THE HORMETIC DOSE RESPONSE

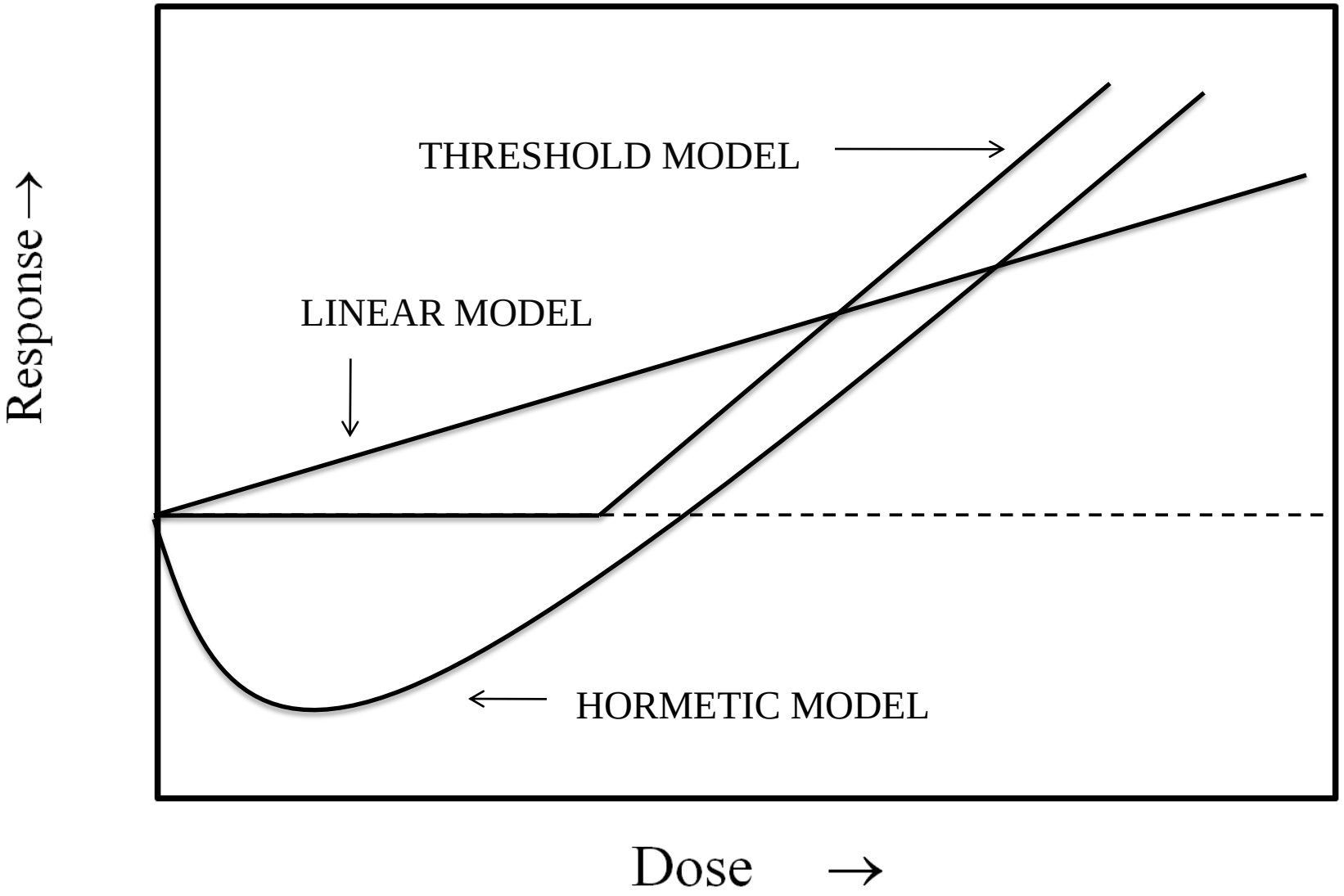
Edward J. Calabrese, Ph.D.
Department of Public Health
Environmental Health Sciences
Morrill I, N344
University of Massachusetts
Amherst, MA 01003
Phone: 413-545-3164
E-mail: edwardc@schoolph.umass.edu

