LESSONS LEARNED: HORMESIS

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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, synthetic chemicals/drugs, phytochemicals) can stimulate a wide range of adaptive responses.

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

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

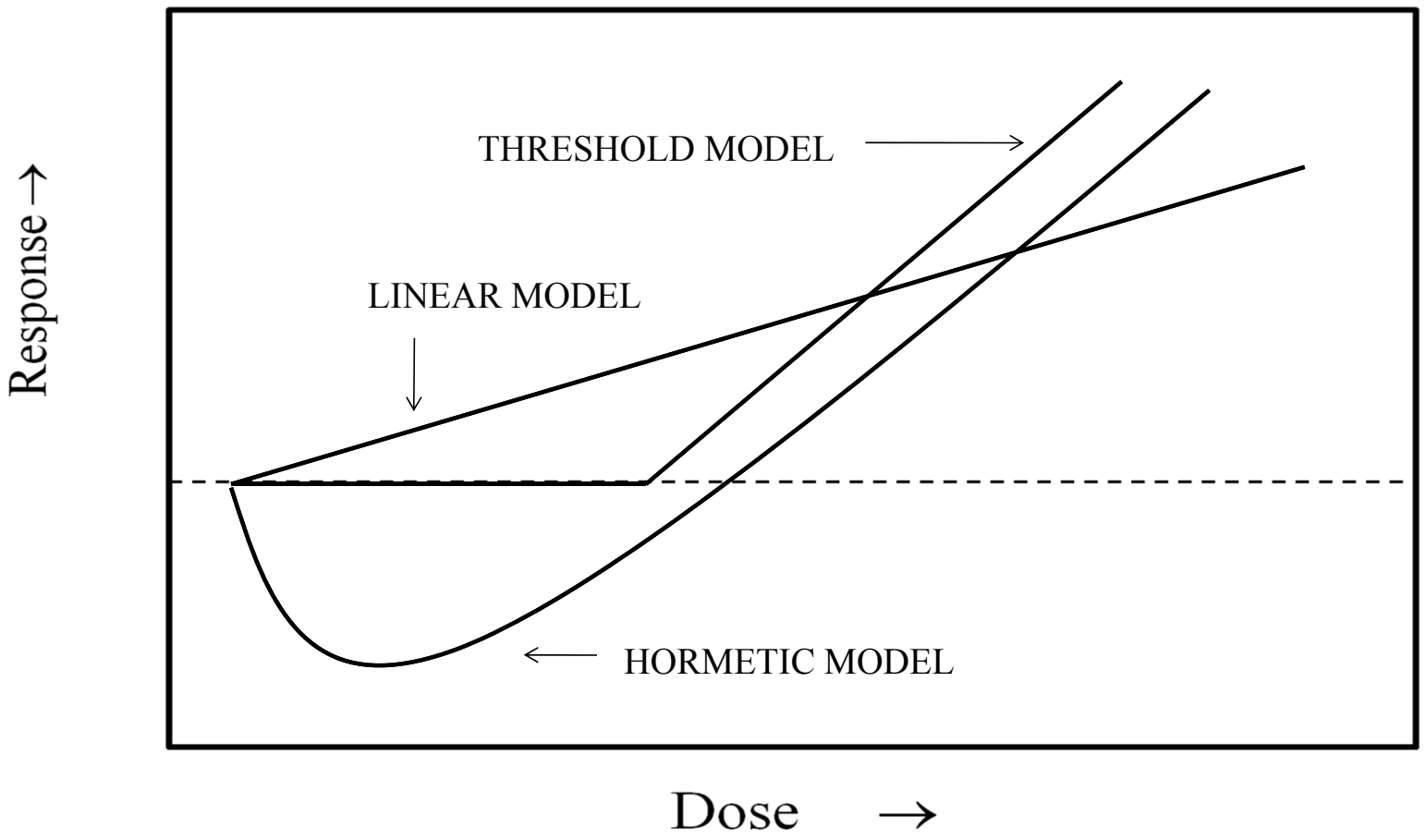
- At the center of this adaptive response concept is the phenomenon of hormesis, a biphasic dose response that mediates processes by which human adaptation and performance may be improved.

- What is hormesis, how can it be used to achieve these public health and medical advances?

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.


Response →
THRESHOLD MODEL
LINEAR MODEL
HORMETIC MODEL
Dose →

- 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.

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:

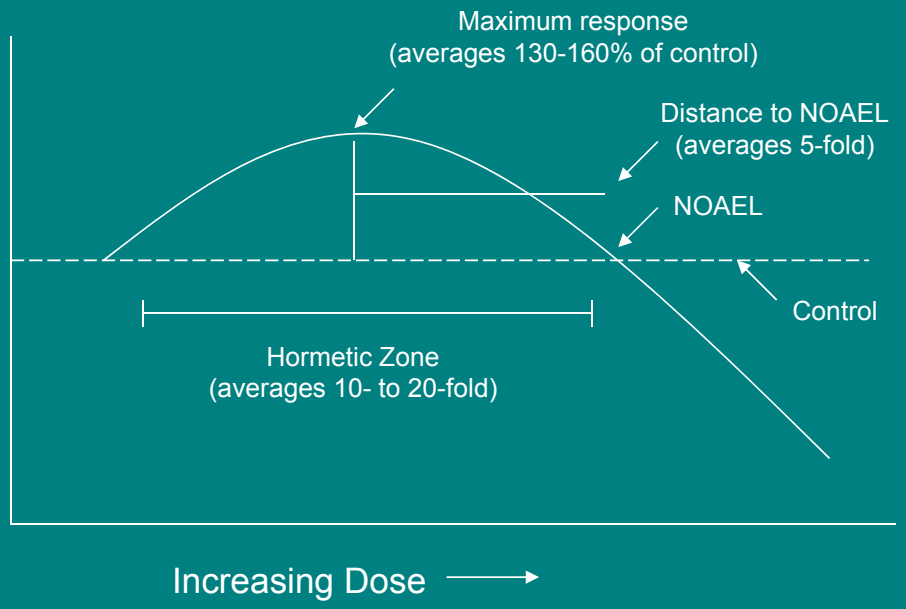
- Modest
- 30-60% Greater Than Control
- Usually Not More Than 100% Greater Than The Control

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

HORMETIC MECHANISMS

- Many studies provide mechanisms to account for hormetic responses;
- Each mechanism is unique to the model, tissue, endpoint and agent;
- Some general examples: Often existence of opposing receptors.

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

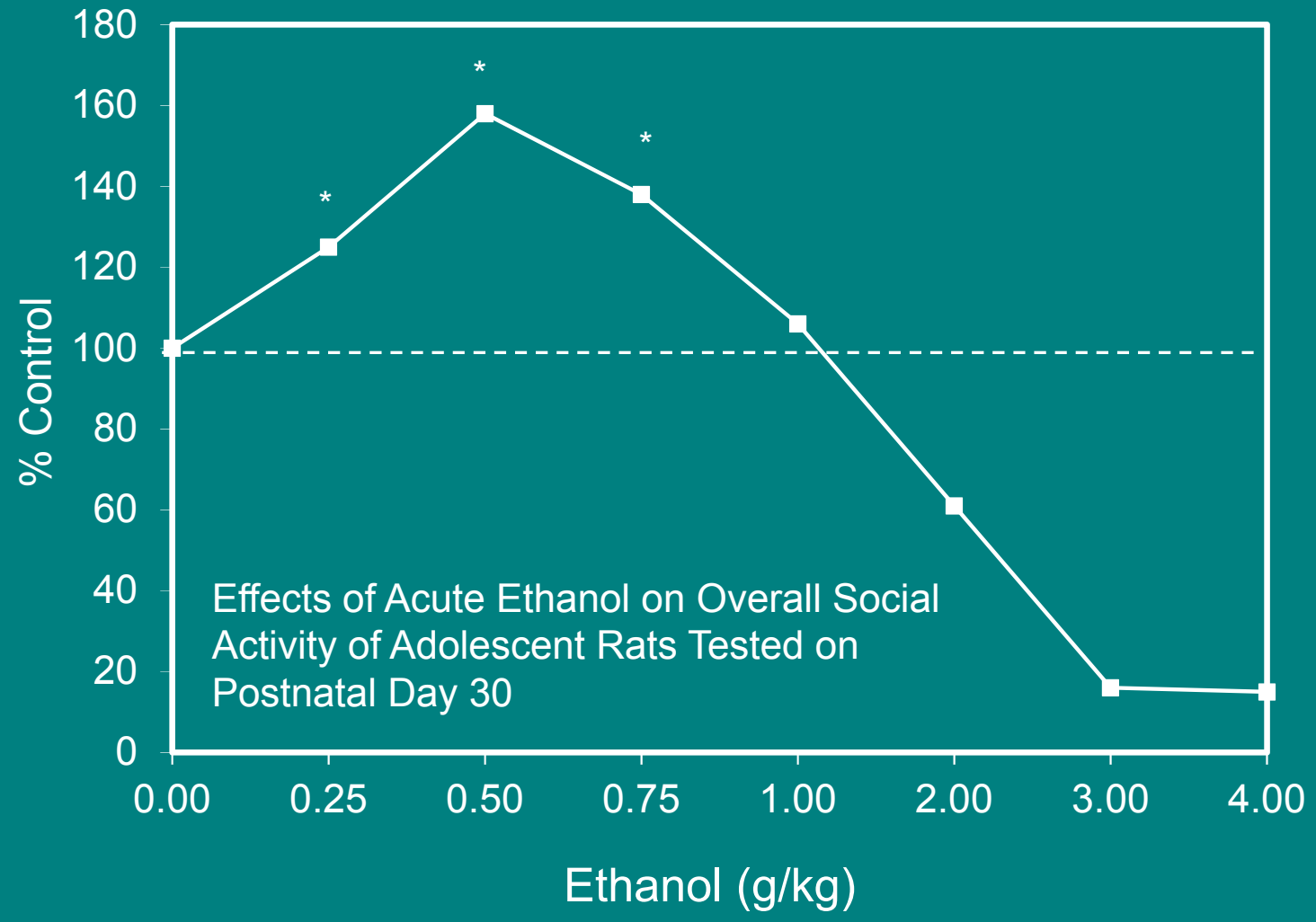
- Nearly one thousand hormetic dose responses have been reliably confirmed with mechanisms at the receptor/signaling pathway level.

