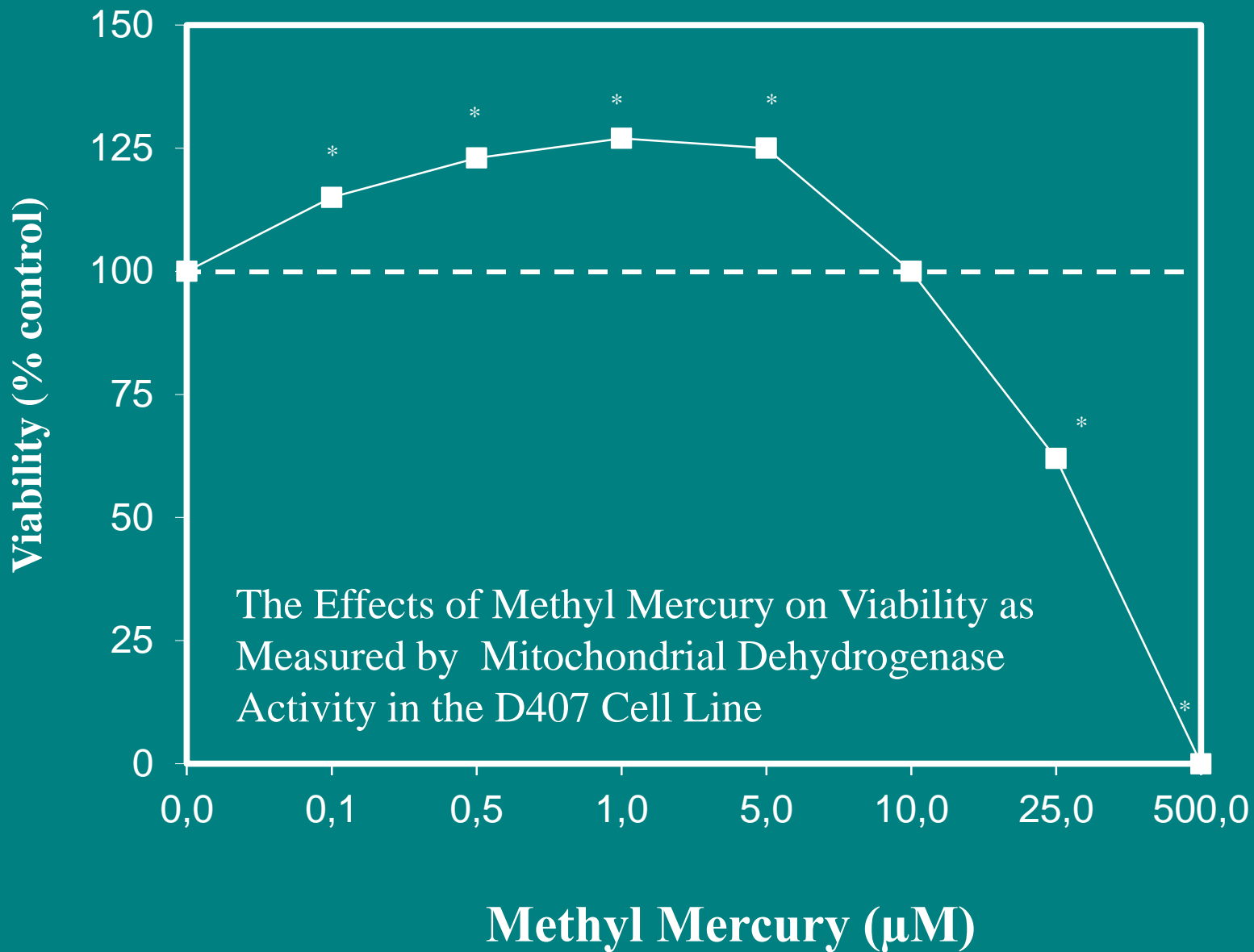
- Cell proliferation
- Fecundity
- Tissue Repair
- Behavioral/Learning
- Disease/Injury Resistance/Pre- Post-Conditioning
- DNA Damage/Tumor Incidence
- Aging/Longevity