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 →

HORMESIS

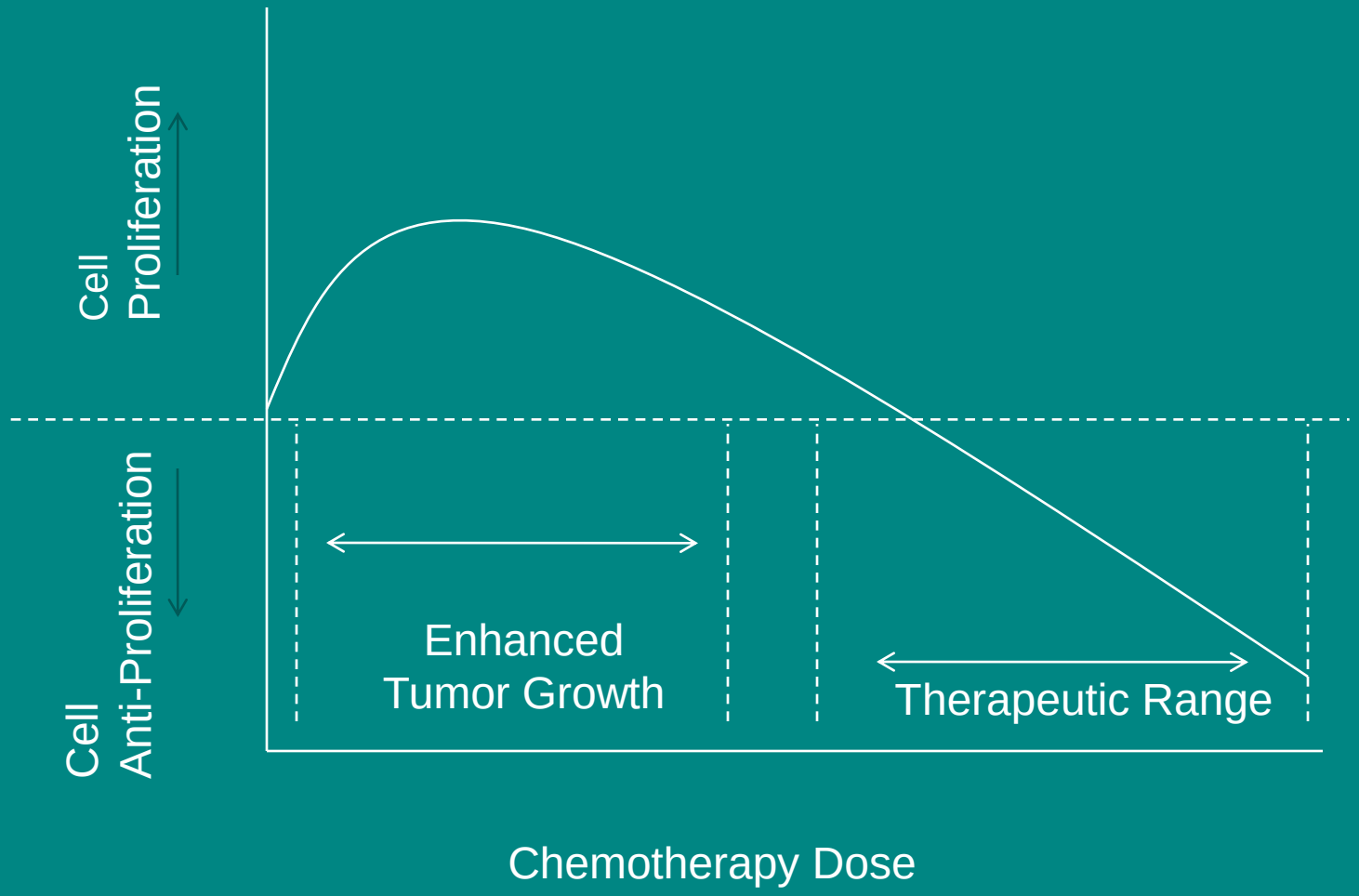
- Generally similar quantitative features with respect to amplitude and range of the stimulatory response.
- Directly induced or the result of compensatory processes following an initial disruption in homeostasis.
- Regardless of the means of induction the quantitative features are similar.