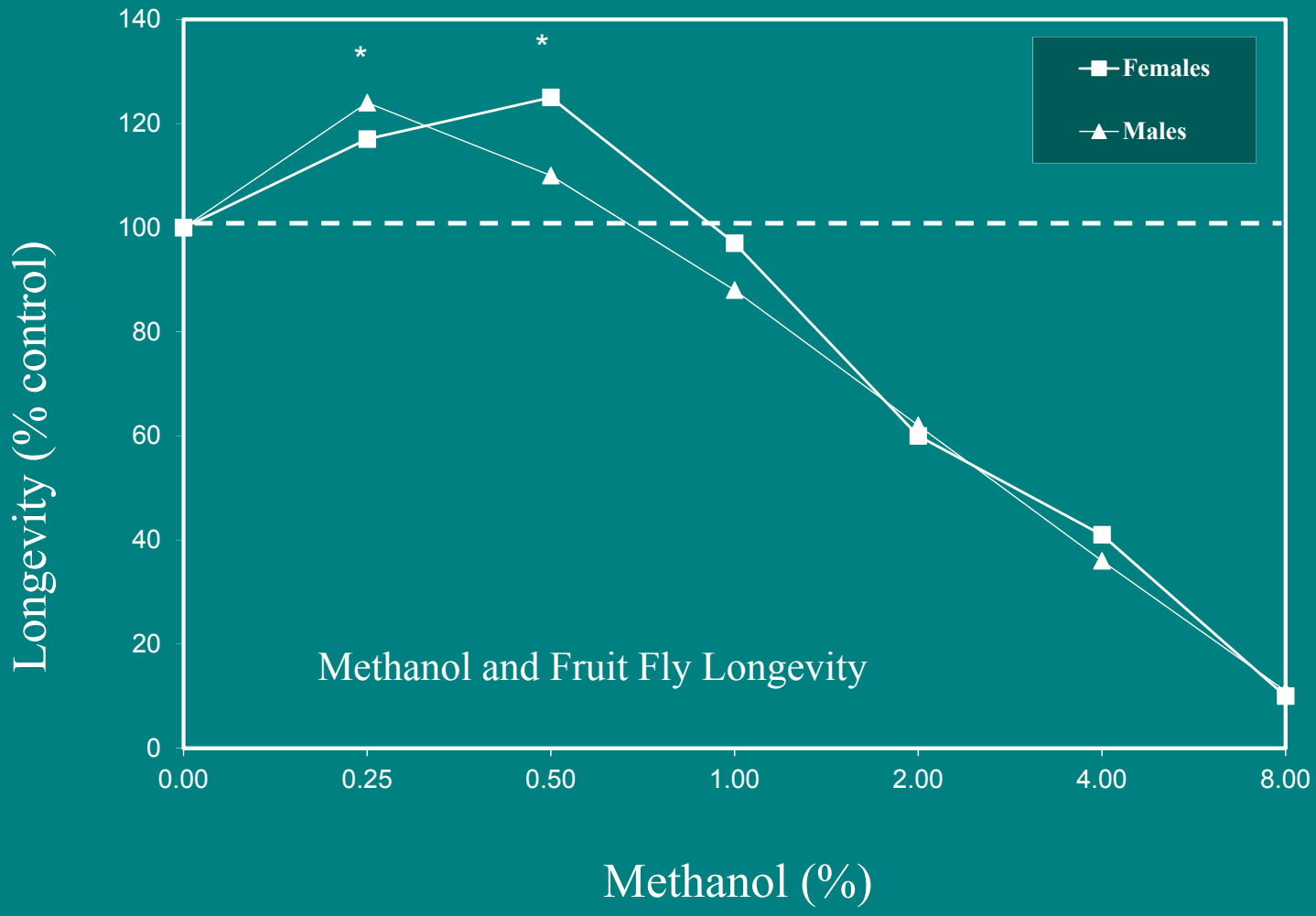
KEY OBSERVATIONS

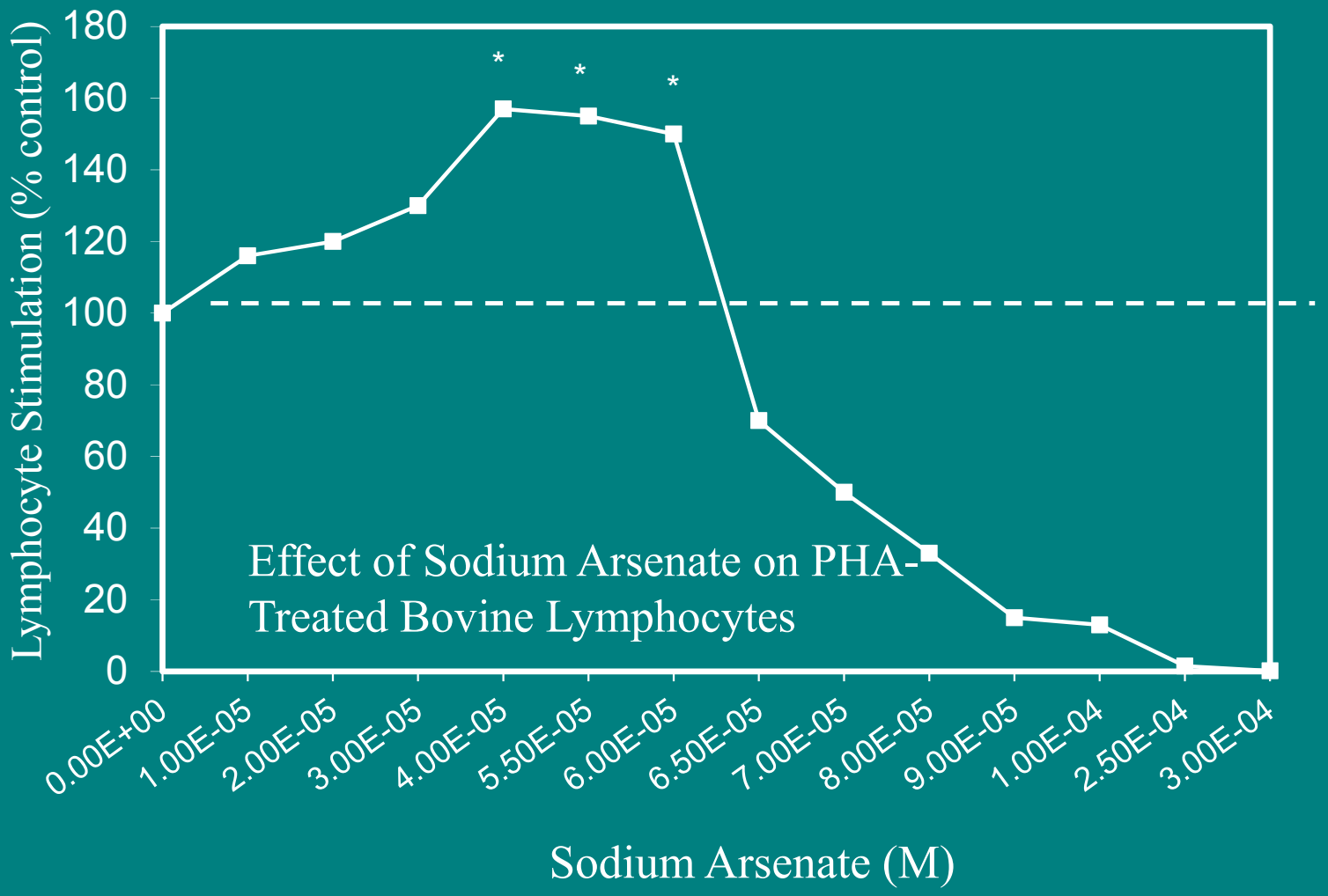
- Regardless of mechanism the quantitative features of the dose response are similar.