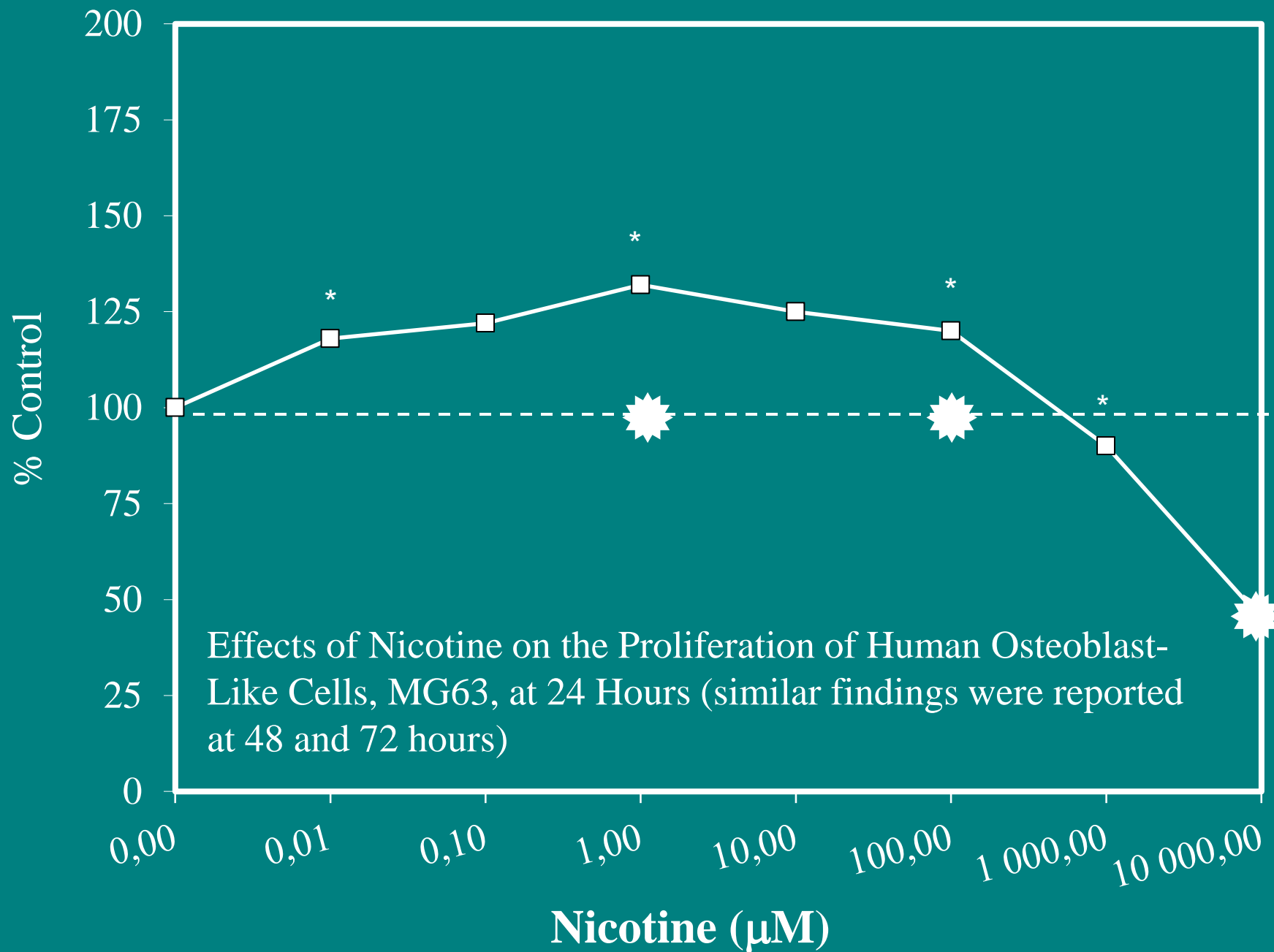




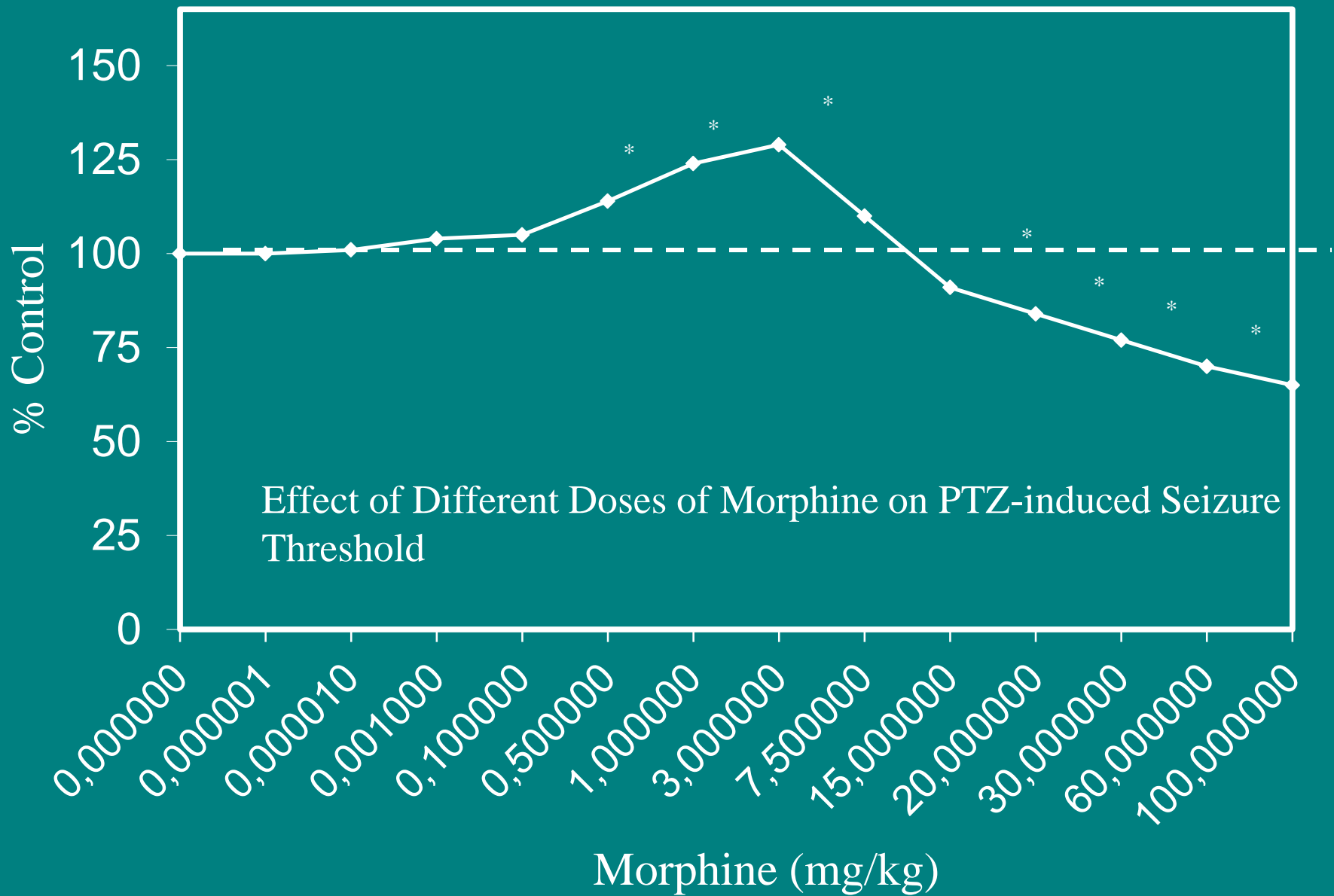


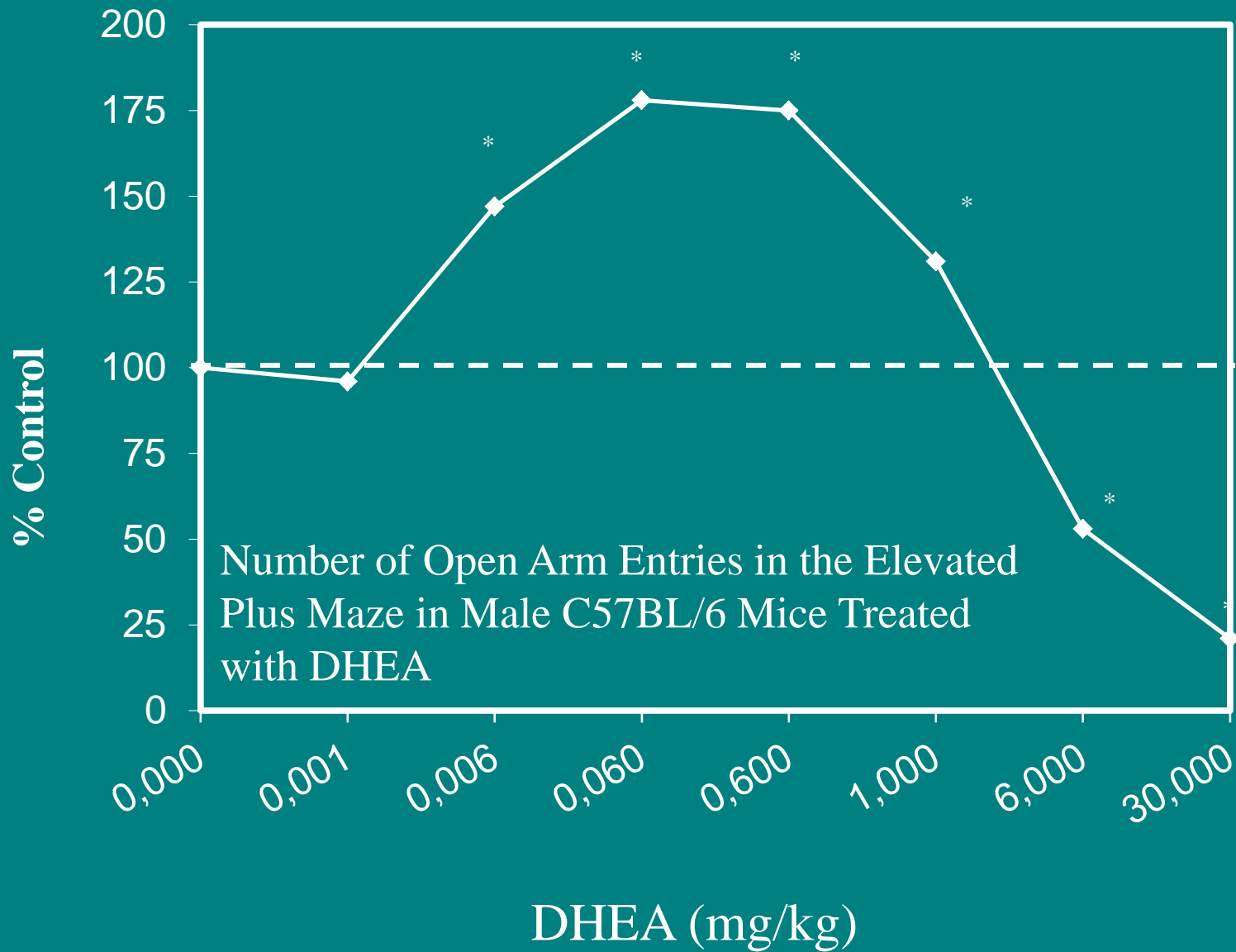