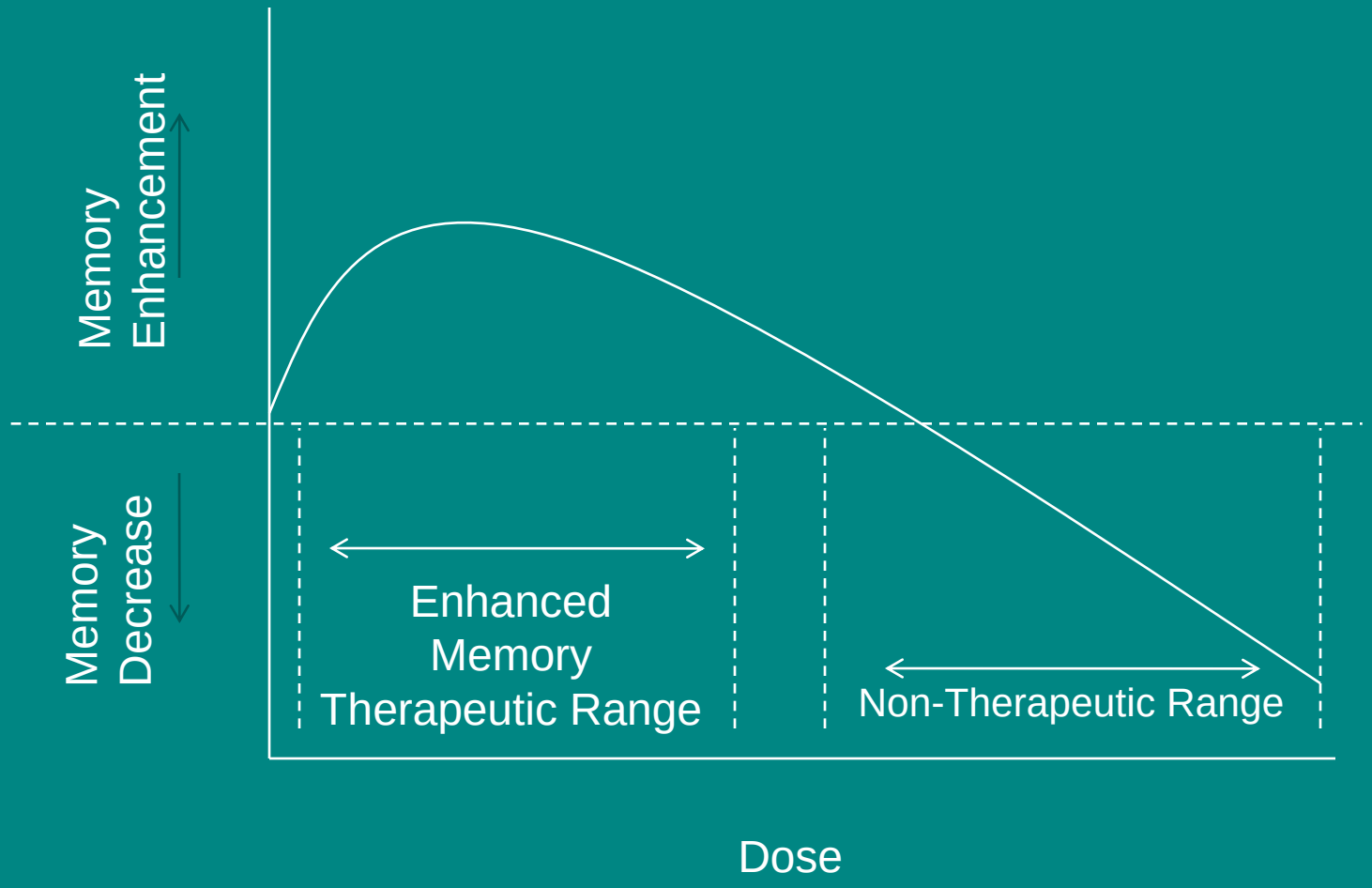
HORMESIS

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.