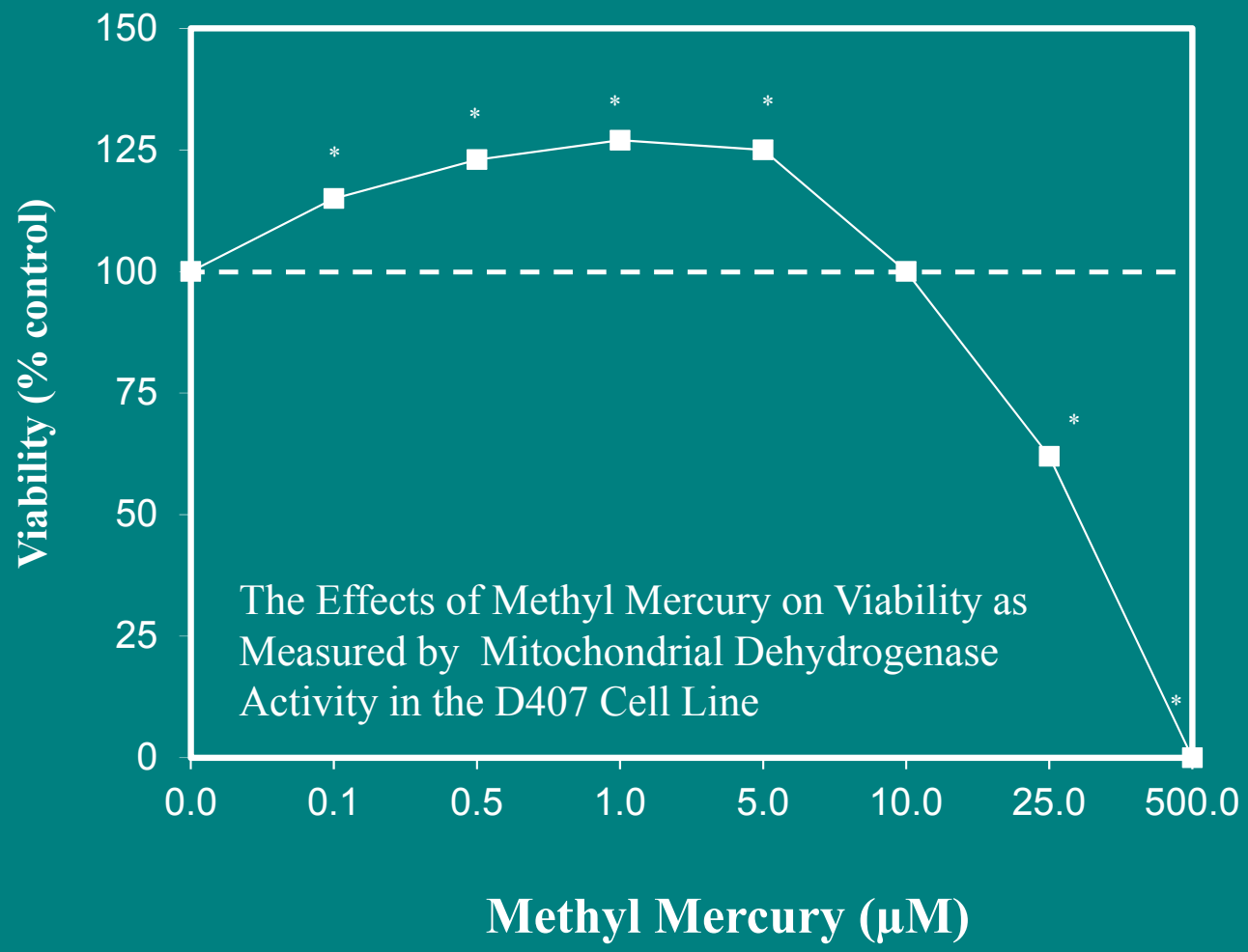
- Hormetic responses are integrative responses across multiple levels of biological organization;

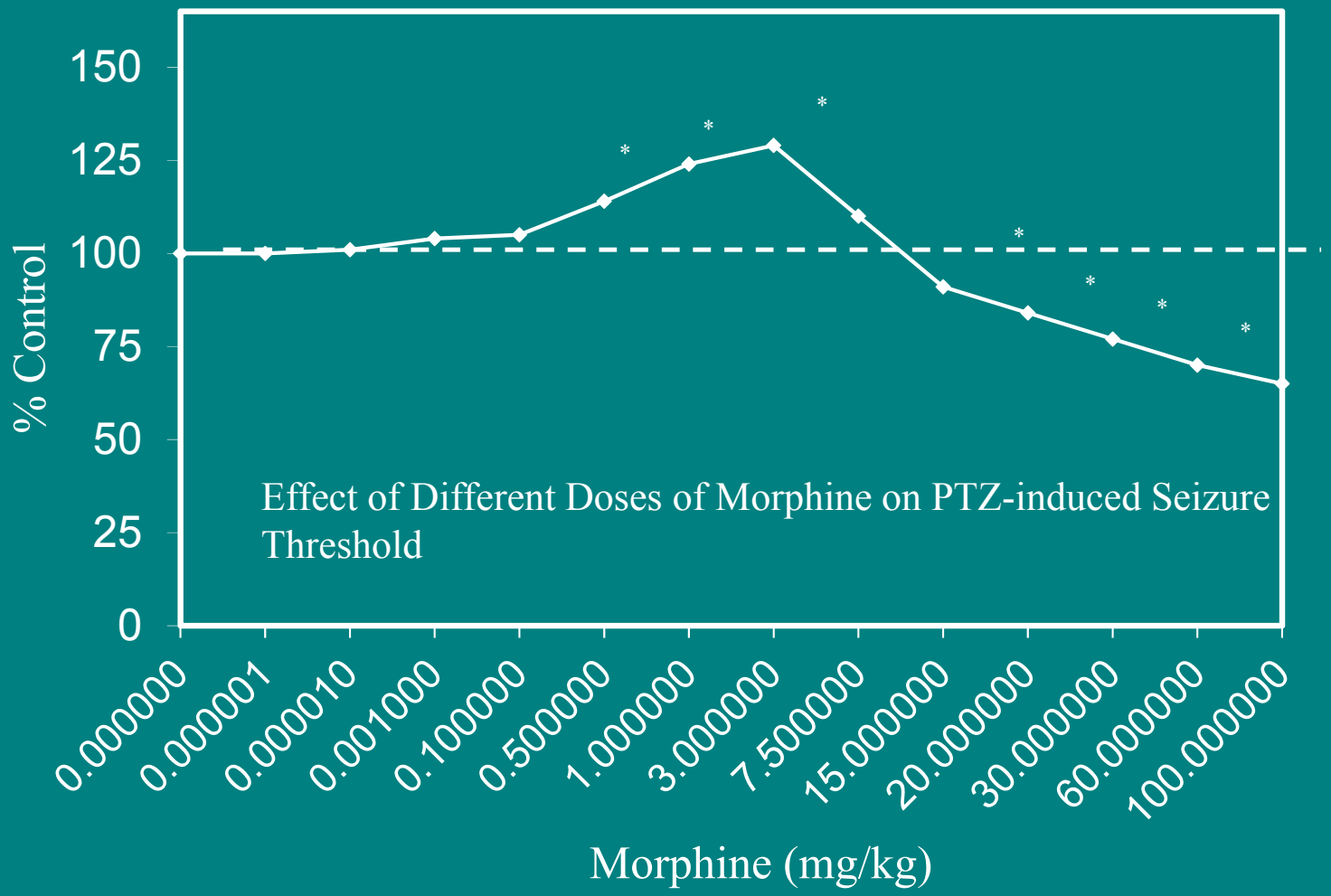
- Cell proliferation
- Fecundity
- Tissue Repair
- Behavioral/Learning
- Disease/Injury Resistance/Pre- Post-Conditioning
- DNA Damage/Tumor Incidence
- Aging/Longevity