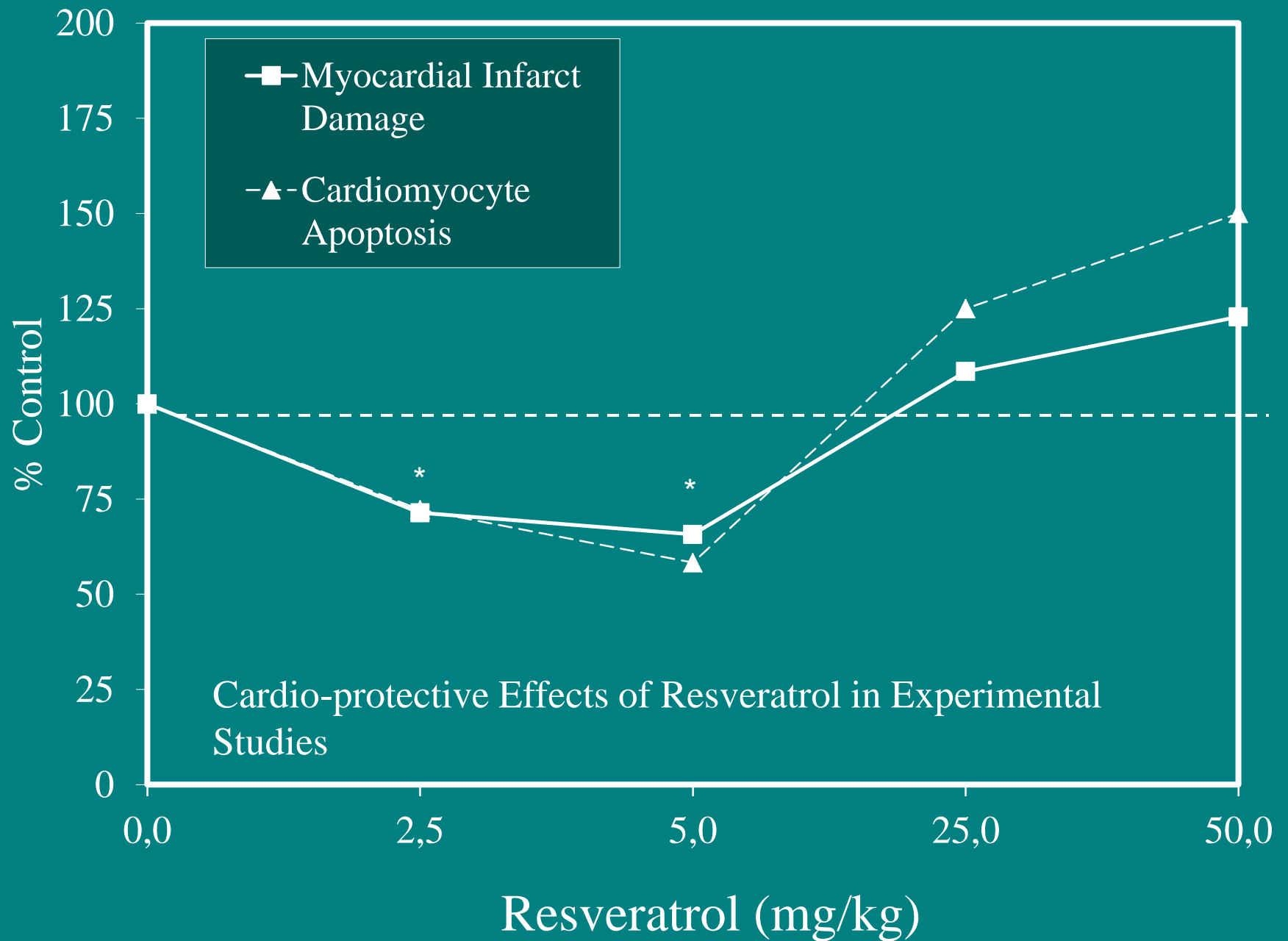


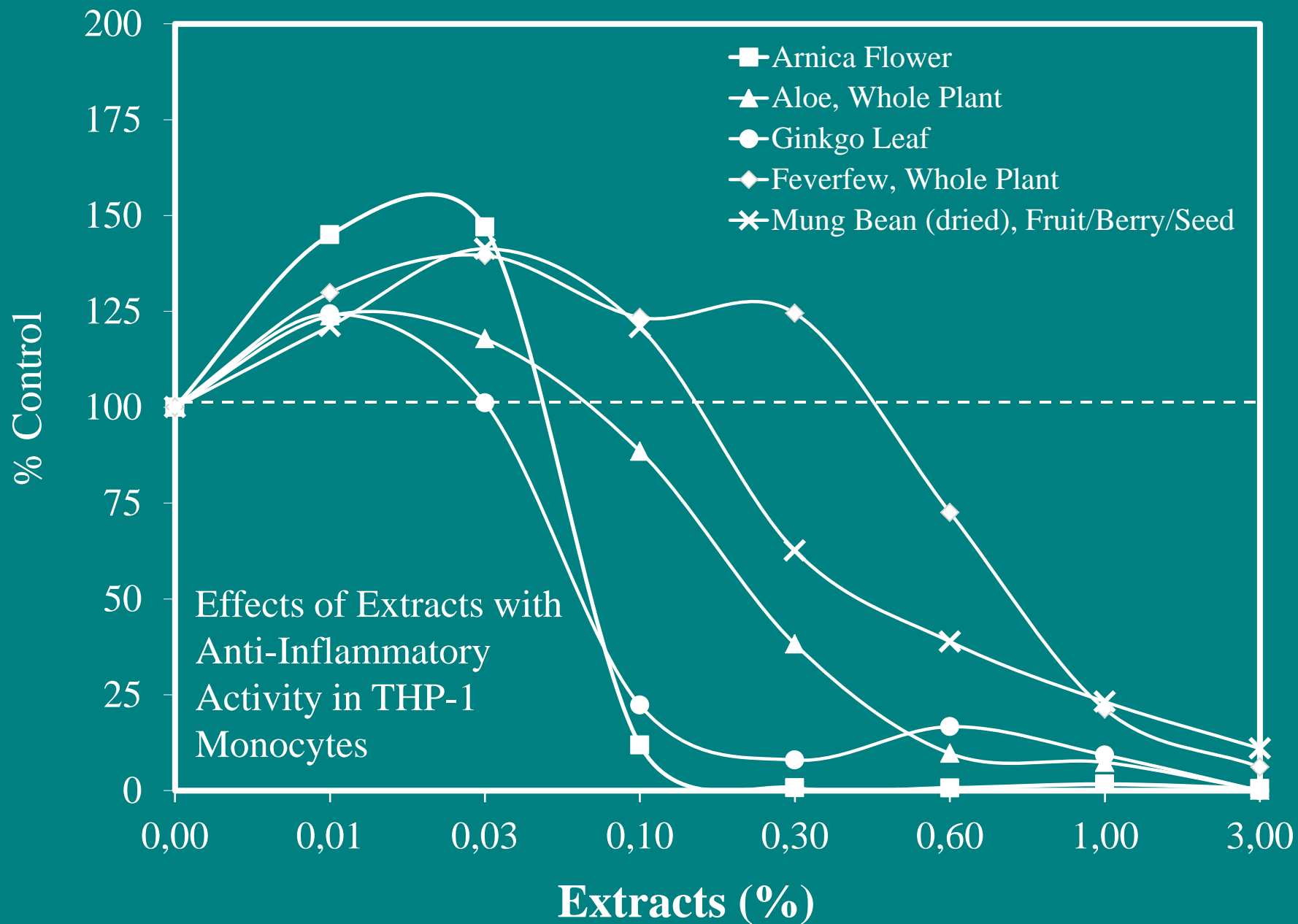








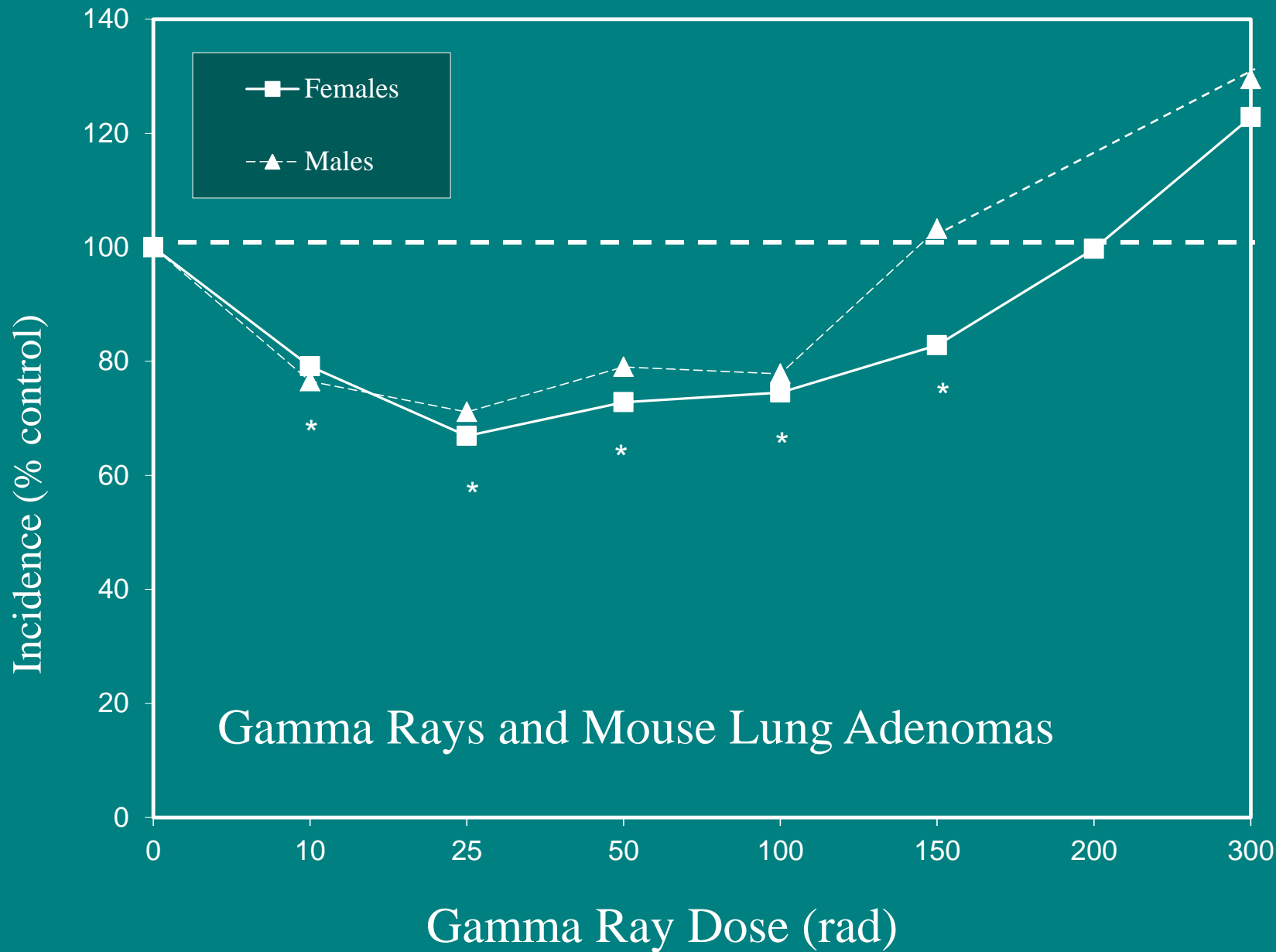




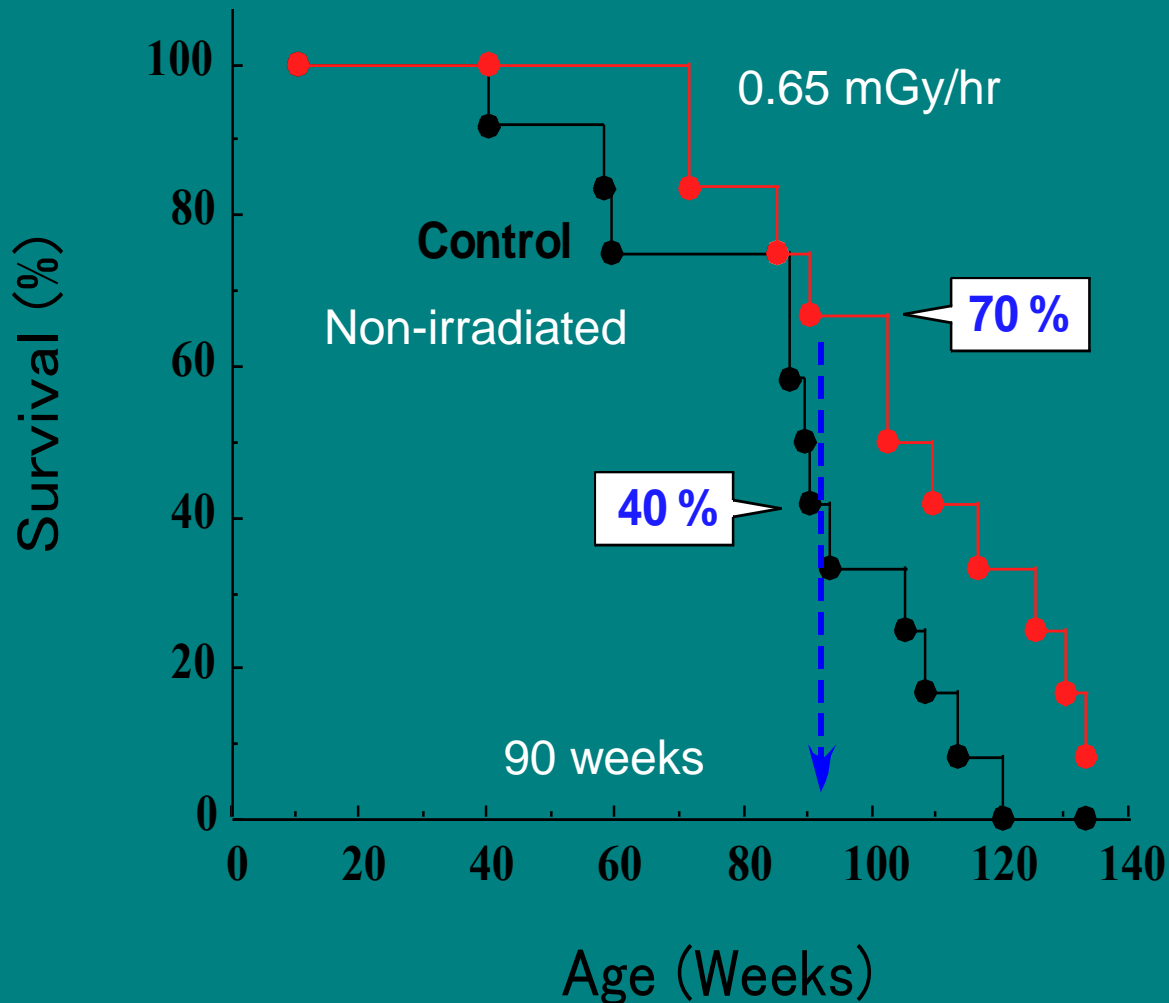
# PRECONDITIONING/ADAPTIVE RESPONSE

- Numerous pre- and post-conditioning/adaptive response studies display hormetic biphasic dose response relationships with mechanistic explanations.
- Thus, pre- and post-conditioning/adaptive responses are manifestations of hormesis.