Cell
Proliferation
Cell
Anti-Proliferation
Enhanced
Tumor Growth
Therapeutic Range
Chemotherapy Dose


Memory Enhancement
Memory Decrease
Enhanced Memory Therapeutic Range
Non-Therapeutic Range
Dose

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:

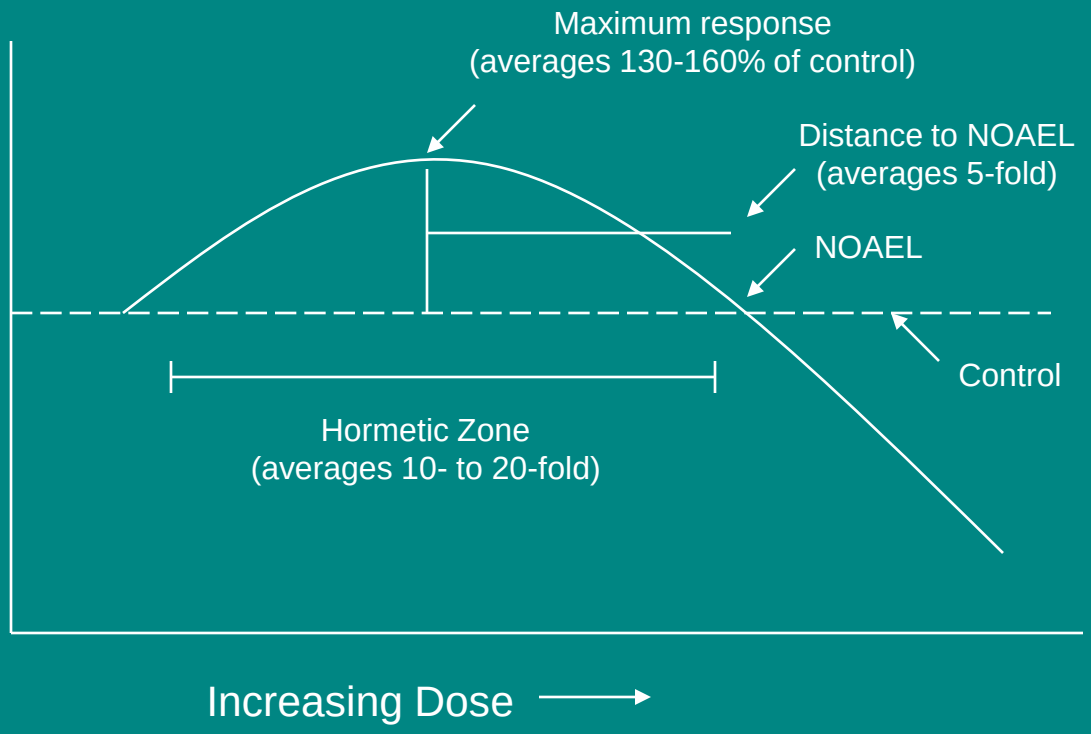
- Modest
- 30-60% Greater Than Control
- Usually Not More Than 100% Greater Than The Control

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

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.

HORMETIC MECHANISMS

- Receptor Level Assessment: Use of receptor antagonists to block response;

- Receptor and Signaling Pathway Assessment: Use of receptor and pathway inhibitors;

HORMETIC MECHANISMS

- 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.

KEY OBSERVATIONS

- Hormetic responses can depend on the physiological state of the biological model.

KEY OBSERVATIONS

- Low doses of IR stimulate immune responses in normal cells/organisms; if the biological model displays inflammation then the same low doses of IR suppress the immune response, creating an anti-inflammatory phenotype.