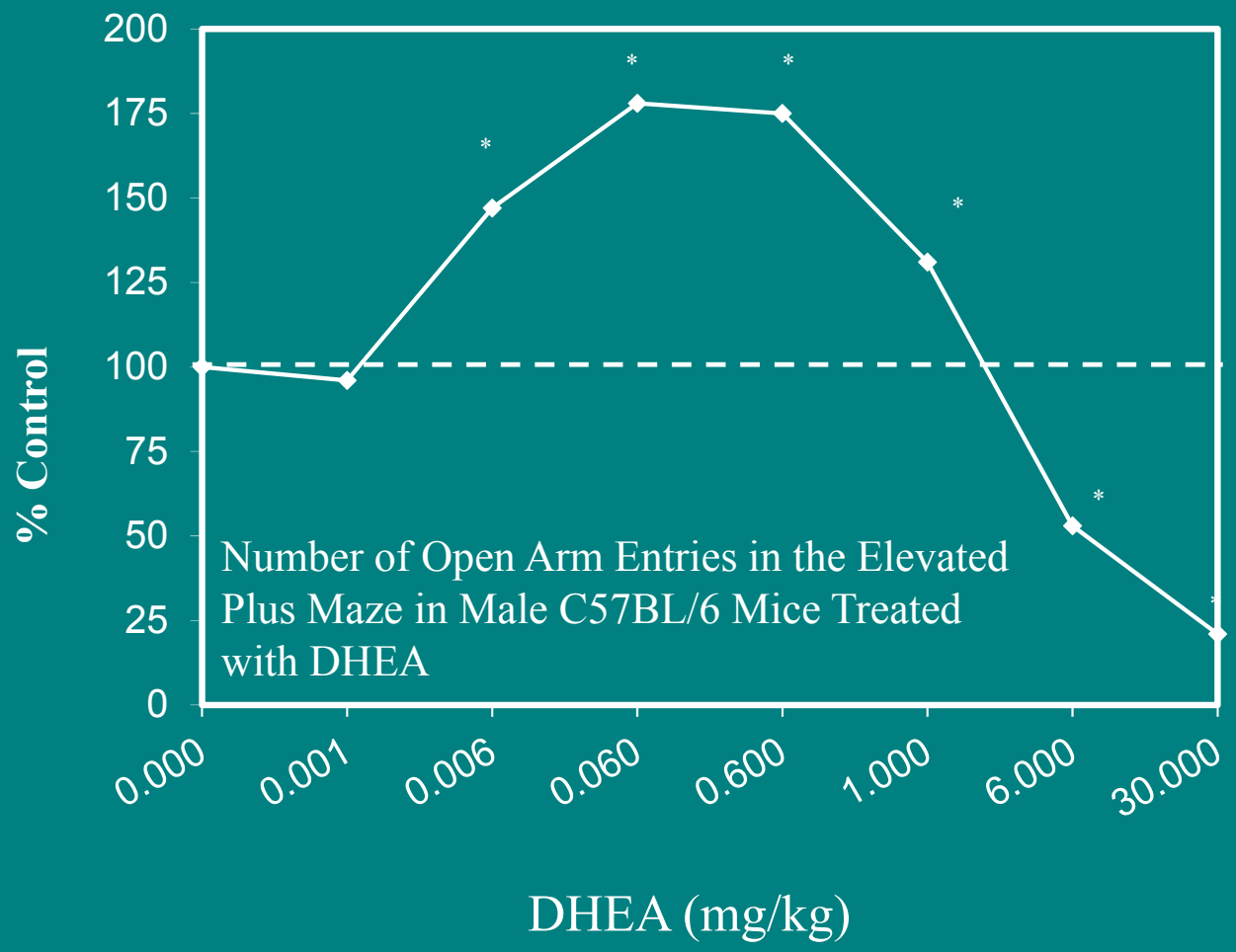

180
160
140
120
100
80
60
40
20
0
% Control
*
*
*
Effects of Acute Ethanol on Overall Social Activity of Adolescent Rats Tested on Postnatal Day 30
0.00
0.25
0.50
0.75
1.00
2.00
3.00
4.00
Ethanol (g/kg)

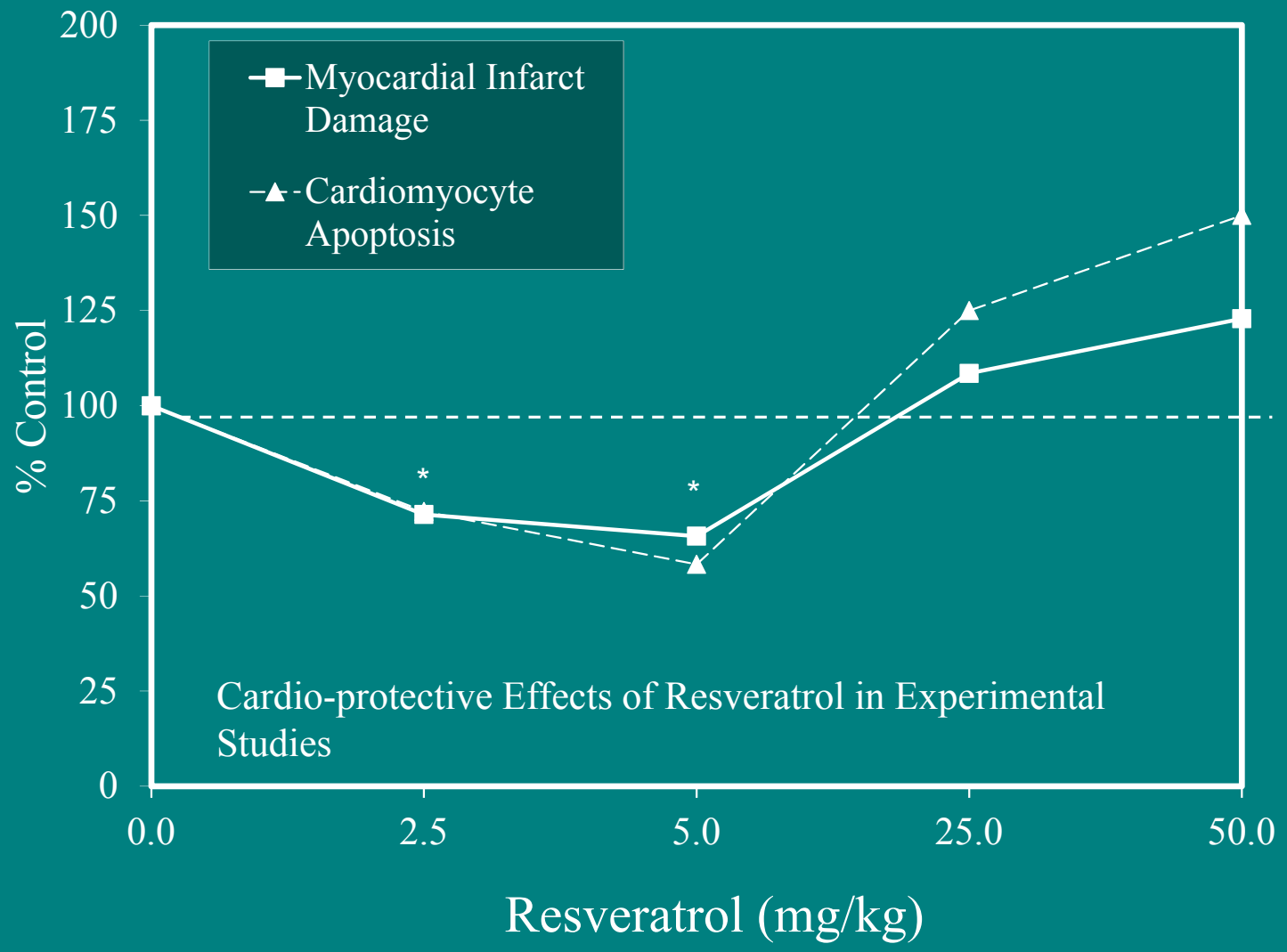

Longevity (% control)
140
120
100
80
60
40
20
0
0.00
0.25
0.50
1.00
2.00
4.00
8.00
*
*
Females
Males
Methanol and Fruit Fly Longevity
Methanol (%)