# HORMESIS: CANCER AND RELATED ENDPOINTS



# Prolongation of Life Span of db/db Mice by Low Dose Rate Irradiation





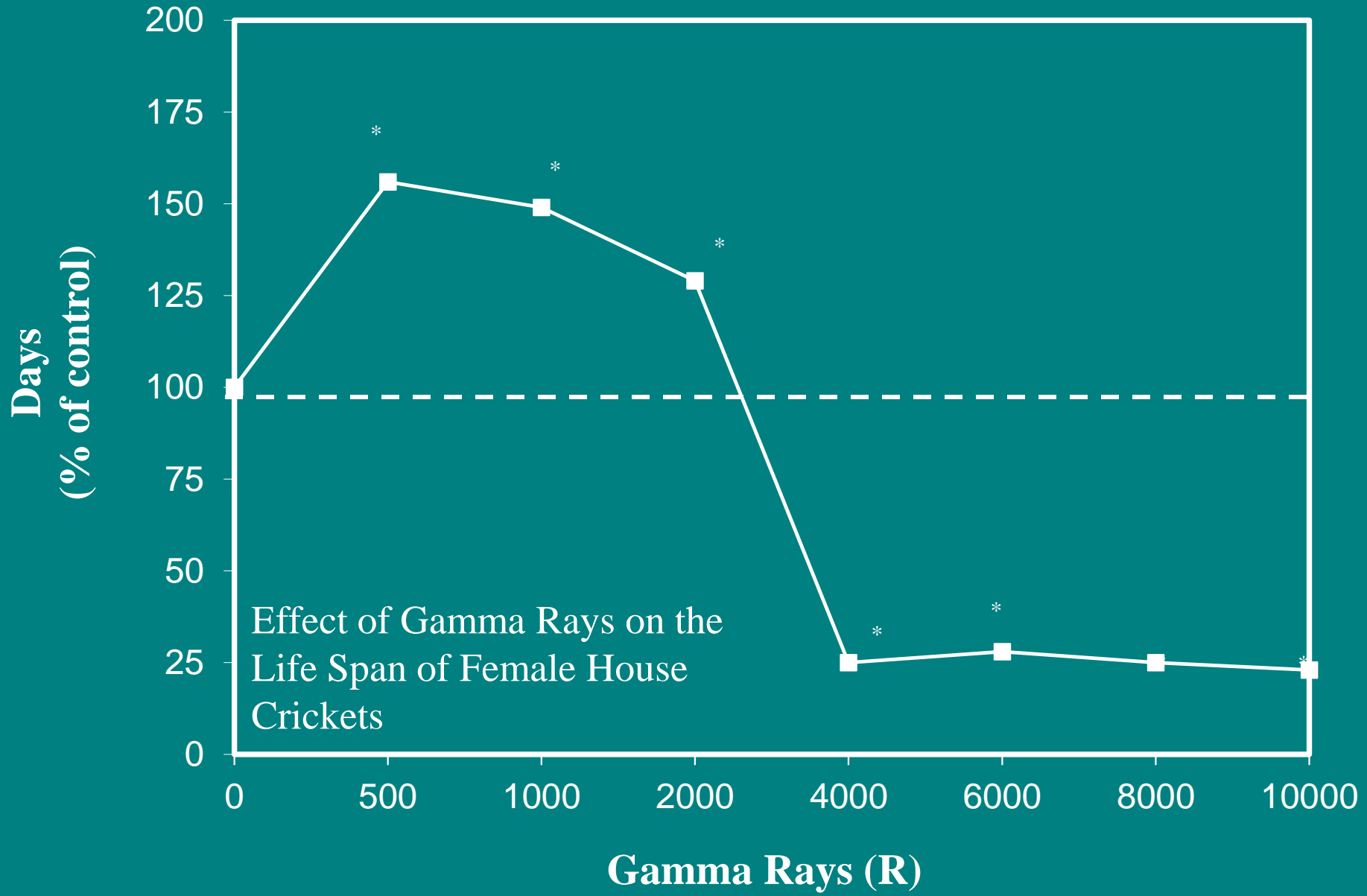
# Appearance of db/db mice at 90<sup>th</sup> week of age