KEY OBSERVATIONS

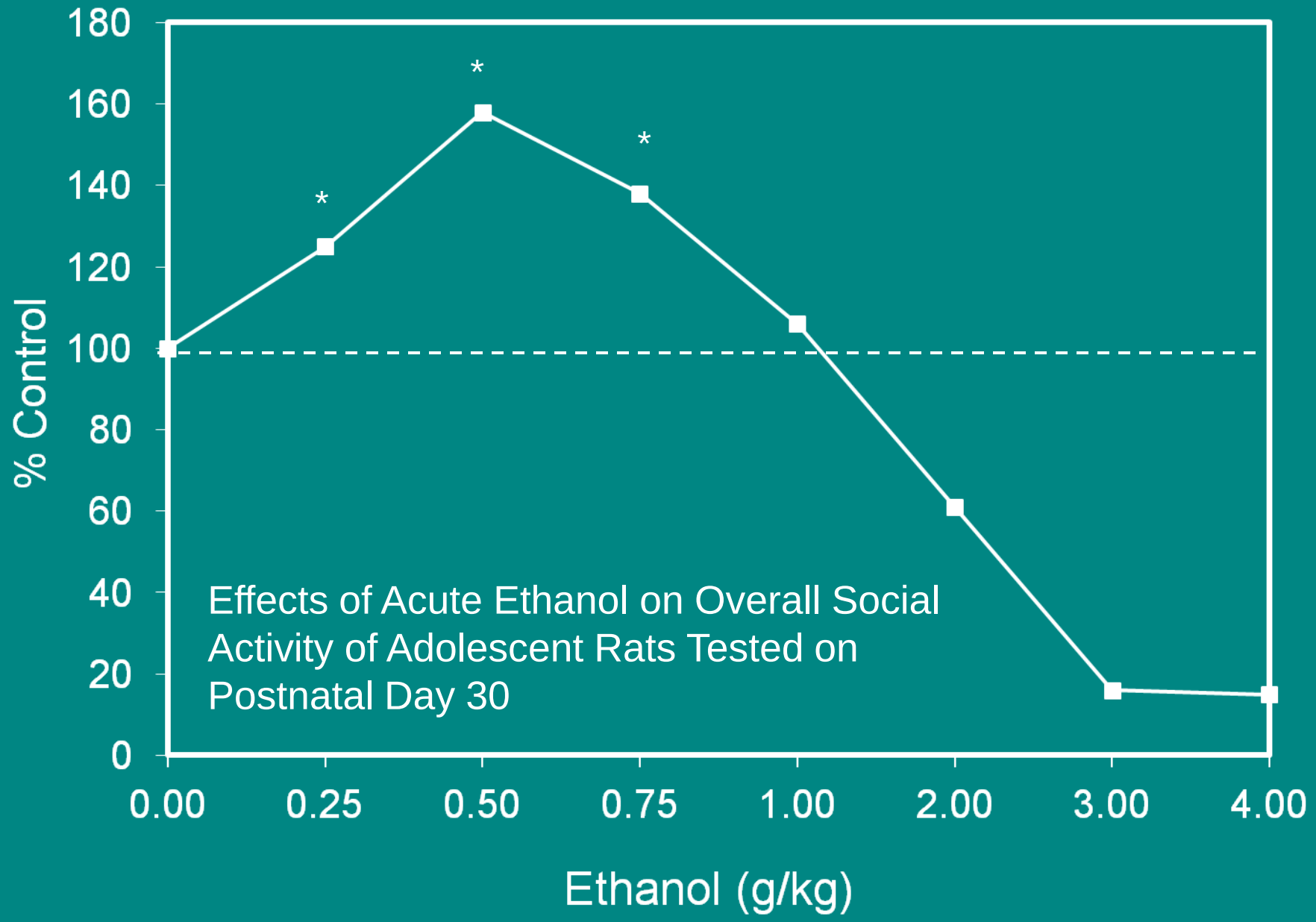
- Multiple animal models for arthritis display biphasic anti-inflammatory responses to IR which significantly reduces damage.