Lymphocyte Stimulation (% control)
180
160
140
120
100
80
60
40
20
0
*
*
*
Effect of Sodium Arsenate on PHA-Treated Bovine Lymphocytes
0.00E+00
1.00E-05
2.00E-05
3.00E-05
4.00E-05
5.50E-05
6.00E-05
6.50E-05
7.00E-05
8.00E-05
9.00E-05
1.00E-04
2.50E-04
3.00E-04
Sodium Arsenate (M)

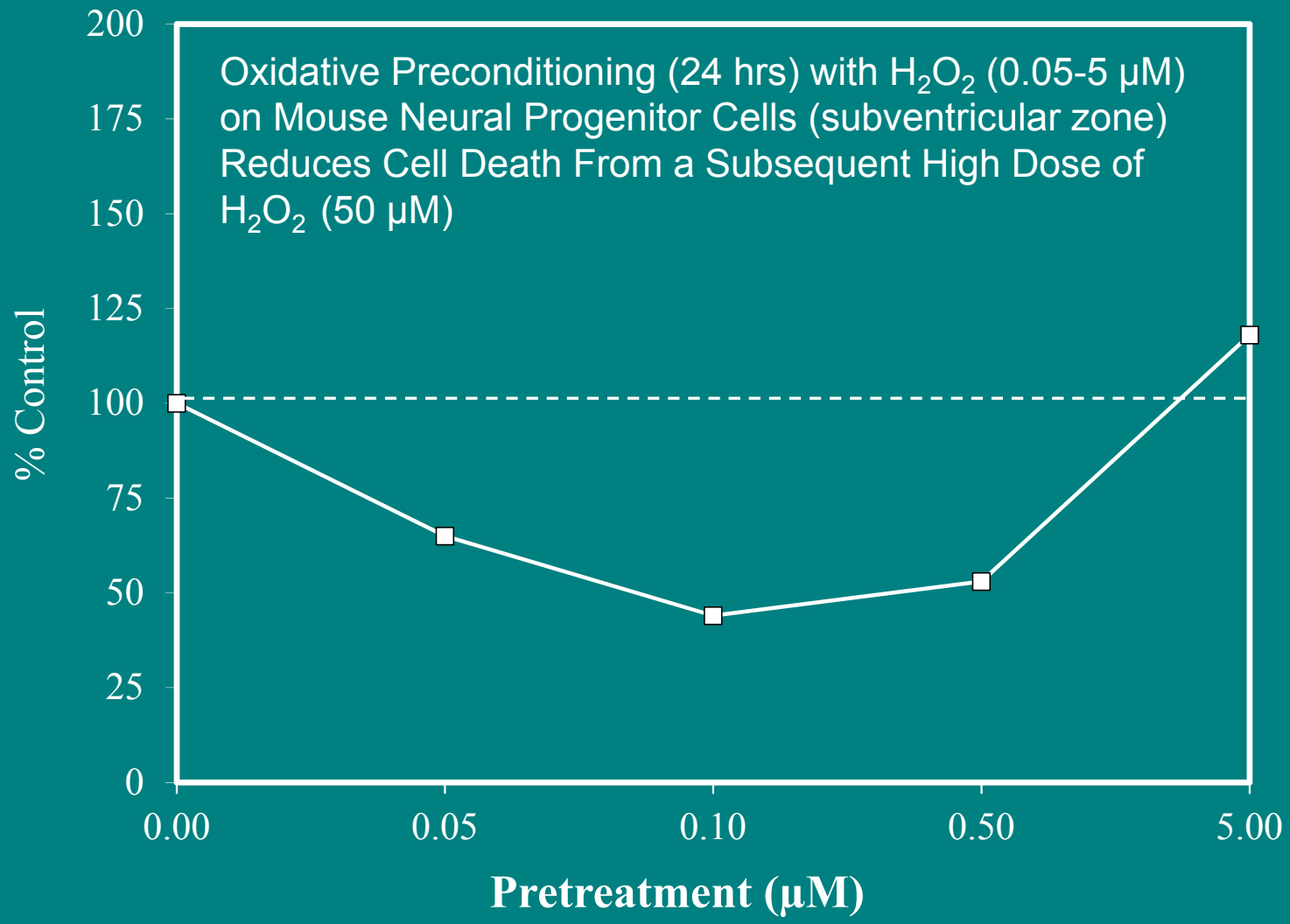

150
125
100
75
50
25
0
Viability (% control)
0.0
0.1
0.5
1.0
5.0
10.0
25.0
500.0
Methyl Mercury (µM)
The Effects of Methyl Mercury on Viability as Measured by Mitochondrial Dehydrogenase Activity in the D407 Cell Line

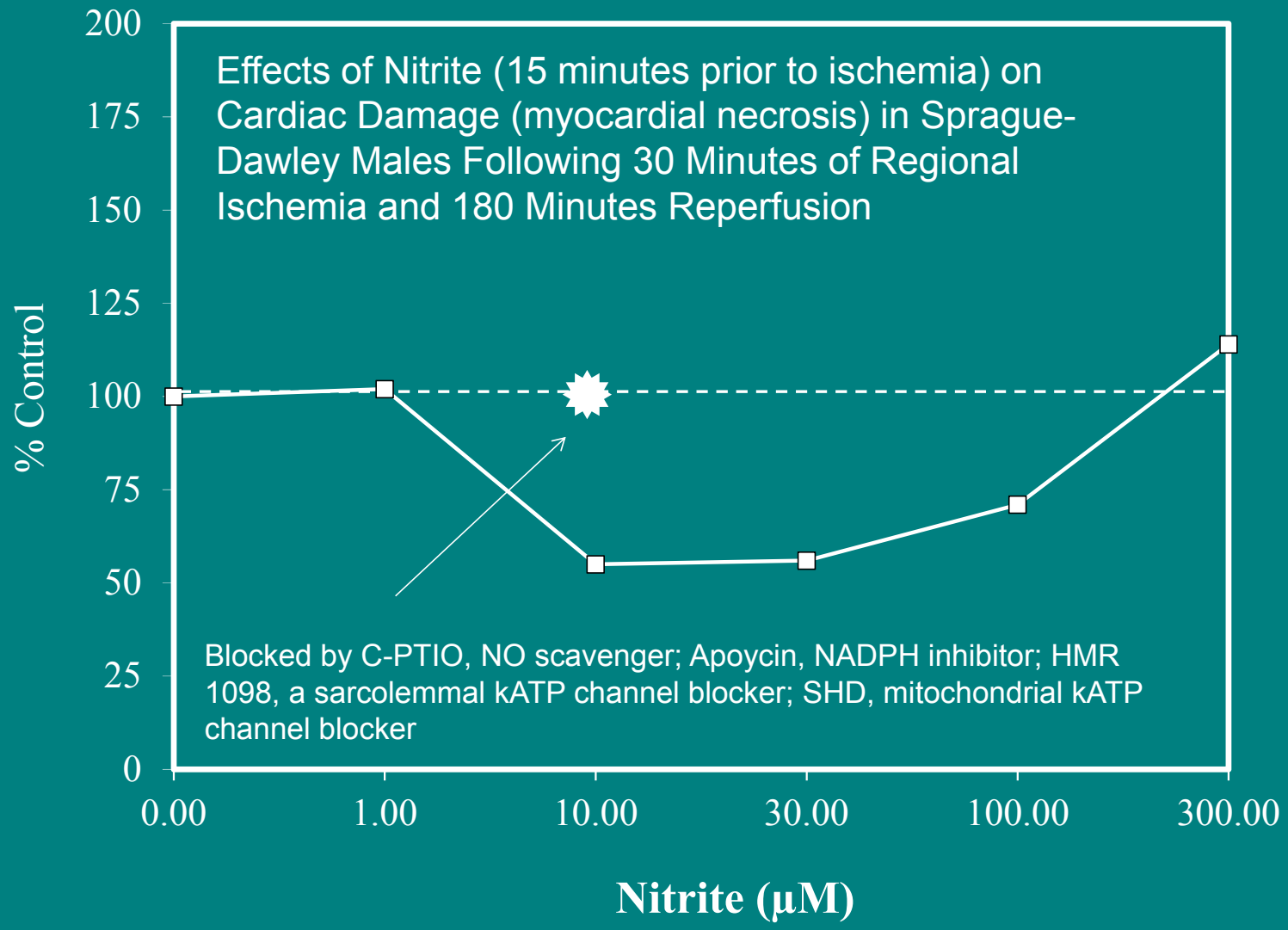

Effect of Different Doses of Morphine on PTZ-induced Seizure Threshold
% Control
150
125
100
75
50
25
0
0.000000
0.000001
0.000010
0.001000
0.100000
0.500000
1.000000
3.000000
7.500000
15.000000
20.000000
30.000000
60.000000
100.000000
Morphine (mg/kg)