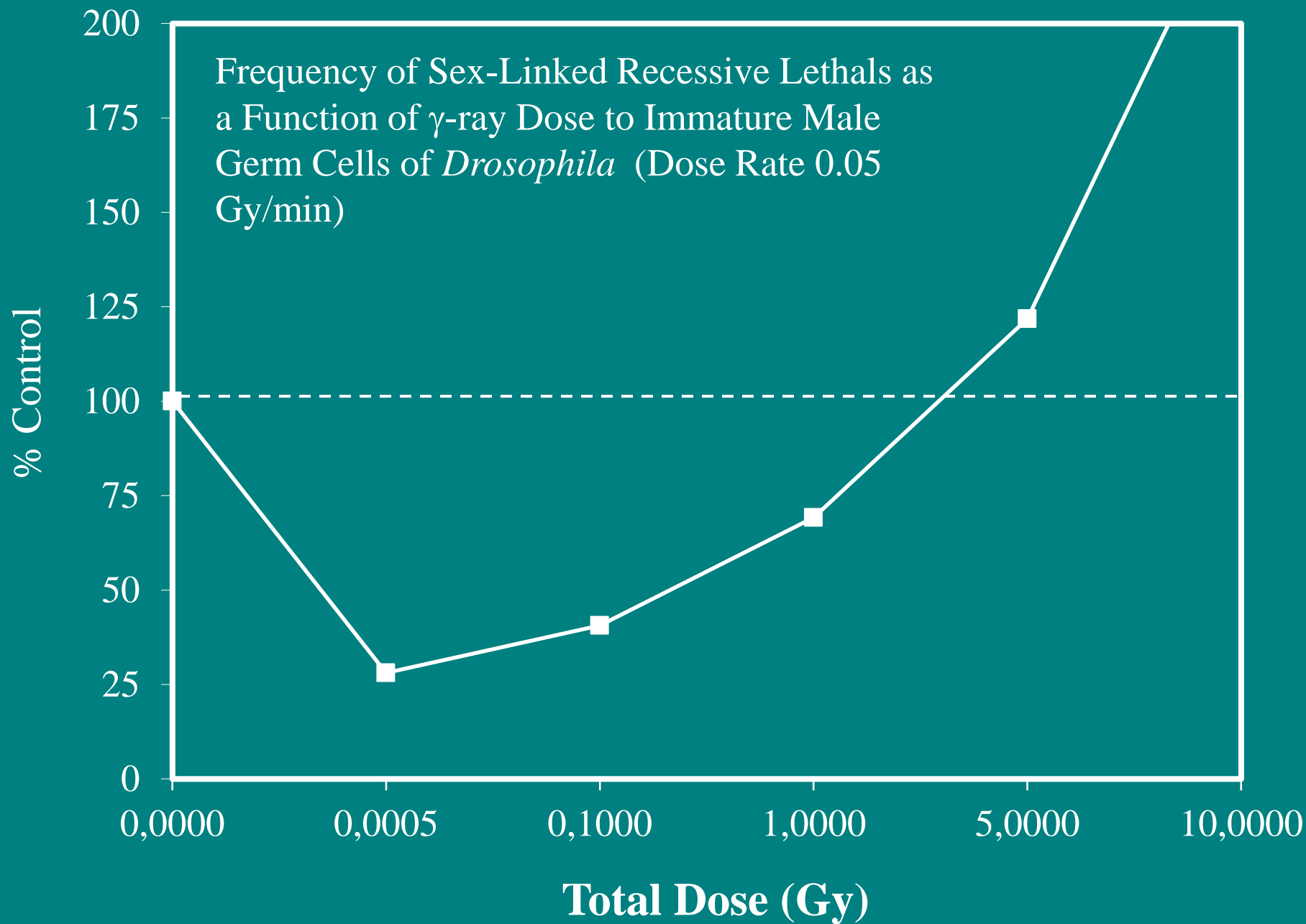
**Irradiated Group**

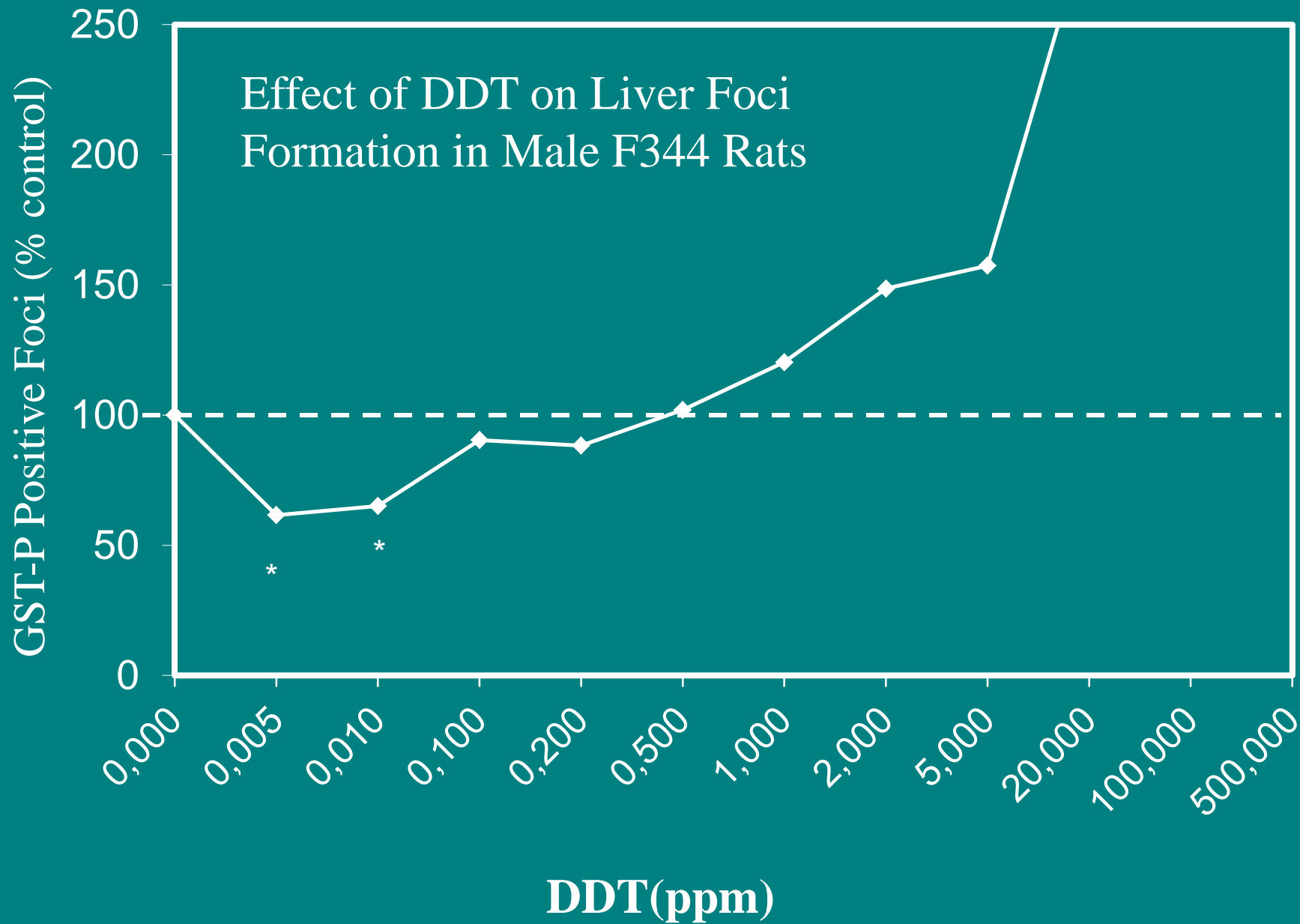


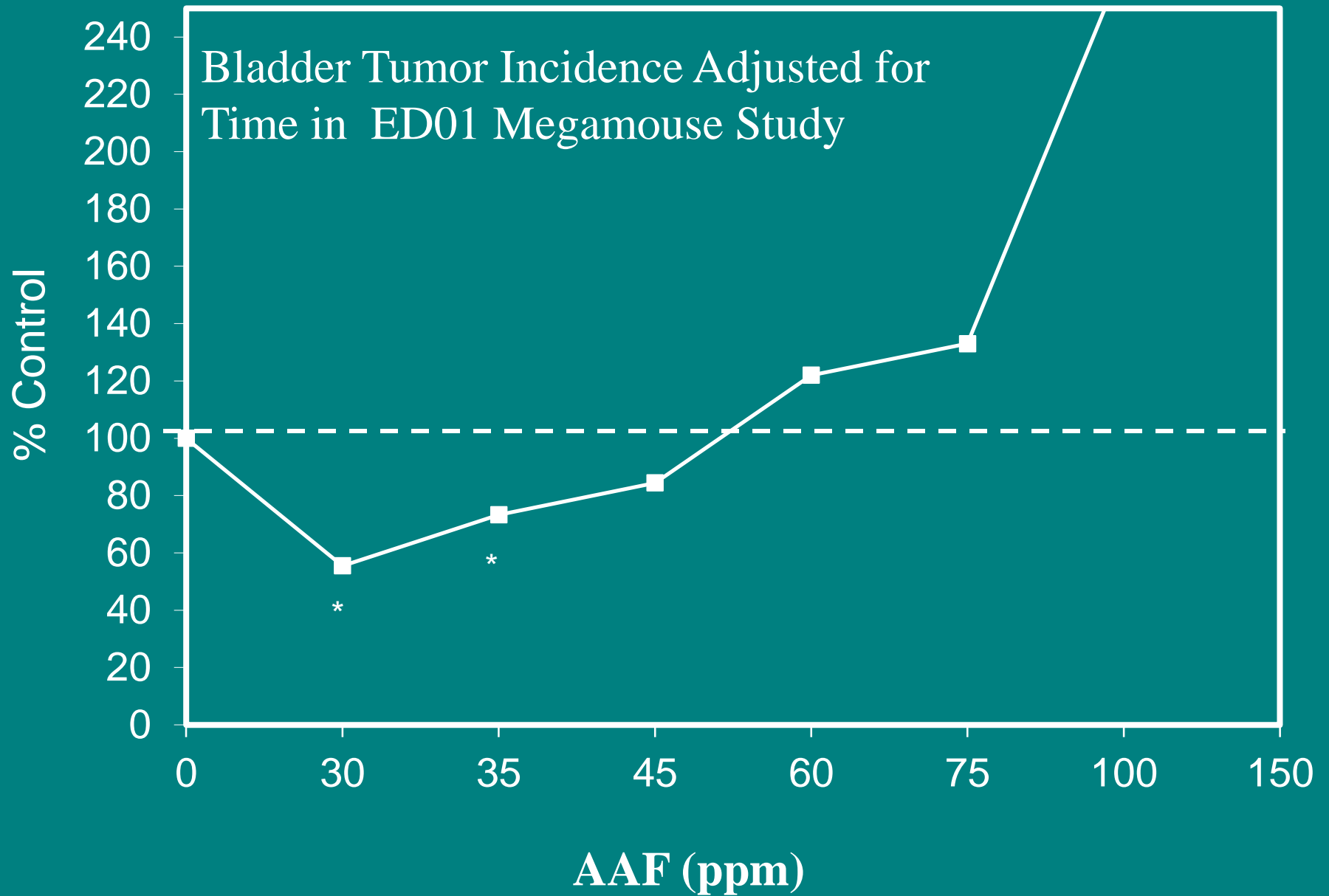
**Control Group**



Effect of Gamma Rays on the Life Span of Female House Crickets







# WHAT IS HORMESIS INDICATING?

- The low dose stimulation is different than the high dose inhibition/toxicity;
- Low dose stimulation: It is a measure of biological performance, not toxicity;
- It determines how much a system can respond.

# WHAT IS HORMESIS INDICATING?

- Hormesis is the first quantitative estimate of biological plasticity.
- The Hormesis stimulatory response is constrained by the limits of plasticity.

# HORMETIC APPLICATIONS

- DRUG DEVELOPMENT
  - Anxiolytic agents
  - Anti-seizure drugs
  - Memory enhancement
  - Osteoporosis drugs
  - Wound healing preparations
  - Multiple inflammatory conditions



# MEDICAL PROCEDURES

- Organ transplantation optimization
- Enhancing surgical success
- Chemotherapy and radiation therapies

# LIFE STYLE AND OTHER FACTORS

- Diet – intermittent fasting and other possibilities
- Exercise
- Sleep, Stress and other factors
- Circadian rhythms

# CONCLUSIONS

- Hormesis is a general and central biological concept.
- It affects all disciplines utilizing the dose response concept.
- It represents a general adaptive strategy through which biological performance is enhanced and mediated.

- Hormesis provides both the theoretical basis and the molecular foundations to create biological shields to protect against chemical, radiological, and microbial threats.

- This has implications for numerous and diverse medical interventions, as well as affecting the health and performance of military personnel, athletes, the general public, including patients, accident victims, and others.

- Failure to consider hormetic dose responses can lead to improper dosing resulting in possible ineffective or potentially harmful effects at low/high doses.
- Failure to consider hormetic dose responses within hazard assessment and risk assessment is a serious failing of modern risk assessment.

- Hormesis can play a significant role in drug discovery, development, and evaluation.
- Hormesis should become fully integrated into educational programs for all biomedical and medical school students, and continuing medical educational programs.