KEY OBSERVATIONS

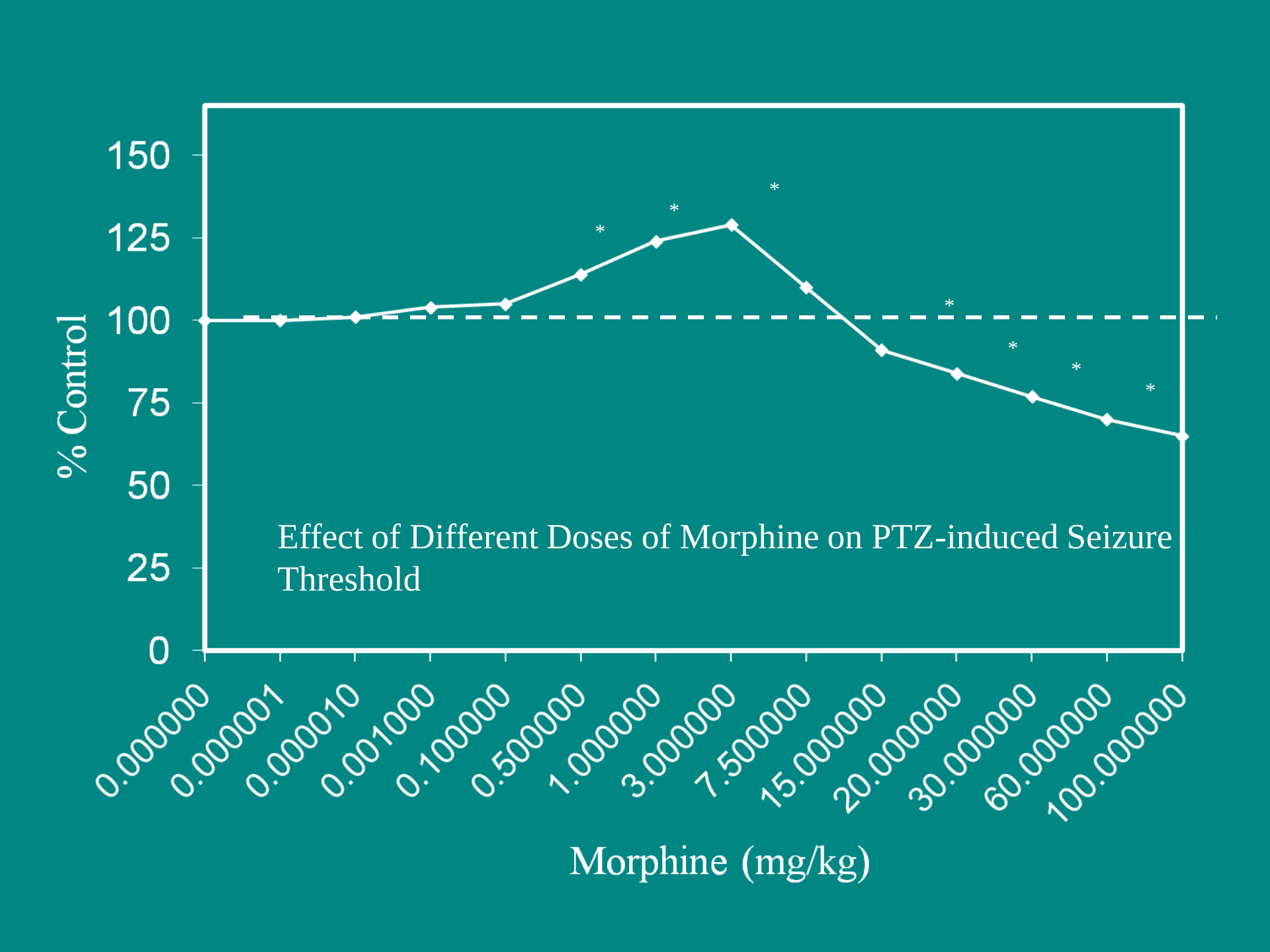
- Hormetic responses are integrative responses across multiple levels of biological organization;