200
175
150
125
100
75
50
25
0
% Control
Number of Open Arm Entries in the Elevated Plus Maze in Male C57BL/6 Mice Treated with DHEA
0.000
0.001
0.006
0.060
0.600
1.000
6.000
30.000
DHEA (mg/kg)

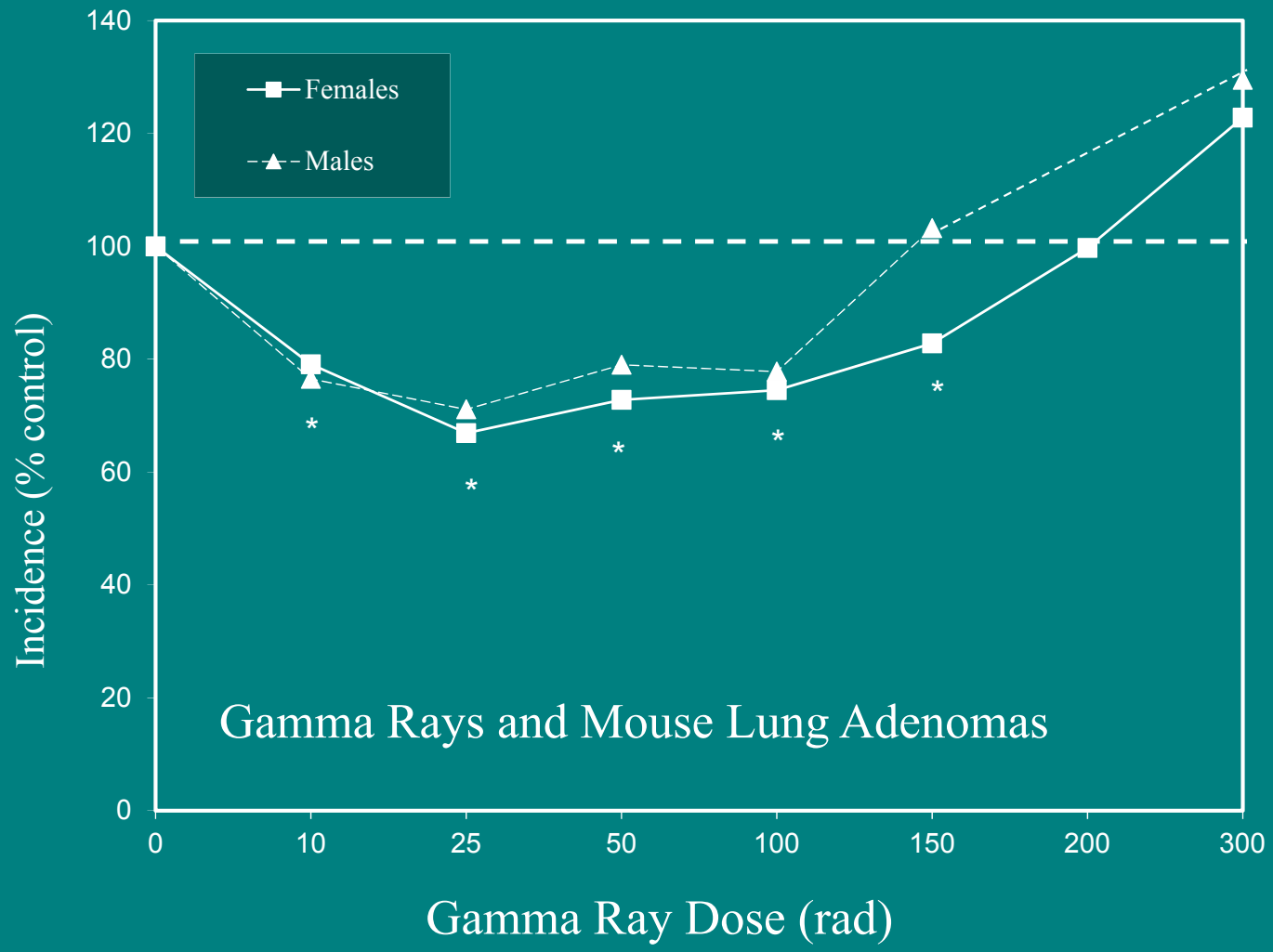

Myocardial Infarct Damage
Cardiomyocyte Apoptosis
% Control
200
175
150
125
100
75
50
25
0
*
*
0.0
2.5
5.0
25.0
50.0
Resveratrol (mg/kg)
Cardio-protective Effects of Resveratrol in Experimental Studies

PRECONDITIONING HORMESIS

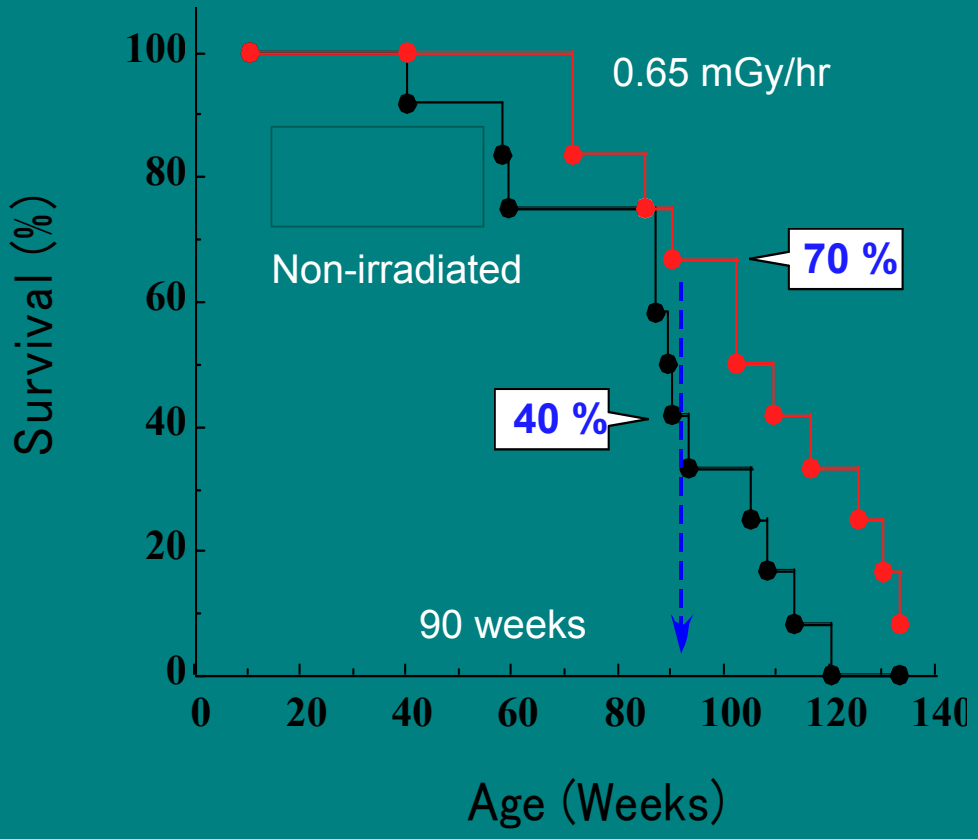

Oxidative Preconditioning (24 hrs) with H_2O_2 (0.05-5 µM) on Mouse Neural Progenitor Cells (subventricular zone) Reduces Cell Death From a Subsequent High Dose of H_2O_2 (50 µM)
% Control
200
175
150
125
100
75
50
25
0
0.00
0.05
0.10
0.50
5.00
Pretreatment (µM)


Effects of Nitrite (15 minutes prior to ischemia) on Cardiac Damage (myocardial necrosis) in Sprague-Dawley Males Following 30 Minutes of Regional Ischemia and 180 Minutes Reperfusion
% Control
200
175
150
125
100
75
50
25
0
0.00
1.00
10.00
30.00
100.00
300.00
Nitrite (µM)
Blocked by C-PTIO, NO scavenger; Apoycin, NADPH inhibitor; HMR 1098, a sarcolemmal kATP channel blocker; SHD, mitochondrial kATP channel blocker

HORMESIS: CANCER AND RELATED ENDPOINTS


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

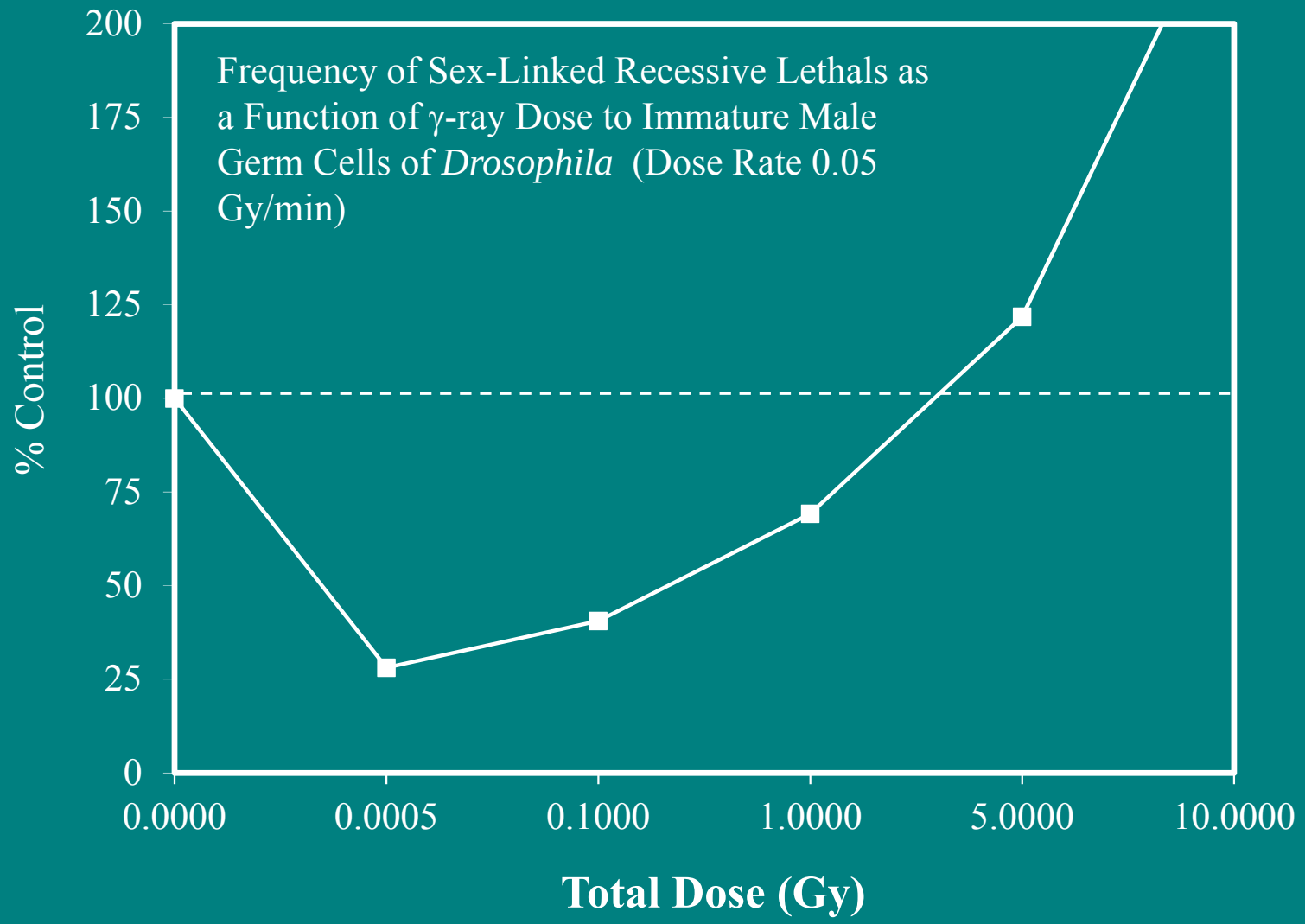
Prolongation of Life Span of db/db Mice by Low Dose Rate Irradiation