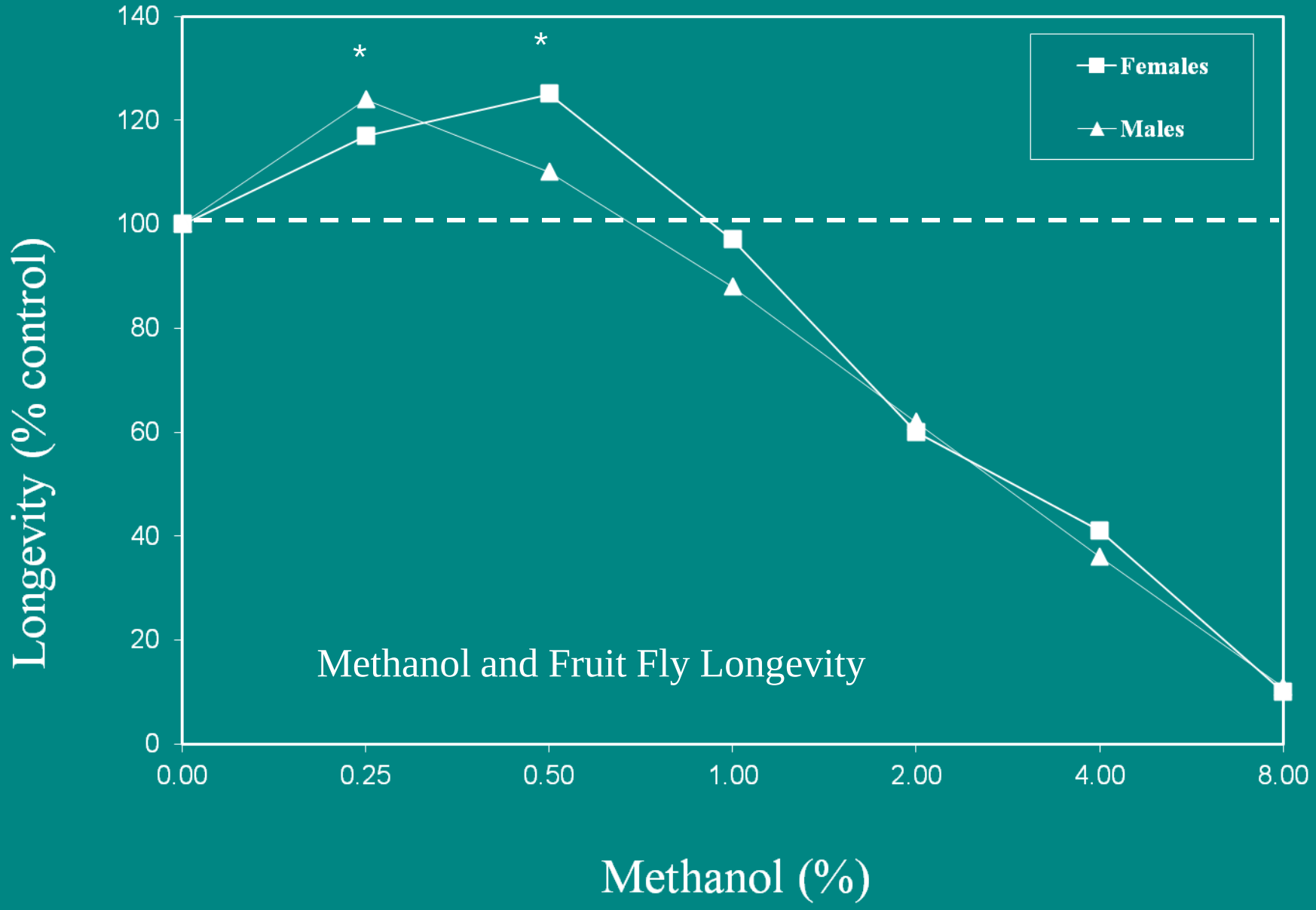
KEY OBSERVATIONS

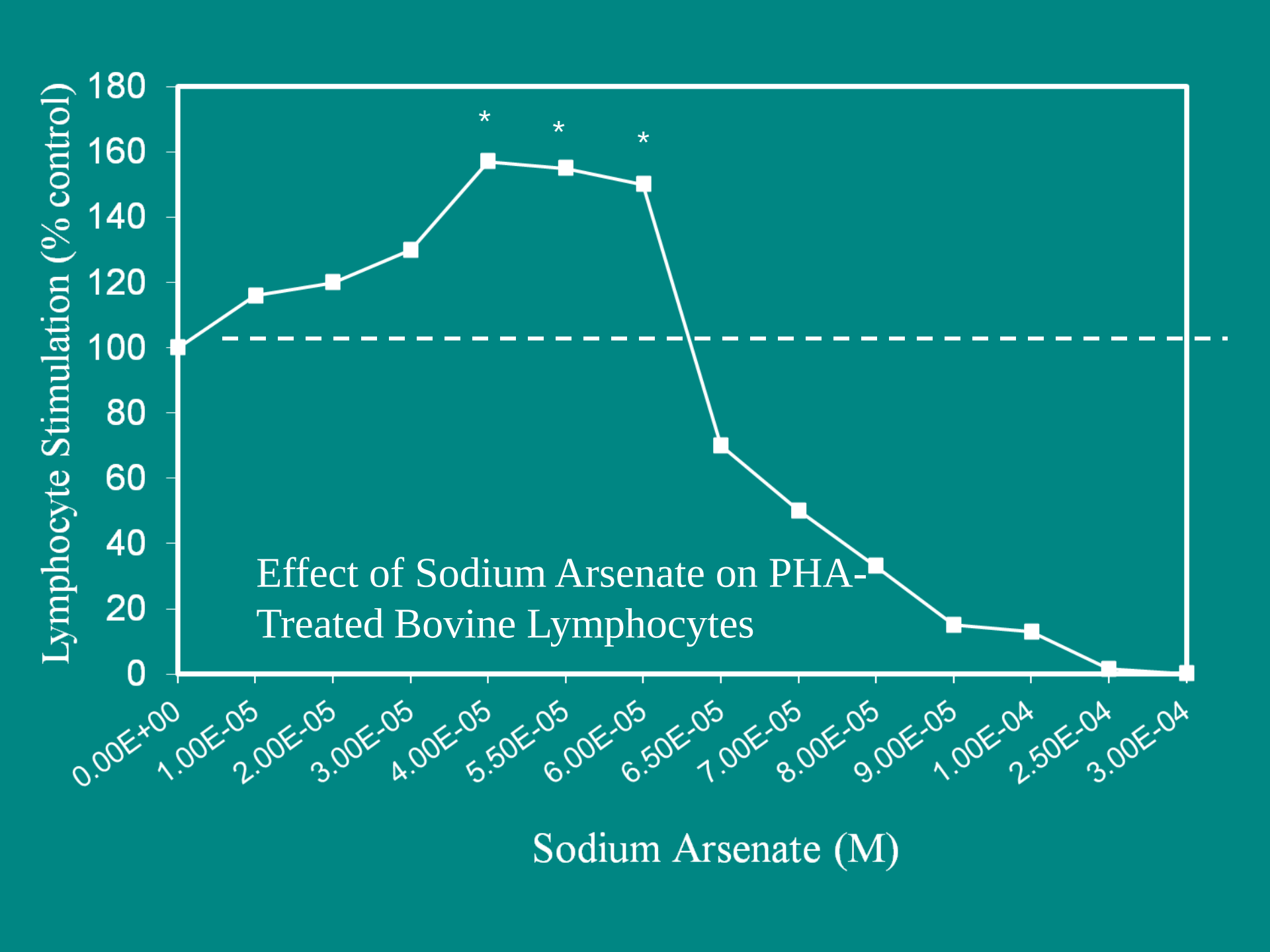
- Cell proliferation
- Fecundity
- Tissue Repair
- Behavioral/Learning
- Disease/Injury Resistance/Pre-Post-Conditioning
- Aging/Longevity


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)


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)


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)


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


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)

HORMETIC APPLICATIONS

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

KEY OBSERVATIONS

- Pre- and post-conditioning display the hormetic dose responses. 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 biological plasticity.

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

KEY OBSERVATIONS

- Harmful Applications
  - Enhancement of tumor growth at low doses of chemotherapeutic/environmental agents;
  - Enhancement of harmful microbial growths;
  - Tissue growth enhancement (e.g. blockage of stents);
  - Enlarged prostate (e.g. cardiac glycosides);
  - Proliferative connective tissue disorders (e.g. Dupuytren's Disorder);

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.

CONCLUSIONS

- 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.