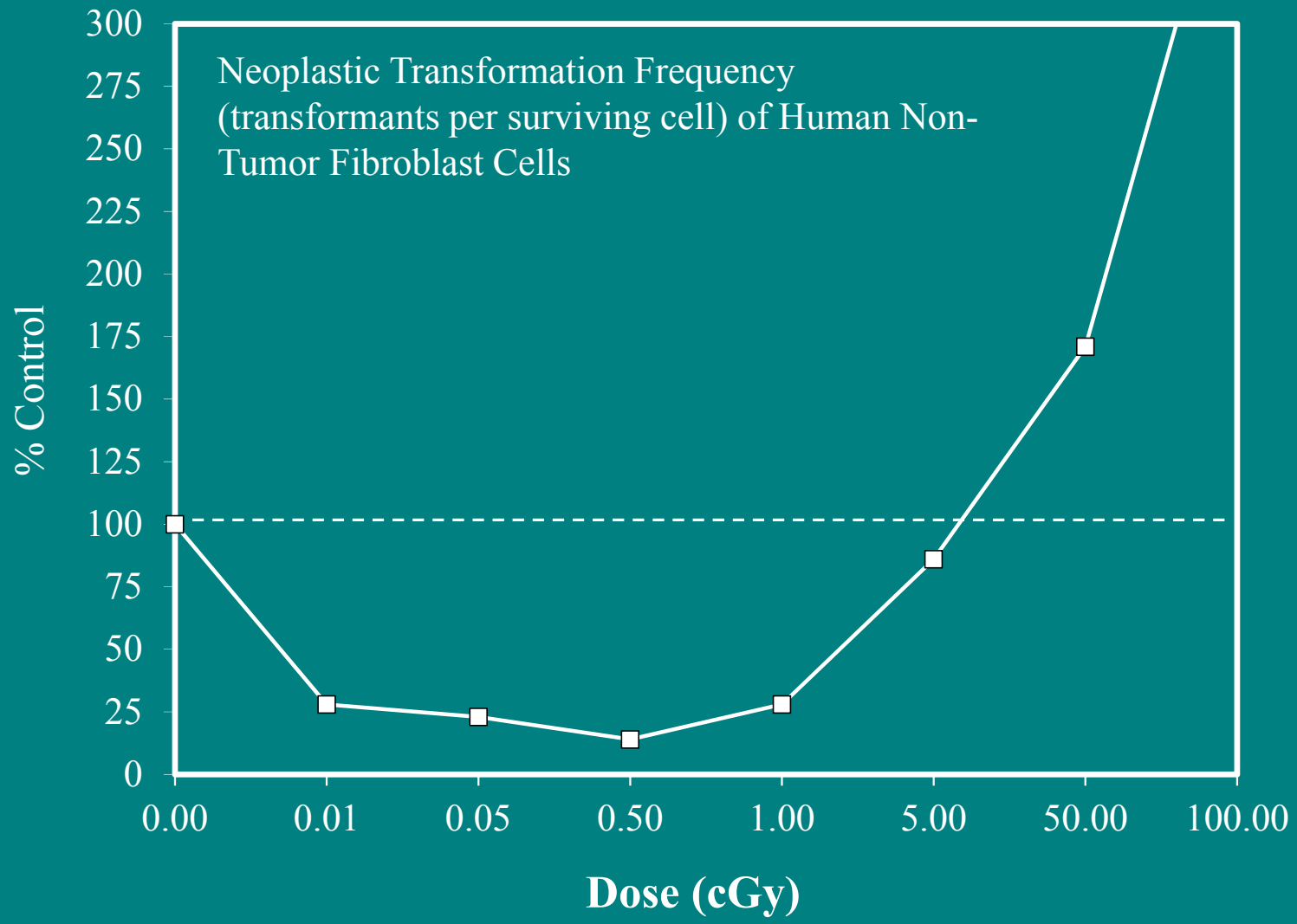


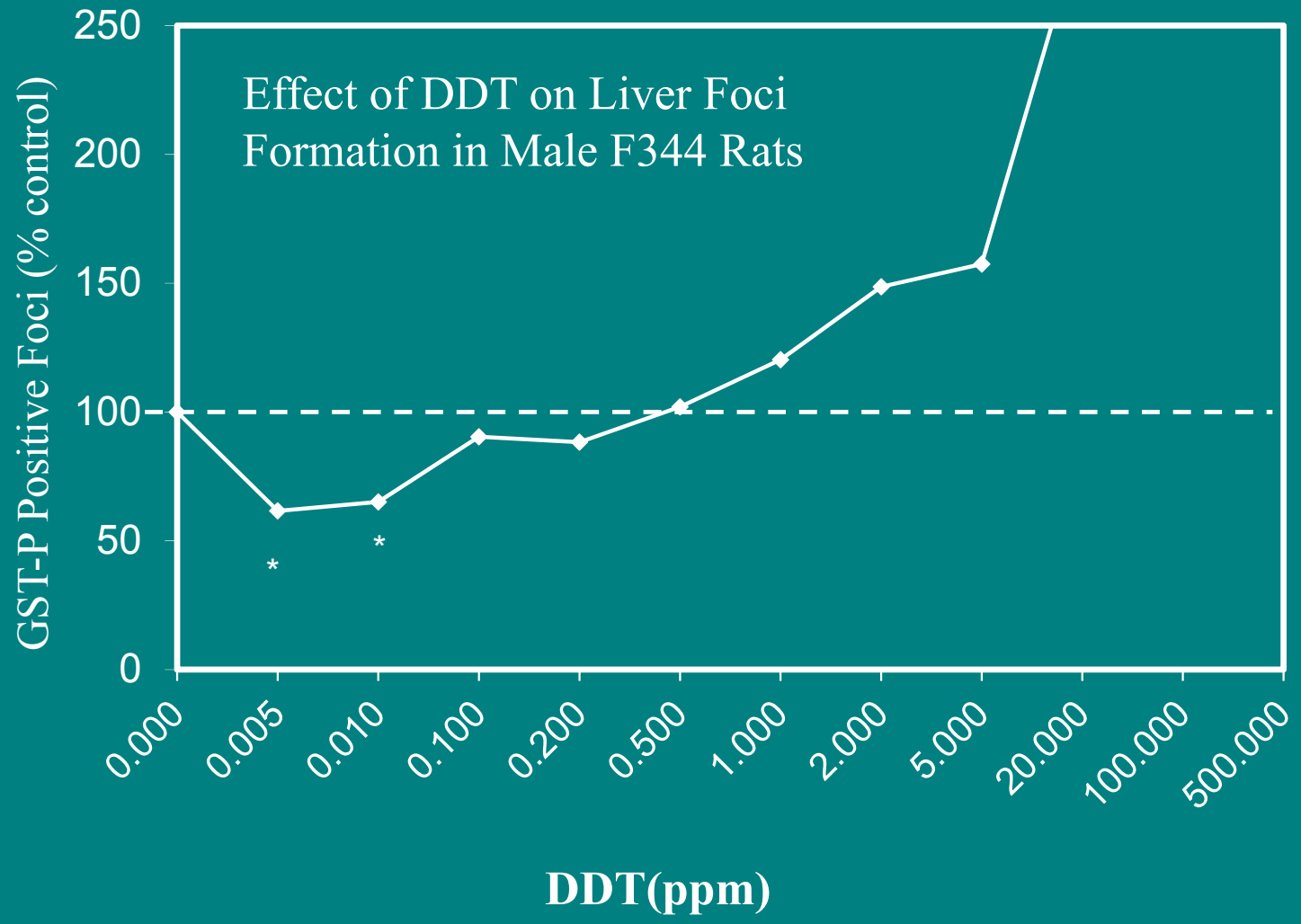
Appearance of db/db mice at 90th week of age

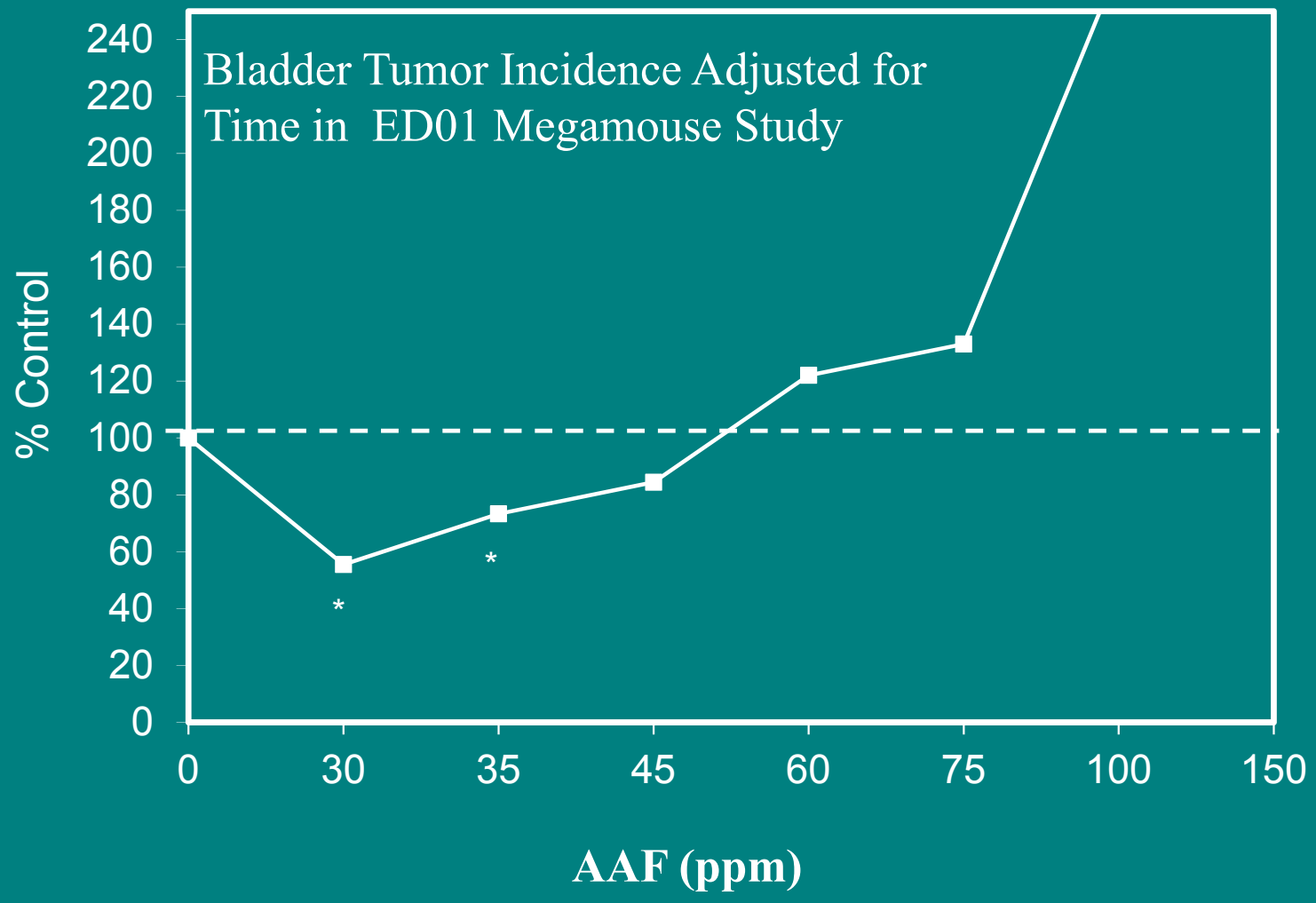
Irradiated Group

Control Group


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
(transformants per surviving cell) of Human Non-Tumor Fibroblast Cells
% 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)


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)

HORMETIC APPLICATIONS

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

KEY OBSERVATIONS

- Numerous pre- and post-conditioning studies display hormetic biphasic dose response relationships with mechanistic explanations.

- Thus, pre- and post-conditioning are manifestations of hormesis.

KEY OBSERVATIONS

- Hormetic-chemical synergies occur within the constraints placed on the quantitative features of the dose response.

- Synergy is seen less on the effect than with the dose in order to achieve the “constrained” synergistic effect.

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.

KEY OBSERVATIONS

- Hormesis is the first quantitative estimate of biological plasticity.

- The Hormesis stimulatory response is constrained by the limits of plasticity.

KEY TAKEAWAYS

- 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, and the general public.

- Failure to consider hormetic dose responses within hazard assessment and risk assessment is a serious failing of modern risk assessment.

- Risk assessment needs to consider the entire dose response continuum in order to serve the public health.

- Hormesis can play a significant role in drug discovery, development, and evaluation.
- Hormesis should become incorporated into educational programs dealing with the dose response.